National Clinical Guideline Centre

Final, August 2015

Type 1 diabetes in adults

Type 1 diabetes in adults: diagnosis and management

NICE's original guidance on Type 1 diabetes in adults: diagnosis and management was published in 2004. It was updated in 2015, 2016 (Recommendation 138 only), 2021 and 2022. See the NICE website for the guideline recommendations and the evidence reviews for the 2022 update. This document preserves evidence reviews and committee discussions for areas of the guideline that were not updated in 2022.

Clinical guideline NG17

Methods, evidence and recommendations

August 2015

2015 update

Commissioned by the National Institute for Health and Care Excellence

Royal College of Physicians
The Royal College of Surgeons of England
Royal College of General Practitioners
Royal College of Nursing
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Disclaimer
Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and/or their guardian or carer.

Funding
National Institute for Health and Care Excellence

Update information
July 2016: Recommendation 138 has been reworded to clarify the role of GPs in referring people for eye screening and also to add information on when this should happen.

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Acknowledgements

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1 Introduction

This section was updated in 2015.

Aim of this guideline

Type 1 diabetes affects over 370,000 adults in the UK, representing approximately 10% of adults diagnosed with diabetes. Given the complexity of its treatment regimens, successful outcomes depend, perhaps more than with any other long-term condition, on full engagement of the adult with type 1 diabetes in life-long day-by-day self-management. In order to support this, the health service needs to provide informed, expert support, education and training as well as a range of other more conventional biomedical services and interventionsfor the prevention and management of long term complications and disability.

The number of adults with type 1 diabetes means that, while the condition is certainly not rare, it is not common enough to provide and maintain all the necessary skills in its management for all healthcare professionals who will deal with it. The aim of this guideline is, therefore, to provide evidence-based, practical advice on the steps necessary to support adults with type 1 diabetes to live full, largely unrestricted, lives and avoid the acute and long-term complications of both the disease and of its treatment. NICE last produced such a guideline in 2004. The present guideline is an update of many sections of that guideline, focusing on areas where new knowledge and new treatment opportunities have arisen in the last decade. There have been many such developments, resulting in improving outcomes for adults with type 1 diabetes, but also presenting more challenges in the diversity and complexity of the tools they now have to achieve these outcomes.

Background

Type 1 diabetes is a long-term hormonal deficiency disorder, in which there is loss of insulin secretion. This results in high plasma glucose concentrations and other metabolic and haematological abnormalities, which have both acute and long-term adverse effects. Type 1 diabetes is usually caused by autoimmune destruction of the insulin-secreting beta cells of the pancreas. These cells make insulin in response to need, with the main driver being circulating glucose concentrations, influenced by a variety of other neurological and endocrine factors signalling the body's state.

Type 1 diabetes can present at any age. Although it commonly presents in children and adolescents, the condition persists into and can start in adult life. Prevalence of type 1 diabetes is highest in the age ranges of 35–60 years.[1] Treatment regimens used to manage diabetes and the demands of living with diabetes are as complex in adults as in younger people.

The treatment of type 1 diabetes is insulin replacement and this insulin is not under endogenous control. In the short term, people with type 1 diabetes face significant challenges to daily living, for example, hyperglycaemia (high plasma glucose) and hypoglycaemia (low plasma glucose), the need for daily administration of insulin and frequent self-monitoring of plasma glucose, and to plan daily activities such as eating and exercising. Over the long term, type1 diabetes carries risk of major complications and reduced life expectancy. At present there is no cure.

Life expectancy for people with type 1 diabetes has increased. In one study from the USA, life expectancy among people diagnosed with type 1 diabetes between 1965 and 1980 improved by 15 years compared with people diagnosed between 1950 and 1964[2], and mortality rates in a UK study are lower than previously reported.[3] Nevertheless, having type 1 diabetes typically reduces life expectancy in the UK by 11-14 years.[4] Risk of death is 135% higher than for people without diabetes of the same age.[5] Most of the deaths are due to chronic complications, although death in acute hypoglycaemia or diabetic ketoacidosis may occur. Rates of diabetic ketoacidosis appear to be

increasing in the UK.[12] There has also been an increase in the number of people with type 1 diabetes needing treatment for end-stage kidney disease.[12]

Strict plasma glucose control reduces risk of all long-term complications and increases life expectancy among people with type 1 diabetes.[6] Every adult with type 1 diabetes should therefore be encouraged and supported to achieve optimum plasma glucose control, using insulin replacement. Effective replacement of insulin requires detailed knowledge of its actions. The insulin user needs to acquire complex skills in insulin management.

Other risk factors for vascular complications of type 1 diabetes should also be addressed. Higher blood pressure is associated with increased complications[7] and should be aggressively managed.[8,9] Controlling lipids within recommended targets for other forms of diabetes is expected to reduce excess cardiovascular risk associated with type 1 diabetes.[7] Early detection and effective management of type 1 diabetes and its complications are also essential to prevent or limit disability in people with type 1 diabetes.

Current practice: ideal and achieved

People with type 1 diabetes manage many aspects of their own care, including administering insulin by injection or infusion, monitoring their plasma glucose concentrations, and adjusting insulin doses accordingly on a regular basis. The aim is to maximise the time that achieved glucose concentrations are within the target levels known to minimise risk of complications, while avoiding problems such as hypoglycaemia or ketosis.

People with type 1 diabetes need education and support from healthcare professionals with expertise in insulin physiology and therapeutics to manage their diabetes effectively. Hypoglycaemia remains a problem for people using insulin and can be reduced by structured education programmes,[10] yet only about 1% of adults with type 1 were recorded as having attended such programmes in England and Wales in 2011-12.[11] Fewer than 30% of people with type 1 diabetes achieve the 2004 NICE-recommended target for blood glucose control. In the last 4 audit cycles, there has been no significant improvement in the proportion of people who meet this target.[11]

People with type 1 diabetes need regular monitoring for complications of diabetes and for the factors that increase their individual risk of developing these. Where these occur, active management is needed. However, only 41.3% of people with type 1 diabetes in England and Wales have records of receiving all 9 of the care processes recommended by NICE.[11] More than 30% of people with type 1 diabetes do not have their annual eye and foot checks for early complications and almost one-half do not have screening appointments for kidney complications. Blood pressure within 2004 NICE guidelines is recorded in nearly 75% of adults with type 1 diabetes; but just under 30% have recorded cholesterol of under 4 mmol/litre.[11]

Diabetes management in hospitals and other places for professional healthcare remains suboptimal. Insulin regimens are the most common cause of drug errors in inpatient prescribing.

People with type 1 diabetes have traditionally received care primarily from specialist services. However, 15–20% of adults with type 1 diabetes have little or no contact with secondary care services, or are offered only infrequent appointments focussed on annual review.

A small number of people with type 1 diabetes experiencing life-threatening episodes of hypoglycaemia undergo pancreatic transplant or islet cell transplantation. Around 200 pancreas transplants are performed in the UK each year. Around 95 islet transplants have been performed in 65 people in the UK to date.

Target audience

This guideline is intended to describe the methods for achieving optimal outcomes for adults with type 1 diabetes and inform service design and delivery for them. Its intended audience therefore includeshealthcare professionals involved in delivering services to adults with type 1 diabetes, service managers and commissioners and adults with type 1 diabetes and their families.

1.1 Living with type 1 diabetes

Type 1 diabetes is a condition where the power lies primarily with the people. Day-to-day monitoring, control and treatment are undertaken by the patient, not by the healthcare professional (hence RD Lawrence's saying "Every diabetic, their own Doctor"). With power comes responsibility: it is the patient's behaviour and daily decisions which determine the level of success in managing the condition. Adherence to insulin regimens, close monitoring of blood glucose, accurate estimation of carbohydrate intake and administration of appropriate insulin doses profoundly affect both immediate and long-term outcomes.

For patients, effective management of type 1 diabetes involves diligence, self-discipline, attention to detail, an analytical approach and numerous decisions – every day. Developing and then using these behaviours consistently is a considerable challenge in itself. However, type 1 diabetes can add further levels of complexity. Patients trying to emulate as closely as possible the blood glucose control of those without diabetes face the twin risks of hypoglycaemia on one side and hyperglycaemia, with its associated likelihood of long-term complications, on the other. Additionally, an individual's diabetes rarely remains static for long periods due to the influence of hormonal variation, activity, stress and a myriad of other factors. Patients employing carefully evolved strategies and approaches to dietary and insulin dose management can see impeccable blood glucose results one week, followed by apparently illogical variability the next.

For healthcare professionals, the challenge of supporting type 1 patients can be exacerbated precisely because the condition is so individualised. Rather than uniform and universal approaches, most patients seek a personalised package of targets, technologies and techniques that allow them to manage their diabetes in different day-to-day situations with the minimum effort necessary for the best results and the highest quality of life. People with type 1 diabetes prefer to fit the condition into their lives, and not the other way round. However, patients will manage their condition more effectively where they can rely upon informed advice and proven interventions.

This updated Guideline therefore aims, in the light of the most recent evidence, to help healthcare professionals in all settings encourage and support optimum lifestyle choices and self-management strategies among patients. For example, newly diagnosed patients may not be aware that there are different types of diabetes with different treatment opportunities. No longer can a diagnosis be presumed solely on the basis of age or weight. An accurate diagnosis by the healthcare professional is key if the patient is to receive the relevant therapies. Rigorous control of blood glucose from the point of diagnosis onwards will yield benefits for the rest of the patient's life. Structured education programmes are an important mechanism for helping the patient understand and embrace the behavioural changes that will secure these benefits. Emotional and psychological support, both at initial diagnosis and on a continuing basis, will enhance the patient's ability to live with diabetes.

A century ago, a diagnosis of diabetes was a death sentence; the chances of survival for any length of time were minimal. Today, people living with diabetes can enjoy long, healthy, active lives with a rich variety of food choices, careers and opportunities: type 1 diabetes need not be a restriction. Modern treatment techniques and technologies make near-normal blood glucose profiles increasingly possible; growing numbers of people who have successfully managed the condition for 50, 60 or 70 years bear witness to this. This Guideline invites patients and healthcare professionals to extend the progress already made.

2 Development of the guideline

This section was updated in 2015.

2.1 What is a NICE clinical guideline?

NICE clinical guidelines are recommendations for the care of individuals in specific clinical conditions or circumstances within the NHS – from prevention and self-care through primary and secondary care to more specialised services. We base our clinical guidelines on the best available research evidence, with the aim of improving the quality of healthcare. We use predetermined and systematic methods to identify and evaluate the evidence relating to specific review questions.

NICE clinical guidelines can:

- provide recommendations for the treatment and care of people by health professionals
- be used to develop standards to assess the clinical practice of individual health professionals and clinical services
- be used in the education and training of health professionals
- help patients to make informed decisions
- improve communication between patient and health professional.

While guidelines assist the practice of healthcare professionals, they do not replace their knowledge and skills.

We produce our guidelines using the following steps:

- Guideline topic is referred to NICE from the Department of Health.
- Stakeholders register an interest in the guideline and are consulted throughout the development process.
- The scope is prepared by the National Clinical Guideline Centre (NCGC).
- The NCGC establishes a Guideline Development Group.
- A draft guideline is produced after the group assesses the available evidence and makes recommendations.
- There is a consultation on the draft guideline.
- The final guideline is produced.

The NCGC and NICE produce a number of versions of this guideline:

- the ‘full guideline’ contains all the recommendations, plus details of the methods used and the underpinning evidence
- the ‘NICE guideline’ lists the recommendations
- ‘information for the public’ is written using suitable language for people without specialist medical knowledge
- NICE Pathways brings together all connected NICE guidance.

This version is the full version. The other versions can be downloaded from NICE at www.nice.org.uk.

2.2 Remit

NICE received the remit for the guideline from the Department of Health. They commissioned the NCGC to produce the guideline.

This is a partial update of 'Type 1 diabetes: Diagnosis and management of type 1 diabetes in children, young people and adults', NICE clinical guideline CG15 (2004). See section 3.4.1 for details of which sections were updated. We carried out a review of all recommendations to ensure they comply with NICE's duties under equalities legislation.

This update was undertaken as part of the guideline cycle review.

2.3 Epidemiology

- Type 1 diabetes is a long-term hormonal deficiency disorder, in which there is loss of insulin secretion. This results in high blood glucose concentrations and other metabolic and haematologicalabnormalities. It is usually caused by autoimmune destruction of the insulin-secreting beta cells of the pancreas. In the short term, people with type 1 diabetes may face significant challenges to daily living, for example, hyperglycaemia (high blood glucose) and hypoglycaemia (low blood glucose), the need for daily administration of insulin and frequent self-monitoring of blood glucose, and to plandaily activities such as eating and exercising.Over the long term, type1 diabetes is associated with major complications and reduced life expectancy. The condition is treated with insulin replacement therapy and at present there is no cure.
- Approximately 10% of adults diagnosed with diabetes have type 1 diabetes. Currently, it is estimated that 0.34-0.55% of the population of England and Wales are known to have type 1 diabetes.Among people aged between 10 and 80 years, there is little difference in prevalence across age groups.
- Type 1 diabetes can present at any age. Although it commonly presents in children and adolescents, the condition persists into and can start in adult life. Treatment regimens used to manage diabetes and the demands of living with diabetesare as complex in adults as in younger people.
- Effective insulin management requires detailed knowledge of its actions.
- Life expectancy for people with type 1 diabetes has increased. In one study from the USA, life expectancy among people diagnosed with type 1 diabetes between 1965 and 1980 improved by 15 years compared with people diagnosed between 1950 and 1964. Nevertheless, having type 1 diabetes typically reduces life expectancy in the UK by 20 years. People with type 1 diabetes in England are 2.6 times more likely to die than people without diabetes of the same age. Most of the deaths are due to chronic complications, although death in acute hypoglycaemia or diabetic ketoacidosis may occur.
- The Diabetes Control and Complications Trial Research Group[a] confirmed that strict blood glucose control reduces risk of long-term complications and is associated with increased life expectancy among people with type 1 diabetes. Effective insulin management requires detailed knowledge of its actions. The insulin user needs to acquire skill in insulin management. Control of blood pressure also reduces risk of complications in people with type 1 diabetes.Controlling lipids within recommended targets for other forms of diabetes is expected to reduce excess cardiovascular risk associated with type 1 diabetes.
- Early detection and effective management of type 1 diabetes and its complications are important to prevent or limit disability in people with type1 diabetes.

[a]The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977-986.

2.4 Who developed this guideline?

A multidisciplinary Guideline Development Group (GDG) comprising health professionals and researchers as well as lay members developed this guideline (see the list of Guideline Development Group members and the acknowledgements).

The National Institute for Health and Care Excellence (NICE) funds the National Clinical Guideline Centre (NCGC) and thus supported the development of this guideline. The GDG was convened by the NCGC and chaired by Professor Stephanie Amiel in accordance with guidance from NICE.

The group met every 6 weeks during the development of the guideline. At the start of the guideline development process all GDG members declared interests including consultancies, fee-paid work, share-holdings, fellowships and support from the healthcare industry. At all subsequent GDG meetings, members declared arising conflicts of interest.

Members were either required to withdraw completely or for part of the discussion if their declared interest made it appropriate. The details of declared interests and the actions taken are shown in Appendix B.

Staff from the NCGC provided methodological support and guidance for the development process. The team working on the guideline included a project manager, systematic reviewers, health economists and information scientists. They undertook systematic searches of the literature, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate and drafted the guideline in collaboration with the GDG.

2.5 What this guideline covers

This guideline covers adults (aged 18 and over) with type 1 diabetes.

It updates the following clinical areas from CG15:

- Diagnosis of type 1 diabetes: differentiation of type 1 diabetes from other forms of diabetes using c-peptide and antibody testing).
- Education programmes and self-care: structured educational programmes.
- Clinical monitoring of blood glucose control: HbA1c, self-monitoring of blood glucose and continuous glucose monitoring.
- Insulin therapy and adjunctive therapy.
- Needle length and injection site for insulin administration.
- Aspirin for primary prevention of cardiovascular disease.
- Treatment of late-stage complications (acute painful neuropathy of rapid glycaemic control, gastroparesis and erectile dysfunction).
- Inpatient management in relation to insulin replacement.

Other clinical topics from CG15 were not updated; these chapters have been reproduced verbatim from CG15.

The following areas were not covered in CG15 and have been added:

- New insulin formulations, including insulin degludec, insulin degludec-aspart combinations and insulin detemir.
- Impaired awareness of hypoglycaemia.
- Monitoring for thyroid disease.

- Ketone monitoring: self-monitoring for the prevention of diabetic ketoacidosis and monitoring of diabetic ketoacidosis.
- Carbohydrate counting and glycaemic index diets.
- Referral criteria for pancreas and islet transplantation.

For further details please refer to the scope in Appendix A and the review questions in Section 0.

2.6 What this guideline does not cover

This guideline does not cover:

- children and young people with type 1 diabetes (this is covered by Diabetes in children and young people, due for publication in August 2015).
- people with type 2 or other types of diabetes (this is covered by Type 2 diabetes in adults, due for publication in August 2015).
- preconception care in women with type 1 diabetes, contraceptive advice in women with type 1 diabetes and diabetes in pregnancy (this is covered by Diabetes in pregnancy, due for publication in February 2015).
- diabetic foot problems(this is covered by the Diabetic foot problems guideline, due for publication in July 2015).

2.7 Relationships between the guideline and other NICE guidance

NICE technology appraisals to be updated by this guidance

Guidance on the use of patient education models for diabetes. NICE technology appraisal guidance 60 (2003).

Guidance on the use of long-acting insulin analogues for the treatment of diabetes – insulin glargine. NICE technology appraisal guidance 53 (2002).

NICE technology appraisals to be incorporated in this guidance

Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus. NICE technology appraisal 151 (2008).

Related NICE technology appraisals

Fluocinolone acetonide intravitreal implant for treating chronic diabetic macular oedema after an inadequate response to prior therapy. NICE technology appraisal TA301 (2013).

Ranibizumab for the treatment of diabetic macular oedema. NICE technology appraisal 274 (2013).

Dexamethasone intravitreal implant for the treatment of macular oedema secondary to retinal vein occlusion. NICE technology appraisal 229 (2011).

Related NICE interventional procedures guidance

Allogeneic pancreatic islet cell transplantation for type 1 diabetes mellitus. NICE interventional procedure guideline 257 (2008).

Gastroelectrical stimulation for gastroparesis. NICE interventional procedure guide 489 (2014).

Related NICE clinical guidelines

Chronic kidney disease (update). NICE clinical guideline (2014).

Lipid modification. NICE clinical guideline 181 (2014).

Neuropathic pain – pharmacological management. NICE guideline 173 (2013).

Patient experience in adult NHS services. NICE clinical guideline 138 (2012).

Lower limb peripheral arterial disease. NICE clinical guideline 147 (2012).

Hyperglycaemia in acute coronary syndromes. NICE clinical guideline 130 (2011).

Hypertension. NICE clinical guideline 127 (2011).

Depression with a chronic physical health problem. NICE clinical guideline 91 (2009).

Depression in adults. NICE clinical guideline 90 (2009).

Medicines adherence. NICE clinical guideline 76 (2009).

Coeliac disease. NICE clinical guideline 86 (2009).

Nutrition support in adults. NICE clinical guideline 32 (2006).

Obesity. NICE clinical guideline 43 (2006)

Related NICE public health guidance

Four commonly used methods to increase physical activity. NICE public health guidance 2 (2006).

Smoking cessation services. NICE public health guidance 1 (2006).

Related NICE guidance currently in development

Diabetes in pregnancy. NICE clinical guideline. Publication expected February 2015.

Diabetic foot problems (update). NICE clinical guideline. Publication expected July 2015.

Type 2 diabetes in adults (update). NICE clinical guideline. Publication expected November 2015.

Diabetes in children and young people (update). NICE clinical guideline. Publication expected August 2015.

Buccal insulin for managing type 1 diabetes. NICE technology appraisal guidance. Publication date to be confirmed.

3 Methods

This section was updated in 2015.

This guidance was developed in accordance with the methods outlined in the NICE guidelines manual 2012.[535]

Amendments to 2004 text

All content from the previous guideline CG15 that has not been updated by new evidence reviews has been left unchanged and included verbatim.Recommendations from 2004 that were not updated were checked to determine whether any changes were essential. These changes were kept to a minimum in line with the NICE guidance on presenting updates in the NICE guidelines manual 2012. All recommendations from 2004 were updated to the active style wherever possible. Details of amendments and deleted recommendations are explained in Appendix S.

3.1 Developing the review questions and outcomes

Review questions were developed in a patient, intervention, comparison and outcome (PICO)framework for intervention reviews, and an adapted PICO framework was used for other types of review (such as diagnosis).

This use of a framework guided the literature searching process, critical appraisal and synthesis of evidence, and facilitated the development of recommendations by the Guideline Development Group (GDG). The review questions were drafted by the NCGC technical team and refined and validated by the GDG. The questions were based on the key clinical areas identified in the scope (Appendix A).

A total of 30 review questions were identified.

Full literature searches, critical appraisals and evidence reviews were completed for all the specified review questions.

Table 1: Review questions

Chapter	Type of review	Review questions	Outcomes
Arterial risk control	Intervention	In adults with type 1 diabetes, is aspirin an effective anti-platelet agent for the primary prevention of cardiovascular events?	• Mortality – all-cause • Mortality – CV • MI – all-cause • MI – fatal • MI – non-fatal • Stroke – all-cause • Stroke – fatal • Stroke – non-fatal • Quality of life – measured by SF-36, DQoL, DSQoL • Adverse events – bleeding or GI complications • HbA1c • Hypoglycaemia • Severe hypoglycaemia
Ketone	Intervention	In adults with type 1 diabetes	• Hospital admissions – for DKA if

Chapter	Type of review	Review questions	Outcomes
monitoring and management of DKA		(including atypical ketosis-prone diabetes), does patient self-monitoring of blood (and urine) ketones reduce the incidence of DKA and hospital admissions?	specified • Duration of admission/length of hospital stay • DKA • HbA1c • Hypoglycaemia • Severe hypoglycaemia • Quality of life – measured by PAID, anxiety • Severity of acidosis at admission - duration of acidosis and degree of acidosis
Ketone monitoring and management of DKA	Intervention	In adults with type 1 diabetes does inpatientmonitoring of blood ketones by the healthcare professional reduce the length of hospital stay, exposure to IV insulin and the development of in-hospital complications: • in patients with suspected DKA? • in patients admitted with DKA and/or those that get it in hospital.	• Length of hospital stay • In-hospital complications of the admission • Exposure to IV insulin • How often admission occurs • HbA1c • Hypoglycaemia • Severe hypoglycaemia • Quality of life
Diagnosis	Observational	In adults and young people with diabetes, what is the best marker (C-peptide plus or minus antibodies) to distinguish between type 1 diabetes, type 2 diabetes and other forms of diabetes?	• Presence of marker (number or % of patients with marker) • Concentration of marker (µg/ml) • Change in marker over time (No. or % of patients with marker) • Change in concentration of marker over time (µg/ml)
Education programmes and self-care	Intervention	In adults with type 1 diabetes, what is the most effective structured education programme?	• HbA1c (continuous) • Hypoglycaemia • Severe hypoglycaemia • Hospital admissions • Hypoglycaemia unawareness • Quality of life – measured by DQoL, DSQoL, PAID, HADS, fear of hypoglycaemia, anxiety, depression • Adverse events • Knowledge • Adherence
Insulin therapy	Intervention	In adults with type 1 diabetes, what are the most effective long-acting insulins (detemir versus degludec versus glargine versus NPH) for optimal diabetic control?	• HbA1c • Hypoglycaemia • Severe hypoglycaemia • Nocturnal hypoglycaemia • Quality of life – measured by

Chapter	Type of review	Review questions	Outcomes
			DQoL or any measure used in the studies retrieved • Adverse events – Cancer • Injection site issues • Weight gain/loss • DKA
Blood glucose monitoring	Intervention	In adults with type 1 diabetes, is retrospective continuous glucose monitoring more effective than care without continuous glucose monitoring (with SMBG) for improving diabetic control?	• HbA1c • Hypoglycaemia • Severe hypoglycaemia if reported • Quality of life – measured by what is shown in the study or patient satisfaction • Adverse events • Adherence
Blood glucose control	Intervention	In adults with type 1 diabetes, is real-time continuous glucose monitoring more effective than SMBG for optimum diabetic control?	• HbA1c • Hypoglycaemia • Severe hypoglycaemia if reported • Quality of life – measured by what is shown in the study or patient satisfaction • Adverse events • Adherence
Blood glucose control	Intervention	In adults with type 1 diabetes, is continuous real-time monitoring more effective than intermittent real-time monitoring for optimum diabetic control?	• HbA1c • Hypoglycaemia • Severe hypoglycaemia if reported • Quality of life – measured by what is shown in the study or patient satisfaction • Adverse events • Adherence
Insulin therapy	Intervention	In adults with type 1 diabetes, are metformin (with or without insulin), or GLP1-agonists (with or without insulin) as effective as insulin alone for optimal diabetic control?	• HbA1c • Hypoglycaemia • Severe hypoglycaemia • Quality of life – measured by what is shown in the papers • Adverse events • Weight loss/change • Dose of insulin
Insulin therapy	Intervention	In adults with type 1 diabetes, what are the most effective mixed insulins for optimal diabetic control?	• HbA1c • Hypoglycaemia • Severe hypoglycaemia • Nocturnal hypoglycaemia • Quality of life – measured by DQoL or any measure used in the studies retrieved

Chapter	Type of review	Review questions	Outcomes
			• Adverse events – Cancer • Injection site issues • Weight gain/loss • DKA
Blood glucose control	Observational	In adults with type 1 diabetes, what is optimum timing and frequency to self-monitor blood glucose for effective diabetic control?	• Hypoglycaemia • Severe hypoglycaemia • Nocturnal hypoglycaemia • Time within range (blood glucose) • HbA1c • Quality of life – measured by any measure specified in the study • DKA • Adherence • Unscheduled care use
Blood glucose control	Observational	In adults with type 1 diabetes, what is the optimum glucose target or profile for self-monitoring of blood glucose for effective diabetic control?	• HbA1c value • Risk of hypoglycaemia • Risk of severe hypoglycaemia • Risk of nocturnal hypoglycaemia • Risk of complications • Quality of life - any measure reported in the study
Blood glucose control	Intervention	In adults with type 1 diabetes, what are the benefits of technologies (bolus calculators and downloads) for self-monitoring of blood glucose?	• Hypoglycaemia • Severe hypoglycaemia • Nocturnal hypoglycaemia • HbA1c • Quality of life – measured by whatever is used in the study • Adverse events • Adherence

Blood glucose control	Observational	In adults with type 1 diabetes, what is the optimum target HbA1c level that should be achieved to reduce the risk of complications?	• Number of people reaching target HbA1c
			• Final HbA1c value
			• Hypoglycaemia
			• Severe hypoglycaemia
			• Nocturnal hypoglycaemia
			• Complications/avoidance:
			  ○ CV events (MI, IHD, Stroke, cardiac and peripheral revascularisation, major amputation)
			  ○ Hypoglycaemia
			  ○ macro- and micro-vascular
			  ○ Retinopathy

Chapter	Type of review	Review questions	Outcomes
			○ Low-level (micro) albuminuria/proteinuria ○ Renal replacement therapy/ESRF ○ Neuropathy ○ Sudden death • Quality of life – measured by whatever is used in the study
Blood glucose control	Intervention, observational	In adults with type 1 diabetes, what is the optimum frequency of HbA1c monitoring for effective diabetic control?	• Hypoglycaemia • Severe hypoglycaemia • HbA1c • Quality of life – measured by any measure reported in the study • Adverse events • Adherence • Complications – such as retinopathy
Insulin therapy	Intervention	In adults with type 1 diabetes, is once-daily basal insulin more effective than twice-daily basal insulin for optimal diabetic control?	• HbA1c (continuous) • Hypoglycaemia • Severe hypoglycaemia Quality of life – measured by whatever is used in the study • Adverse events
Insulin therapy	Intervention	In adults with type 1 diabetes, which are the most effective rapid-acting insulins for meal times: analogues versus human (intermediate NPH), for optimal diabetic control?	• HbA1c • Hypoglycaemia • Severe hypoglycaemia • Nocturnal hypoglycaemia • Quality of life – measured by DQoL or any measure used in the studies retrieved • Patient satisfaction • Adverse events – Cancer • Injection site issues • Weight gain/loss • DKA
Insulin therapy	Intervention	In adults with type 1 diabetes, what is the optimum needle length for insulin delivery?	• Pain • Discomfort) • Patient satisfaction • HbA1c • Quality of life – measured by whatever is used by the study • Adverse events • Adherence
Insulin therapy	Intervention	In adults with type 1 diabetes, what is the optimum injection site and rotation for insulin delivery?	• HbA1c • Hypoglycaemia • Severe hypoglycaemia

Chapter	Type of review	Review questions	Outcomes
			• Nocturnal hypoglycaemia • Quality of life – measured by whatever is used in the study • Adverse events • Adherence
Management of complications	Intervention	In adults with type 1 diabetes, what is the most effective treatment for gastroparesis?	• Hospital admissions • Severe hypoglycaemia • Vomiting (including frequency) • Weight loss • Quality of Life (SF-36) • HbA1c • Symptom control (as defined by the study)
Inpatient management	Intervention	In adults with type 1 diabetes who have been admitted to hospital (elective and emergency), what are the most effective intravenous insulin dose-adjustment devices and regimens for optimal diabetic control?	• Achieving target BG levels (measure used by the study) • Hypoglycaemia • Severe hypoglycaemia • Time spent out of target glucose (hypoglycaemia/hyperglycaemia) • Duration of IV treatment • In-patient stay • In-patient mortality • Infection rate/wound healing • Quality of life – measured by SF-36, DQoL, DSQoL
Education and self-care	Intervention	In adults with type 1 diabetes, what is the clinical and cost-effectiveness of carbohydrate counting or restriction for optimal diabetic control?	• HbA1c • Hypoglycaemia • Severe hypoglycaemia • Nocturnal hypoglycaemia • Quality of life – measured by whatever is used in the study • Adverse events
Impaired awareness of hypoglycaemia	Observational	In adults with type 1 diabetes, how is impaired awareness of hypoglycaemia best identified and quantified?	• Ability to predict severe hypoglycaemia (incidence of severe hypoglycaemia) • Ability to predict driving or work related accidents (incidence of accidents)
Impaired awareness of hypoglycaemia	Intervention	In adults with type 1 diabetes and impaired awareness of hypoglycaemia, what is the most effective strategy for recovering hypoglycaemia awareness?	• HbA1c • Autonomic symptoms/symptom scores during hypoglycaemia clamp study • Hypoglycaemia

Chapter	Type of review	Review questions	Outcomes
			• Severe hypoglycaemia • Nocturnal hypoglycaemia • Hospital admissions • Hypoglycaemia unawareness or awareness • Quality of life – measured by DQoL, DSQoL, PAID, HADS, fear of hypoglycaemia, anxiety, depression, cognitive function • Road traffic accidents and work related accidents
Management of complications	Observational	How should adults with type 1 diabetes be monitored for thyroid disease, and how frequently?	• Detection of thyroid disease – thyroid tests, for example, TSH, T4 • Incidence of thyroid disease • Frequency of treatment
Referral for islet or pancreas transplantation	Observational and real-life data	Which adults with type 1 diabetes are most suitable to be considered for a pancreas transplant, or pancreatic islet cell transplantation?	Outcomes • Current UK referral criteria Clinical outcomes from real-life UK data • HbA1c • Severe hypoglycaemia • Longevity of the transplant/organ survival (C-peptide and insulin independence) • Insulin dependence at 1 year and 5 years • Mortality - in-hospital/procedural • Mortality – long-term • Quality of life – any measure used in the paper
Education and self-care	Intervention	In adults with type 1 diabetes, what is the clinical and cost-effectiveness of a diet based on the glycaemic index for optimal diabetic control?	• HbA1c • Severe hypoglycaemia • Nocturnal hypoglycaemia • Quality of life – measured by DQoL or any measure used in the studies retrieved • Patient satisfaction • Adherence
Management of complications	Intervention	What pharmacological treatment should be used to manage erectile dysfunction in men with type 1 diabetes?	• Erectile function • HbA1c • Blood glucose control • Body weight

Chapter	Type of review	Review questions	Outcomes
			• Lipid parameters • Adverse events
Management of complications	Observational study	In adults with type 1 diabetes, what is the most effective treatment for acute painful neuropathy of rapid glycaemic control?	• Pain scores (continuous) • Retinopathy – incidence (dichotomous) • Low-level (micro) albuminuria - incidence (dichotomous) • Resolution of symptoms (continuous) • Improvement in pain scores (dichotomous)

3.2 Searching for evidence

3.2.1 Clinical literature search

Systematic literature searches were undertaken to identify all published clinical evidence relevant to the review questions. Searches were undertaken according to the parameters stipulated within the guidelines manual 2012[535]. Databases were searched using relevant medical subject headings, free-text terms and study design filters where appropriate. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in English. All searches were conducted in Medline, Embase and The Cochrane Library. All searches were updated on 28 August 2014. No papers published after this date were considered.

Search strategies were quality assured by cross-checking reference lists of highly relevant papers, analysing search strategies in other systematic reviews, and asking GDG members to highlight any additional studies. The questions, the study types applied, the databases searched and the dates covered can be found in Appendix F.

The titles and abstracts of records retrieved by the searches were sifted for relevance, with potentially significant publications obtained in full text. These were assessed against the inclusion criteria.

During the scoping stage, a search was conducted for guidelines and reports on the websites listed below and on those of organisations relevant to the topic. Searching for grey literature or unpublished literature was not undertaken. All references sent by stakeholders were considered.

- Guidelines International Network database (www.g-i-n.net)
- National Guideline Clearing House (www.guideline.gov)
- National Institute for Health and Care Excellence (NICE) (www.nice.org.uk)
- NICE Evidence Search (evidence.nhs.uk)

3.2.2 Health economic literature search

Systematic literature searches were also undertaken to identify health economic evidence within published literature relevant to the review questions. The evidence was identified by conducting a broad search relating to type 1 diabetes in the NHS Economic Evaluation Database (NHS EED), the Health Technology Assessment database (HTA) and the Health Economic Evaluations Database (HEED) with no date restrictions. Additionally, the search was run on Medline and Embase using an economic filter, from 2009, to ensure recent publications that had not yet been indexed by the

economic databases were identified. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in English.

The health economic search strategies are included in Appendix F. All searches were updated on 28 August 2014. No papers published after this date were considered.

3.3 Evidence of effectiveness

The evidence was reviewed following the steps shown schematically in Figure 1:

- Potentially relevant studies were identified for each review question from the search results by reviewing titles and abstracts. Full papers were then obtained.
- Full papers were reviewed against pre-specified inclusion and exclusion criteria to identify studies that addressed the review question in the appropriate population (review protocols are included in Appendix C).
- Relevant studies were critically appraised using the appropriate checklist as specified in The guidelines manual[535].
- Key information was extracted on the study's methods, PICO factors and results. These were presented in summary tables (in each review chapter) and evidence tables (in Appendix G).
- Summaries of evidence were generated by outcome (included in the relevant review chapters) and were presented in GDG meetings:
    - Randomised studies: data were meta-analysed where appropriate and reported in GRADE profiles (for intervention reviews).
    - Observational studies – comparative studies: data were presented narratively or results were tabulated, and reported in GRADE profiles (for intervention reviews).
    - Observational studies – non-comparative studies: data were presented narratively or results were tabulated.

Figure 1: Step-by-step process of review of evidence in the guideline

3.3.1 Inclusion and exclusion criteria

The inclusion and exclusion of studies was based on the review protocols, which can be found in Appendix C. Excluded studies by review question (with the reasons for their exclusion) are listed in Appendix K. The GDG was consulted about any uncertainty regarding inclusion or exclusion.

Randomised trials, non-randomised trials, and observational studies were included in the evidence reviews as appropriate.

Literature reviews, posters, letters, editorials, comment articles, unpublished studies, conference abstracts (unless stated in cases where there was limited evidence) and studies not in English were excluded.

The review protocols are presented in Appendix C.

3.3.2 Methods of combining clinical studies

3.3.2.1 Data synthesis for intervention reviews

Where possible, meta-analyses were conducted to combine the results of studies for each review question using Cochrane Review Manager (RevMan5) software. Fixed-effects (Mantel-Haenszel) techniques were used to calculate risk ratios (relative risk) for binary outcomes,and mean differences for continuous outcomes where there was no considerable heterogeneity. Random effects techniques were used when there was considerableheterogeneity between the trials. For the critical outcomes, if there was considerableheterogeneity, then this was explored by subgroup analyses. The

subgroups were pre-specified by the GDG and are outlined in the protocols. If heterogeneity could not be explained by the subgroup analyses, then a random effects meta-analysis was used. Statistical heterogeneity was assessed by visually examining the forest plots, and by considering the chi-squared test for significance at $p<0.1$ or an I-squared inconsistency statistic (with an I-squared value of more than 50% indicating considerable heterogeneity).

For continuous outcomes, measures of central tendency (mean) and variation (standard deviation) were required for meta-analysis. Data for continuous outcomes were analysed using an inverse variance method for pooling weighted mean differences. However, in cases where standard deviations were not reported per intervention group, the standard error (SE) for the mean difference was calculated from other reported statistics (p values or 95% CIs); meta-analysis was then undertaken for the mean difference and SE using the generic inverse variance method in RevMan5. When the only evidence was based on studies that summarised results by presenting medians (and interquartile ranges), or only p values were given, this information was reported narratively and generally included in the GRADE tables without calculating the relative or absolute effects. Consequently, aspects of quality assessment such as imprecision of effect could not be assessed for evidence of this type. Where reported, and possible to calculate, time-to-event data was presented as a HR.

Where p values were used as part of calculations for continuous outcomes, if a p value was reported as 'less than', a conservative approach was undertaken. For example, if p value was reported as '$p\leq0.001$', the calculations for standard deviations will be based on a p value of 0.001. If these statistical measures were not available then data were reported narratively.

For interpretation of the binary outcome results, differences in the absolute event rate were calculated using the GRADEpro software, for the median event rate across the control arms of the individual studies in the meta-analysis. Absolute risk differences (ARDs) were presented in the GRADE profiles and in clinical summary of findings tables, for discussion with the GDG. For binary outcomes, absolute event rates were also calculated using the GRADEpro software using event rate in the control arm of the pooled results.

A network meta-analysis (NMA) was conducted for the review on long-acting insulin. This type of analysis simultaneously compares multiple treatments in a single meta-analysis, preserving the randomisation of RCTs included in the reviews of direct comparisons trials. The aim of the NMA was to include all relevant evidence in order both to answer questions on the clinical effectiveness of interventions when no direct comparison was available and to give a ranking of treatments in terms of efficacy. The output was expressed as the mean effect estimates (expressed as the median of the posterior distribution for the mean change) and 95% credible intervals (CrIs), along with the ranks of eachlong-acting insulin regimenand the95% CrIs of the ranks.

A Bayesian NMA was performed using the software WinBUGS version 1.4.3. That allowed inclusion of multi-arm trials and accounts for the correlation between arms in the trials with any number of trial arms.

The following were the main outputs from the NMA:

- Hazard ratios of severe/major hypoglycaemic events (with their 95% CrIs) calculated using direct and indirect evidence
- Change in HbA1c level (with their 95% CrIs) calculated using direct and indirect evidence
- Ranking of each insulin regimen, based on its relative effect compared to insulin NPH (twice daily) (with 95% CrIs for the ranks) for each network.

A full technical account can be found in Appendix M.

3.3.3 Type of studies

For most intervention reviews in this guideline, parallel randomised controlled trials (RCTs) were included because they are considered the most robust type of study design that could produce an unbiased estimate of the intervention effects. If the GDG believed RCT data were not appropriate or there was limited evidence from RCTs, well-conducted non-randomised studies were included. Please refer to Appendix C for full details on the study design of studies selected for each review question. It was considered unlikely that the search would find any RCTs.

Where data from observational studies were included, the GDG decided that the results for each outcome should be presented separately for each study and meta-analysis was not conducted.

3.3.4 Appraising the quality of evidence by outcomes

The evidence for outcomes from the included RCTs and, where appropriate, comparative observational studies were evaluated and presented using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group (http://www.gradeworkinggroup.org/). The software developed by the GRADE working group (GRADEpro) was used to assess the quality of each outcome, taking into account individual study quality factors and the meta-analysis results. Results were presented in GRADE profiles ('GRADE tables'), which consist of 2 sections: the 'Clinical evidence profile' table includes details of the quality assessment while the 'Clinical evidence summary of findings' table includes pooled outcome data, where appropriate, an absolute measure of intervention effect and the summary of quality of evidence for that outcome. In this table, the columns for intervention and control indicate summary measures and measures of dispersion (such as mean and standard deviation or median and range) for continuous outcomes and frequency of events (n/N: the sum across studies of the number of patients with events divided by sum of the number of completers) for binary outcomes. Reporting or publication bias was taken into consideration in the quality assessment and only included in the 'Clinical evidence profile' table if it was apparent from GDG members.

The evidence for each outcome was examined separately for the quality elements listed and defined inTable 2**.** Each element was graded using the quality levels listed in Table 3. The main criteria considered in the rating of these elements are discussed below (see Section 3.3.5). Footnotes were used to describe reasons for grading a quality element as having serious or very serious problems. The ratings for each component were summed to obtain an overall assessment for each outcome (Table 4).

The GRADE toolbox is currently designed only for randomised trials and comparative observational studies, for non-comparative observational studies, the results, study limitations and overall quality assessment ratings were reported narratively.

Table 2: Description of the elements in GRADE used to assessthe quality of intervention studies

Quality element	Description
Risk of bias ('Study limitations')	Limitations in the study design and implementation may bias the estimates of the treatment effect. High risk of bias for the majority of the evidencedecreases confidence in the estimate of the effect
Inconsistency	Inconsistency refers to an unexplained heterogeneity of results
Indirectness	Indirectness refers to differences in study population, intervention, comparator and outcomes between the available evidence and the review question, or recommendation made, such that the effect estimate is changed
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of the effect. Imprecision

Quality element	Description
	results if the confidence interval includes the clinically important threshold
Publication bias	Publication bias is a systematic underestimate or an overestimate of the underlying beneficial or harmful effect due to the selective publication of studies

Table 3: Levels of quality elements in GRADE

Level	Description
None	There are no serious issues with the evidence
Serious	The issues are serious enough to downgrade the outcome evidence by 1 level
Very serious	The issues are serious enough to downgrade the outcome evidence by 2 levels

Table 4: Overall quality of outcome evidence in GRADE

Level	Description
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

3.3.5 Grading the quality of clinical evidence: RCTs and comparative observational studies

After results were pooled, the overall quality of evidence for each outcome was considered. The following procedure was adopted when using GRADE:

1. A quality rating was assigned, based on the study design. RCTs start as High, observational cohort studies as Low.
2. The rating was then downgraded for the specified criteria: risk of bias (study limitations), inconsistency, indirectness, imprecision and publication bias. These criteria are detailed below. Evidence fromobservational cohort studies (which had not previously been downgraded) was upgraded if there was: a large magnitude of effect, a dose–response gradient, and if all plausible confounding would reduce a demonstrated effect or suggest a spurious effect when results showed no effect. Each quality element considered to have 'serious' or 'very serious' risk of bias was rated down by 1 or 2 points respectively.
3. The downgraded or upgraded marks were then summed and the overall quality rating was revised. For example, all RCTs started as High and the overall quality became Moderate, Low or Very low if 1, 2 or 3 points were deducted respectively.
4. The reasons or criteria used for downgrading were specified in the footnotes.

The details of the criteria used for each of the main quality element are discussed further in the following Sections (3.3.8, 3.3.9 and 3.3.10).

3.3.6 Grading the quality of clinical evidence: non-comparative observational studies.

A customised quality assessment checklist (adapted from the NICE prognostic studies checklist) has been used for assessing the quality of non-comparative observational studies (for example, cross-sectional studies or case-series), and so for reviews that included these study types, the main criteria considered in assessing study quality were:

- The study design: if it is retrospective or prospective, or cross-sectional. Retrospective studies are more likely to be at higher risk of bias.

- The study sample is representative of the population of interest with regard to key characteristics, sufficient to limit potential bias to the results
- The outcome of interest is adequately measured in study participants, sufficient to limit bias
- Important potential confounders are appropriately accounted for in the statistical analysis, limiting potential bias with respect to the outcomes of interest, and the presentation of invalid results

All non-comparative observational studies were graded as Low quality due to the inherent high risk of bias associated with these study designs. However, the specific methodological limitations of the studies included in the guideline update, have been summarised in tables within Appendix I, in order to give an overview of the quality of each individual study. As GRADE is currently not designed for these types of study, quality has been assessed by study only, rather than by outcome in the review. Raw data, or odds ratios, relative risks or hazard ratios, with their 95% confidence intervals, from multivariate analyses were extracted from the papers where appropriate to the review question. Data for the outcomes defined in the review protocols has been summarised in tables within the relevant review chapter. Full data for all the outcomes has been reported in the evidence tables (see Appendix G) for each individual observational study.

3.3.7 Risk of bias

Bias can be defined as anything that causes a consistent deviation from the truth. Bias can be perceived as a systematic error, for example, multiple replications of the same study would reach the wrong answer on average.

The risk of bias for a given study and outcome is associated with the risk of over- or underestimation of the true effect.

The risks of bias are listed in Table 5.

A study with a poor methodological design does not automatically imply high risk of bias; the bias is considered individually for each outcome and it is assessed whether this poor design will impact on the estimation of the intervention effect.

Table 5: Risk of bias in RCTs

Risk of bias	Explanation
Allocation concealment	Those enrolling patients are aware of the group to which the next enrolled patient will be allocated (this is a major problem in 'pseudo' or 'quasi' randomised trials with, for example,allocation by day of week, birth date, chart number)
Lack of blinding	Patient, caregivers, those recording outcomes, those adjudicating outcomes, or data analysts are aware of the arm to which patients are allocated
Incomplete accounting of patients and outcome events	Missing data not accounted for and failure of the trialists to adhere to the intention-to-treat principle when indicated
Selective outcome reporting	Reporting of some outcomes and not others on the basis of the results
Other risks of bias	For example: • Stopping early for benefit observed in randomised trials, in particular in the absence of adequate stopping rules • Use of unvalidated patient-reported outcomes • Recruitment bias in cluster-randomised trials

3.3.8 Inconsistency

Inconsistency refers to an unexplained heterogeneity of results. When estimates of the treatment effect across studies differ widely (that is, there is heterogeneity or variability in results), this suggests true differences in underlying treatment effect.

Heterogeneity in meta-analyses was examined and sensitivity and subgroup analyses performed as pre-specified in the protocols (Appendix C).

When heterogeneity exists (chi-squared $p<0.1$, I-squared inconsistency statistic of more than 50%, or evidence from examining forest plots), but no plausible explanation can be found (for example, duration of intervention or different follow-up periods), the quality of evidence was downgraded by 1 or 2 levels, depending on the extent of uncertainty to the results contributed by the inconsistency in the results. In addition to the I-squared and chi-squared values, the decision for downgrading was also dependent on factors such as whether the intervention is associated with benefit in all other outcomes or whether the uncertainty about the magnitude of benefit (or harm) of the outcome showing heterogeneity would influence the overall judgment about net benefit or harm (across all outcomes).

3.3.9 Indirectness

Directness refers to the extent to which the populations, intervention, comparisons and outcome measures are similar to those defined in the inclusion criteria for the reviews. Indirectness is important when these differences are expected to contribute to a difference in effect size, or may affect the balance of harms and benefits considered for an intervention.

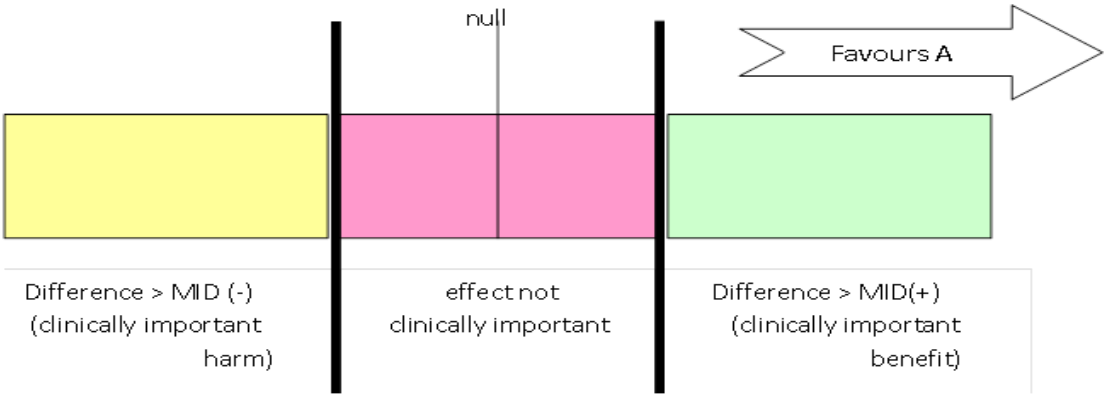
3.3.10 Imprecision

Imprecision in guidelines concerns whether the uncertainty (confidence interval) around the effect estimate means that it is not clear whether there is a clinically important difference between interventions or not. Therefore, imprecision differs from the other aspects of evidence quality, in that it is not really concerned with whether the point estimate is accurate or correct (has internal or external validity) instead it is concerned with the uncertainty about what the point estimate is. This uncertainty is reflected in the width of the confidence interval.

The 95% CI is defined as the range of values that contain the population value with 95% probability. The larger the trial, the smaller the 95% CI and the more certain the effect estimate.

Imprecision in the evidence reviews was assessed by considering whether the width of the 95% CI of the effect estimate is relevant to decision-making, considering each outcome in isolation. Figure 2 considers a positive outcome for the comparison of treatment A versus B. Three decision-making zones can be identified, bounded by the thresholds for clinical importance (minimal important difference – MID) for benefit and for harm. The MID for harm for a positive outcome means the threshold at which drug A is less effective than drug B by an amount that is clinically important to patients (favours B).

Figure 2: Illustration of precise and imprecise outcomes based on the confidence interval of outcomes in a forest plot



When the confidence interval of the effect estimate is wholly contained in one of the 3 zones (for example, clinically important benefit), we are not uncertain about the size and direction of effect (whether there is a clinically important benefit, or the effect is not clinically important, or there is a clinically important harm), so there is no imprecision.

When a wide confidence interval lies partly in each of 2 zones, it is uncertain in which zone the true value of effect estimate lies, and therefore there is uncertainty over which decision to make (based on this outcome alone). The confidence interval is consistent with 2 decisions and so this is considered to be imprecise in the GRADE analysis and the evidence is downgraded by 1 level ('serious imprecision').

If the confidence interval of the effect estimate crosses into 3 zones, this is considered to be very imprecise evidence because the confidence interval is consistent with 3 clinical decisions and there is a considerable lack of confidence in the results. The evidence is therefore downgraded by 2 levels in the GRADE analysis ('very serious imprecision').

Implicitly, assessing whether the confidence interval is in, or partially in, a clinically important zone, requires the GDG to estimate an MID or to say whether they would make different decisions for the 2 confidence limits.

The GDG was asked whether they were aware of any acceptable MIDs in the clinical community but there were none known. Therefore, the GDG agreed that the default values stated in GRADEpro were appropriate for our outcomes. For dichotomous outcomes, the default thresholds suggested by GRADE are a relative risk reduction of 25% (relative risk of 0.75 for negative outcomes) or a relative risk increase of 25% (risk ratio 1.25 for positive outcomes). For continuous outcomes, the default approach of multiplying 0.5 by the standard deviation of the baseline values was employed.

3.3.11 Assessing clinical importance

The GDG assessed the evidence by outcome in order to determine if there was, or potentially was, a clinically important benefit, a clinically important harm or no clinically important difference between interventions. To facilitate this, binary outcomes were converted into ARDs using GRADEpro software: the median control group risk across studies was used to calculate the ARD and its 95% CI from the pooled risk ratio.

The assessment of benefit, harm, or no benefit or harm was based on the point estimate of absolute effect for intervention studies

This assessment was carried out by the GDG for each outcome, and an evidence summary table was produced to compile the GDG's assessments of clinical importance per outcome, alongside the evidence quality and the uncertainty in the effect estimate (imprecision).

3.3.12 Evidence statements

Evidence statements are summary statements that are presented after the GRADE profiles, summarising the key features of the clinical effectiveness evidence presented. The wording of the evidence statements reflects the certainty or uncertainty in the estimate of effect. The evidence statements encompass the following key features of the evidence:

- the intervention and comparison group under investigation
- the outcome measure being assessed
- an indication of the direction of effect (if one treatment is beneficial or harmful compared with the other, or whether there is no difference between the 2 tested treatments). Determination of benefit, harm, or no difference, is based on the GDG's interpretation of whether the absolute effect could be considered clinically beneficial, clinically harmful, or no clinical effect or difference between the intervention and comparison groups.
- the time-point the outcomes have been assessed at
- a description of the overall quality of evidence (GRADE overall quality).

3.4 Evidence of cost effectiveness

The GDG is required to make decisions based on the best available evidence of both clinical and cost effectiveness. Guideline recommendations should be based on the expected costs of the different options in relation to their expected health benefits (that is, their 'cost effectiveness') rather than the total implementation cost.[535]Thus, if the evidence suggests that a strategy provides significant health benefits at an acceptable cost per patient treated, it should be recommended even if it would be expensive to implement across the whole population.

Evidence on cost effectiveness related to the key clinical issues being addressed in the guideline was sought. The health economist:

- Undertook a systematic review of the published economic literature.
- Undertook new cost-effectiveness analysis in priority areas.

3.4.1 Literature review

The health economist:

- Identified potentially relevant studies for each review question from the economic search results by reviewing titles and abstracts. Full papers were then obtained.
- Reviewed full papers against prespecified inclusion and exclusion criteria to identify relevant studies (see below for details).
- Critically appraised relevant studies using the economic evaluations checklist as specified in The guidelines manual.[535]
- Extracted key information about the studies' methods and results into evidence tables (included in Appendix H).
- Generated summaries of the evidence in NICE economic evidence profiles (included in the relevant chapter for each review question) – see below for details.

3.4.1.1 Inclusion and exclusion criteria

Full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost–utility, cost-effectiveness, cost–benefit and cost–consequence analyses) and comparative costing studies that addressed the review question in the relevant population were considered potentially includable as economic evidence.

Studies that only reported cost per hospital (not per patient), or only reported average cost-effectiveness without disaggregated costs and effects, were excluded. Literature reviews, abstracts, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded.

Remaining studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high quality, directly applicable UK analysis was available, then other less relevant studies may not have been included. Where selective exclusions occurred on this basis, this is noted in the relevant section.

For more details about the assessment of applicability and methodological quality see the economic evaluation checklist (Appendix E of the guidelines manual [535] and the health economics review protocol in Appendix C).

When no relevant economic studies were found from the economic literature review, relevant UK NHS unit costs related to the compared interventions were presented to the GDG to inform the possible economic implications of the recommendations.

3.4.1.2 NICE economic evidence profiles

The NICE economic evidence profile has been used to summarise cost and cost-effectiveness estimates. The economic evidence profile shows an assessment of applicability and methodological quality for each economic evaluation, with footnotes indicating the reasons for the assessment. These assessments were made by the health economist using the economic evaluation checklist from The guidelines manual.[535] It also shows the incremental costs, incremental effects (for example, quality-adjusted life years [QALYs]) and incremental cost-effectiveness ratio for the base case analysis in the evaluation, as well as information about the assessment of uncertainty in the analysis. See Table 6 for more details.

If a non-UK study was included in the profile, the results were converted into pounds sterling using the appropriate purchasing power parity.[559]

Table 6: Content of NICE economic evidence profile

Item	Description
Study	First author name, reference, date of study publication and country perspective.
Applicability	An assessment of applicability of the study to the clinical guideline, the current NHS situation and NICE decision-making[(a)]: • Directly applicable – the study meets all applicability criteria, or fails to meet one or more applicability criteria but this is unlikely to change the conclusions about cost effectiveness. • Partially applicable – the study fails to meet one or more applicability criteria, and this could change the conclusions about cost effectiveness. • Not applicable – the study fails to meet one or more of the applicability criteria, and this is likely to change the conclusions about cost effectiveness. Such studies would usually be excluded from the review.
Limitations	An assessment of methodological quality of the study[(a)]: • Minor limitations – the study meets all quality criteria, or fails to meet one or

Item	Description
	more quality criteria, but this is unlikely to change the conclusions about cost effectiveness. • Potentially serious limitations – the study fails to meet one or more quality criteria, and this could change the conclusions about cost effectiveness. • Very serious limitations – the study fails to meet one or more quality criteria, and this is highly likely to change the conclusions about cost effectiveness. Such studies would usually be excluded from the review.
Other comments	Particular issues that should be considered when interpreting the study.
Incremental cost	The mean cost associated with one strategy minus the mean cost of a comparator strategy.
Incremental effects	The mean QALYs (or other selected measure of health outcome) associated with one strategy minus the mean QALYs of a comparator strategy.
Cost effectiveness	Incremental cost-effectiveness ratio (ICER): the incremental cost divided by the incremental effects.
Uncertainty	A summary of the extent of uncertainty about the ICER reflecting the results of deterministic or probabilistic sensitivity analyses, or stochastic analyses of trial data, as appropriate.

(a) Applicability and limitations were assessed using the economic evaluation checklist in Appendix G of The guidelines manual (2012)[535]

3.4.2 Undertaking new health economic analysis

As well as reviewing the published economic literature for each review question, as described above, new economic analysis was undertaken by the health economist in selected areas. Priority areas for new health economic analysis were agreed by the GDG after formation of the review questions and consideration of the available health economic evidence.

The following general principles were adhered to in developing the cost-effectiveness analysis:

- Methods were consistent with the NICE reference case.[536]
- The GDG was involved in the design of the model, selection of inputs and interpretation of the results.
- Model inputs were based on the systematic review of the clinical literature supplemented with other published data sources where possible.
- When published data was not available GDG expert opinion was used to populate the model.
- Model inputs and assumptions were reported fully and transparently.
- The results were subject to sensitivity analysis and limitations were discussed.
- The model was peer-reviewed by another health economist at the NCGC.

Full methods for the cost-effectiveness analyses conducted for this guideline are described in Appendix N, O and P.

3.4.3 Cost-effectiveness criteria

NICE's report 'Social value judgements: principles for the development of NICE guidance' sets out the principles that GDGs should consider when judging whether an intervention offers good value for money.[525] In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible):

- the intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or

- the intervention cost less than £20,000 per QALY gained compared with the next best strategy.

If the GDG recommended an intervention that was estimated to cost more than £20,000 per QALY gained, or did not recommend one that was estimated to cost less than £20,000 per QALY gained, the reasons for this decision are discussed explicitly in the 'Recommendations and link to evidence' section of the relevant chapter, with reference to issues regarding the plausibility of the estimate or to the factors set out in 'Social value judgements: principles for the development of NICE guidance'.[525]

3.4.4 In the absence of economic evidence

When no relevant published studies were found, and a new analysis was not prioritised, the GDG made a qualitative judgement about cost-effectiveness by considering expected differences in resource use between options and relevant UK NHS unit costs, alongside the results of the clinical review of effectiveness evidence. The UK NHS costs reported in the guideline were those presented to the GDG and they were correct at the time recommendations were drafted; they may have been revised subsequently by the time of publication. However, we have no reason to believe they have been changed substantially.

3.5 Developing recommendations

Over the course of the guideline development process, the GDG was presented with:

- Evidence tables of the clinical and economic evidence reviewed from the literature. All evidence tables are in Appendices [G and H].
- Summaries of clinical and economic evidence and quality (as presented in Chapters [6–16]).
- Forest plots and summary ROC curves (Appendix J).
- A description of the methods and results of the cost-effectiveness analysis(ses) undertaken for the guideline (Appendices N-P).

Recommendations were drafted on the basis of the GDG interpretation of the available evidence, taking into account the balance of benefits, harms and costs between different courses of action. This was either done formally in an economic model, or informally. Firstly, the net benefit over harm (clinical effectiveness) was considered, focusing on the critical outcomes. When this was done informally, the GDG took into account the clinical benefits and harms when one intervention was compared with another. The assessment of net benefit was moderated by the importance placed on the outcomes (the GDG's values and preferences), and the confidence the GDG had in the evidence (evidence quality). Secondly, it was assessed whether the net benefit justified any differences in costs.

When clinical and economic evidence was of poor quality, conflicting or absent, the GDG drafted recommendations based on their expert opinion. The considerations for making consensus-based recommendations include the balance between potential harms and benefits, the economic costs compared with the economic benefits, current practices, and recommendations made in other relevant guidelines, patient preferences and equality issues. The consensus recommendations were agreed through discussions in the GDG. The GDG considered whether the uncertainty was sufficient to justify delaying making a recommendation to await further research, taking into account the potential harm of failing to make a clear recommendation (see Appendix R).

The wording of recommendations was agreed by the GDG and focused on the following factors:

- The actions health professionals need to take.
- The information readers need to know.

- The strength of the recommendation (for example the word 'offer' was used for strong recommendations and 'consider' for weak recommendations).
- The involvement of patients (and their carers if needed) in decisions on treatment and care.
- Consistency with NICE's standard advice on recommendations about drugs, waiting times and ineffective interventions.

The main considerations specific to each recommendation are outlined in the 'recommendations and link to evidence' sections within each chapter.

3.5.1 Research recommendations

When areas were identified for which good evidence was lacking, the GDG considered making recommendations for future research. Decisions about inclusion were based on factors such as:

- the importance to patients or the population
- national priorities
- potential impact on the NHS and future NICE guidance
- ethical and technical feasibility.

3.5.2 Validation process

This guidance is subject to a 12 week public consultation and feedback as part of the quality assurance and peer review of the document. All comments received from registered stakeholders are responded to in turn and posted on the NICE website.

3.5.3 Updating the guideline

A formal review of the need to update a guideline is usually undertaken by NICE after its publication. NICE will conduct a review to determine whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an update.

3.5.4 Disclaimer

Healthcare providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by practitioners in light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.

The National Clinical Guideline Centre disclaims any responsibility for damages arising out of the use or non-use of this guideline and the literature used in support of this guideline.

3.5.5 Funding

The National Clinical Guideline Centre was commissioned by the NICE to undertake the work on this guideline.

3.6 Methods 2004

3.6.1 Aims and principles

This chapter describes the resources and techniques used to reach the clinical recommendations in this guideline.

Clinical guidelines have been formally defined as 'systematically developed statements to assist both practitioner and patient decisions in specific circumstances'.6 This guideline aims to offer the best practice advice on the care of adults (defined as those aged 18 years or older) with Type 1 diabetes. It gives guidance on the management, monitoring and support of people with Type 1 diabetes. The context of the intended guidance is the primacy of the needs of the individual with diabetes, reflecting the difficulties of reconciling the problems of insulin replacement therapy with personal lifestyles.

The current guideline is aimed at helping all healthcare professionals provide optimal services for people with Type 1 diabetes by:

- providing healthcare professionals with a set of explicit statements on the best known ways to assist people with diabetes with their most common clinical problems, while maximising the effectiveness of the service in supporting the population with Type 1 diabetes
- giving commissioning organisations and provider services specific guidance on the best way to provide complex services in a way that maximises efficiency and equity (service organisation is, however, outside the scope of this clinical guideline)
- informing people with diabetes of the optimal methods for helping them self-manage their diabetes.

Others, including the general public, may find the guideline of use in understanding the global and clinical approach to Type 1 diabetes. Separate short-form documents for the public and for healthcare professionals are available; they summarise the recommendations without giving full details of the supporting evidence.

The main principles behind the development of this guideline are that it should:

- consider all the most important issues in the management of people with Type 1 diabetes using published evidence wherever this is available
- be useful to and usable by all professionals
- take full account of the perspectives of the person with Type 1 diabetes and their carers
- indicate areas of uncertainty or controversy needing further research.

3.6.2 The developers

3.6.2.1 The National Collaborating Centre for Chronic Conditions

The National Collaborating Centre for Chronic Conditions (NCC-CC) is housed by the Royal College of Physicians (RCP) but governed by a multiprofessional partners board, which includes patient groups and NHS management. It was set up in 2000 to undertake commissions from the National Institute for Clinical Excellence (NICE) to develop clinical guidelines for the NHS in England and Wales.

The technical team

The technical team consisted of:

- an information scientist

- a health services research fellow
- a clinical advisor
- a health economist
- the chair of the Guideline Development Group (GDG)
- a project manager

and was supported by administrative personnel. It took part in the GDG meetings, and also met separately each month.

3.6.2.2 The Guideline Development Group

The GDG met monthly for 10 months to review the evidence identified by the technical team, to comment on its completeness and to develop and refine clinical recommendations based on that evidence and other considerations.

Editorial responsibility for this guideline rests solely with the GDG.

Nominations for group members were invited from various stakeholder organisations, which were selected to ensure an appropriate mix of clinical professions and patient groups. These made up the Consensus Reference Group (CRG, see below) and from their members the GDG was selected to represent the groups involved in the day-to-day management of Type 1 diabetes. It included two representatives of people with Type 1 diabetes. Each nominee was expected to serve as an individual expert in their own right and not as a mandated representative, although they were encouraged to keep their parent organisation informed of the process. Group membership details can be found at the front of this document.

All group members made a formal 'declaration of interests' at the start of the guideline development and provided updates throughout. The NCC-CC and the GDG Chair monitored these.

- The Consensus Reference Group

The larger Consensus Reference Group (CRG) met twice during the process, once early in the development to ensure the aims and clinical questions (see Appendix A) were appropriate, and again at the end of the process to review the validity of the recommendations drafted by the GDG. The formal consensus technique used for this purpose was developed by the NCC-CC and is a modification of the RAND Nominal Group Technique.

- Involvement of people with Type 1 diabetes

The NCC-CC believes that the views of people with diabetes and their carers are an integral part of the development process of a guideline on Type 1 diabetes. Patient organisation representation (Diabetes UK) was secured on the Guideline Development Group and included a non-healthcare professional with Type 1 diabetes. People with diabetes were also present as part of the GDG and CRG and were involved at every stage of the guideline development process.

3.6.2.3 Searching for the evidence

There were four stages to evidence identification and retrieval:

5. The technical team set out a series of specific clinical questions (see Appendix A) that covered the issues identified in the project scope. The CRG met to discuss, refine and approve these questions as suitable for identifying appropriate evidence from within the published literature.

6. A total of 74 questions were identified. The technical team and project executive agreed that a full literature search and critical appraisal process could not be undertaken for all of these areas due to the time limitations of the guideline development process. The technical team identified questions where it was felt that a full literature search and critical appraisal were essential. Reasons for this included an awareness of new or unclear evidence, or a particular clinical need for evidence-based guidance in the area.
7. The information scientist, with the assistance of the clinical advisor, developed a search strategy for each question to identify the available evidence. Identified titles and abstracts were reviewed for relevance to the agreed clinical questions and full papers obtained as appropriate. These were assessed for inclusion according to predefined criteria as developed by the Scottish Intercollegiate Guidelines Network (SIGN).
8. The full papers were critically appraised by the health services research fellow and the pertinent data entered into evidence tables. These were then reviewed and analysed by the GDG as the basis upon which recommendations were formulated.

Due to the large amount of literature potentially relevant to Type 1 diabetes, the inclusion criteria aimed to limit the included studies to those of a higher level (see 2.6) conducted primarily in people with Type 1 diabetes. Where these were not available, lower-level studies, well-conducted studies outside Type 1 diabetes (in Type 2 diabetes or in the non-diabetic population), or more methodologically-limited studies in people with Type 1 diabetes, were included.

Limited details of the databases and constraints used in the searches can be found in Appendix A. No formal contact was made with the authors of identified studies. Additional contemporary articles identified by the GDG on an ad hoc basis, and further published evidence identified by national stakeholder organisations, were incorporated where appropriate after having been assessed for inclusion by the same criteria as evidence provided by the electronic searches.

Searches were rerun at the end of the guideline development process, thus including evidence published and included in the literature databases up to 27 May 2003. Studies recommended by stakeholders or GDG members that were published after this date were not considered for inclusion. The date should be the starting point for searching for new evidence for future updates to this guideline.

3.6.2.4 Synthesising the evidence

Abstracts of articles identified by the searches were screened for relevance, and hard copies were ordered of papers that appeared to provide useful evidence relevant to each clinical question. Using a validated appraisal tool, each paper was assessed for its methodological quality against pre-defined criteria. Papers that met the inclusion criteria were then assigned a level according to the evidence hierarchy given under 2.6. Owing to practical limitations, selection, critical appraisal and data extraction were undertaken by one reviewer only. Evidence was, however, considered carefully by the GDG for accuracy and completeness.

Each clinical question dictated the study design that was prioritised in the search strategy. In addition, certain topics within any one clinical question at times required different evidence types to be considered. Randomised control trials (RCTs) were the most appropriate study design for some clinical questions as they lend themselves particularly well to research into medicines. They were not, however, appropriate for all clinical questions, for example the evaluation of diagnostic tests.

RCTs are difficult to perform in areas such as rehabilitation and lifestyle, where interventions are often tailored to the needs of the individual. As a consequence, pharmaceutical inter- ventions tend to be placed higher in the evidence hierarchy than other, equally important, interventions. This should not be interpreted as a preference for a particular type of intervention or as a reflection of

the quality of the evidence, particularly for those clinical areas where non-RCT evidence is valid and most appropriate.

Where available, evidence from well-conducted systematic reviews was appraised and presented. Trials included within these reviews are listed in the evidence table but were not critically appraised. Studies identified in addition to those included in the systematic review were included in the appraisal process.

At times, evidence was not available from studies that included a Type 1 diabetes population. Where a Type 2 or mixed diabetes population, or non-diabetes population, is considered, it is indicated in the relevant evidence statement.

On occasion the group identified a clinical question that could not be appropriately answered through undertaking a rigorous literature review (because the evidence was scarce, or conflicting). These questions were addressed by group consensus, and the group considered a summary of the area in an expert-drafted discussion paper. In these instances there was no formal assessment of the studies cited.

Finally, national and international evidence-based guidelines were referred to during the development process. These were not formally appraised because of the consistency of process and of evidence base can be difficult to ascertain across such documents.

The evidence statements should be read with the following caveats in mind:

- all comparisons discussed are statistically significant unless otherwise stated
- where evidence is available from a good quality systematic review or meta-analysis, then individual studies are not reviewed and referenced. Any additional RCT evidence presented relates to studies published since the completion of systematic review(s) included or those considered relevant to this guideline, but which may not have been suitable for inclusion in the systematic review(s)
- unless explicitly stated, all studies relate to diabetes populations. The inclusion of studies of Type 1, Type 2 or mixed Type 1 and Type 2 diabetes populations varies between questions (see Appendix A)
- descriptions of studies of poor methodological quality in evidence statements include details on all relevant interventions in a specified question. However, no positive recommendations have been based solely on such studies
- evidence statements in this guideline derived from one systematic review may be graded with different hierarchy of evidence in different places, due to some topics within the review being based on a synthesis of the outcomes of well-conducted randomised controlled trials and others being based on a synthesis of non-randomised studies, prevalence studies and diagnostic studies, or on consensus
- when other guidelines are reviewed, some of their recommendations are presented here as evidence statements. These may not necessarily reflect the recommendations made in this guideline and are clearly labelled
- where individual trials are referred to in the evidence statements as small, medium, or large, this equates to the following number of participants (at baseline): small, less than 50; medium, from 50 to 200; large, greater than 200. Exact numbers for each trial can be found in the online evidence tables.

3.6.2.5 Health economic evidence

While evidence on cost-effectiveness was extracted from the clinical literature searches wherever it existed, this was rare. As such, a separate search was conducted to isolate the health economic evidence that attempted to identify the cost of, and the benefits accruing from, each strategy or intervention. An a priori study design criterion was not imposed, so information may come from sources other than RCTs and formal economic evaluations.

As the management of diabetes is complex, many of the areas covered by this guideline have little economic evidence; within clinical trials it is not always clear which of a range of inter- ventions and strategies actually improves health. The GDG therefore expected the useful cost- effectiveness evidence to fall within a limited range of areas. Where searching produced either no evidence or insufficient evidence for a substantive health economic evidence statement, this fact is indicated.

The health economist presented the economic evidence to the GDG alongside the clinical evidence. There is no standard measure to assess the quality of the economic evidence, and reported costs and benefits experienced in other healthcare systems may not apply in the UK. The GDG had to assess not only the results but also their applicability.

Health economic analysis can provide a framework for combining information from a variety of sources to form a standard comparison of cost and benefits. However, the task of producing these estimates is complex and labour intensive, and requires a level of clinical evidence that is not always readily available. Evidence on the costs and benefits of a broad range of interventions was presented to the GDG, but the issue of cultured human dermis for foot ulceration was identified as a particularly important area for further economic analysis. The choice was made on the grounds that:

- this treatment does not have good quality economic evidence attached
- it has a potentially large health benefit
- if made available, the treatment could have a large effect on NHS resources given the prevalence of diabetic foot ulcers
- there are uncertainties surrounding both the benefits and resources, and an absence of cost-utility studies.

3.6.2.6 Drafting recommendations

- Evidence for each topic was extracted into tables and summarised in evidence statements. The GDG reviewed the evidence tables and statements at each meeting and reached a group opinion. Recommendations were explicitly linked to the evidence supporting them and graded according to the level of the evidence upon which they were based, using the grading system in the table below.
- It should be noted that it is the level of evidence that determines the grade assigned to each recommendation. The grade does not necessarily reflect the clinical importance attached to the recommendation.

Hierarchy of evidence	
Ia	Evidence from meta-analysis of randomised controlled trials.
Ib	Evidence from at least one randomised controlled trial.
IIa	Evidence from at least one controlled study without randomisation.
IIb	Evidence from at least one other type of quasi-experimental study.
III	Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies and case control studies.
IV	Evidence from expert committee reports or opinions and/or clinical experience of respected authorities.
DS	Evidence from diagnostic studies.
NICE	Evidence from NICE guidelines or health technology appraisal programme.

Typical grading of recommendations	
A	Based on category I evidence.
B	Based on category II evidence or extrapolated from category I.
C	Based on category III evidence or extrapolated from category I or II.
D	Directly based on category IV evidence or extrapolated from category I, II or III.
DS	Evidence from diagnostic studies.
NICE	Evidence from NICE guidelines or health technology appraisal programme.

3.6.2.7 Agreeing recommendations

Once the evidence review had been completed and an early draft of the guideline produced, a one-day meeting of the CRG was held to finalise the recommendations. This included a pre- meeting vote on the recommendations and a further vote at the CRG meeting, where the group was asked to consider the draft guideline in two stages:

1. Are the evidence-based statements acceptable and is the evidence cited sufficient to justify the grading attached?
2. Are the recommendations derived from the evidence justified and are they sufficiently practical so that those at the clinical front line can implement them? Three types of recommendation were considered:
   a. A recommendation from the GDG based on strong evidence, usually non- controversial unless there was important evidence that had been missed or misinterpreted
   b. A recommendation that was based on good evidence but where it was necessary to extrapolate the findings to make it useful in the NHS. The extrapolation was approved by consensus
   c. Recommendations for which no evidence existed but which address important aspects of care, and for which a consensus on best practice could be reached.

This formal consensus method has been established within the NCC-CC, drawing on the knowledge set out in a health technology appraisal,7 the work of the Royal College of Nursing Institute1 and practical experience. It approximates to a modification of the RAND Nominal Group Technique and will be fully described in future publications.

3.6.2.8 Writing the guideline

The draft version of the guideline was drawn up by the technical team in accordance with the decisions of the guideline groups. Prior to publication, it was circulated to stakeholders according to the formal NICE stakeholder consultation and validation phase.

Modifications were made to this document in response to comments received. Changes were approved by the Guideline Development Group, who retain the final editorial authority for the content.

3.6.2.9 Structure of the guideline

The part of this document which contains recommendations (chapter 4 onwards) is divided into sections, each of which covers a set of related topics. For each topic the layout is the same:

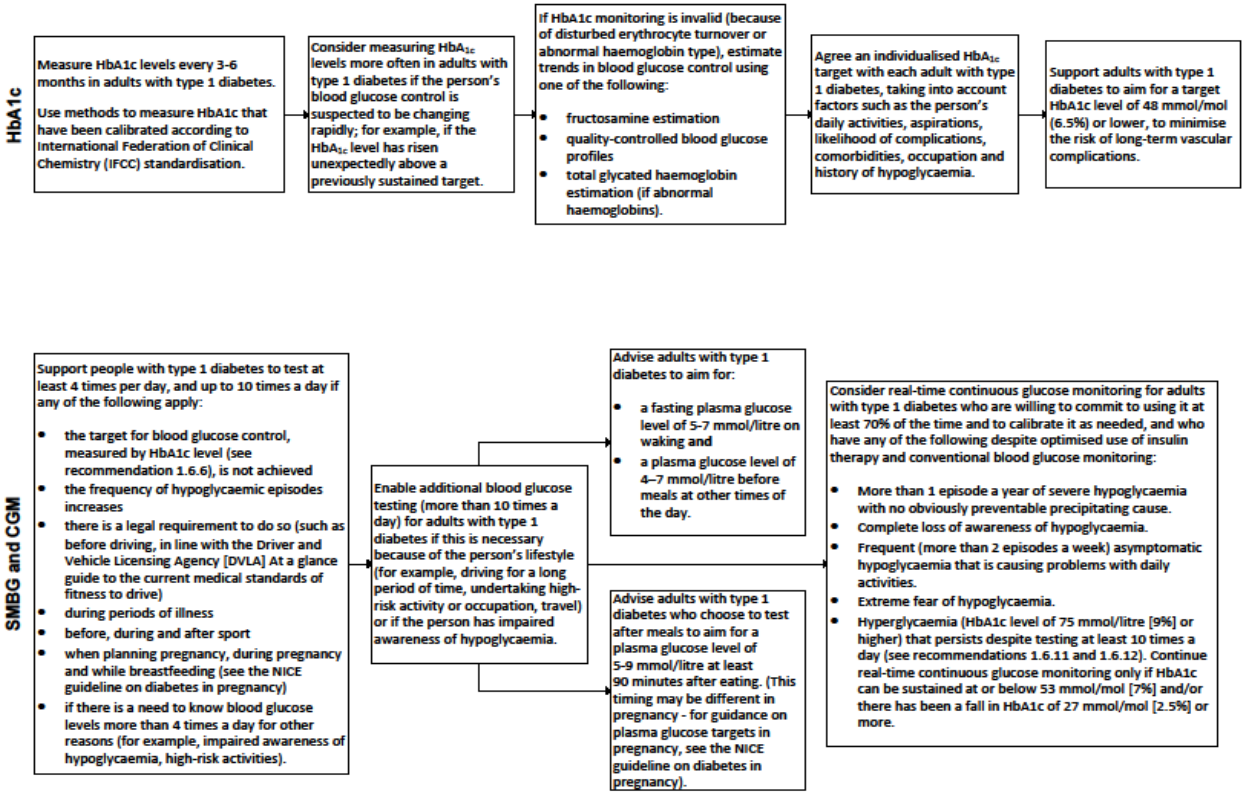
- the rationale for including the topic is provided in one or two paragraphs that simply set the recommendations in the context of their clinical importance
- the evidence statements, both clinical and health economic, are then given, summarising the evidence (more detail can be found in the evidence tables, available on the web at www.rcplondon.ac.uk/pubs/books/dia/index.asp) Specific health economic evidence statements also follow the clinical evidence when available. The evidence statements and tables aim to contextualise and explain each recommendation
- the evidence statements are followed by a consideration that reflects the thinking of the GDG in making the recommendations. This is intended to explain how the evidence was used to formulate the recommendations

the recommendations follow. These are graded to indicate the level of the evidence behind the recommendation, rather than how valid the GDG believes them to be. In some sections of the guideline, additional text providing more detailed guidance is contained within the recommendations.

4 Guideline summary

4.1 Algorithms

4.1.1 Blood glucose monitoring: frequency, timing and targets. This section was updated in 2015.

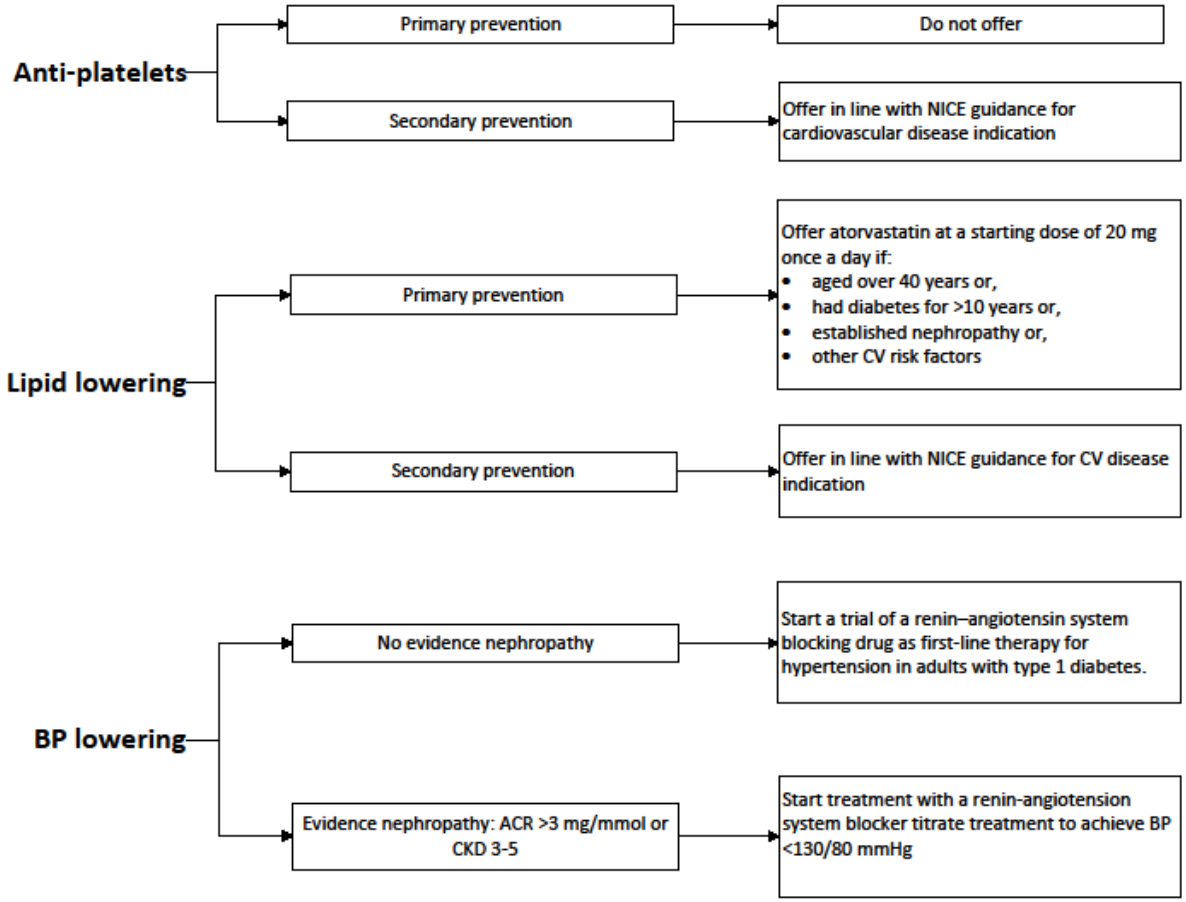


4.1.2 Treatment

This section was updated and replaced in 2021.

See https://www.nice.org.uk/guidance/ng17/evidence for the 2021 evidence reviews.

4.1.3 Non-glycaemic management of CV risk factors



4.2 Key priorities for implementation

From the full set of recommendations, the GDG selected 8 key priorities for implementation. The criteria used for selecting these recommendations are listed in detail in The guidelines manual.[535]The reason that each of these recommendations was chosen are shown in the table linking the evidence to the recommendation in the relevant chapter.

- Offer all adults with type 1 diabetes a structured education programme of proven benefit, for example the DAFNE (dose adjustment for normal eating) programme. Offer this programme 6-12 months after diagnosis. [new 2015]
- Support adults with type 1 diabetes to aim for a target HbA1c level of 48 mmol/mol (6.5%) or lower, to minimise the risk of long-term vascular complications. [new 2015]
- Agree an individualised HbA1c target with each adult with type 1 diabetes, taking into account factors such as the person's daily activities, aspirations, likelihood of complications, comorbidities, occupation and history of hypoglycaemia. [new 2015]
- Support adults with type 1 diabetes to test at least 4 times a day, and up to 10 times a day if any of the following apply:
  - the desired target for blood glucose control, measured by HbA1c level (see recommendation 41), is not achieved
  - the frequency of hypoglycaemic episodes increases
  - there is a legal requirement to do so (such as before driving, in line with the Driver and Vehicle Licensing Agency [DVLA] At a glance guide to the current medical standards of fitness to drive)
  - during periods of illness
  - before, during and after sport
  - when planning pregnancy, during pregnancy and while breastfeeding (see the NICE guideline on diabetes in pregnancy)
  - if there is a need to know blood glucose levels more than 4 times a day for other reasons (for example, impaired awareness of hypoglycaemia, high-risk activities). [new 2015]
- Advise adults with type 1 diabetes to aim for:
  - a fasting plasma glucose level of 5-7 mmol/litre on waking **and**
  - a plasma glucose level of 4-7 mmol/litre before meals at other times of the day. [new 2015]
- Offer multiple daily injection basal–bolus insulin regimens, rather than twice-daily mixed insulin regimens, as the insulin injection regimen of choice for all adults with type 1 diabetes. Provide the person with guidance on using multiple daily injection basal–bolus insulin regimens. [new 2015]
- Assess awareness of hypoglycaemia in adults with type 1 diabetes at each annual review. [new 2015]
- Enable adults with type 1 diabetes who are hospital inpatients to self-administer subcutaneous insulin if they are willing and able and it is safe to do so. [new 2015]

4.3 Full list of recommendations

The current guideline recommendations can be found at

https://www.nice.org.uk/guidance/ng17

4.4 Full list of research recommendations

1. This research recommendation was deleted as part of the 2022 update.
2. This research recommendation was deleted as part of the 2022 update.

3. In adults with type 1 diabetes, what methods can be used to increase the uptake of structured education programmes and to improve their clinical outcomes (particularly achieving and sustaining blood glucose control targets)?

4. In adults with newly diagnosed type 1 diabetes, what is the optimal timing and method of delivering structured education in terms of clinical and cost-effectiveness?

5. In adults with type 1 diabetes, what is clinical and cost effectiveness of bolus calculators used in conjunction with self-monitoring blood glucose meters?

6. In adults with type 1 diabetes, what is the clinical and cost effectiveness of different types of diet and dietary constituents, particularly in terms of the effect on insulin requirement and blood glucose control?

7. What methods and interventions are effective in increasing the number of adults with type 1 diabetes who achieve the recommended HbA1c targets without risking severe hypoglycaemia or weight gain?

8. Can a risk stratification tool be used to aid the setting of individualised HbA1c targets for adults with type 1 diabetes?

9. In adults with type 1 diabetes, is HbA1c measurement by laboratory analysis more cost-effective compared to site of care HbA1c testing?

10. In adults with type 1 diabetes, what is the clinical and cost effectiveness of post-prandial blood glucose monitoring?

11. In adults with type 1 diabetes who have chronically poor control of blood glucose levels, what is the clinical and cost effectiveness of continuous glucose monitoring technologies?

12. In adults with type 1 diabetes, what is the clinical and cost effectiveness of basal insulins with longer action profiles compared to existing regimens, particularly in terms of dose adjustment for flexible lifestyles, such as intermittent exercise or alcohol consumption, and their long term safety data?

13. In adults with type 1 diabetes who have recently been diagnosed, what is the clinical and cost effectiveness (particularly in terms of preservation of residual insulin secretion and other long-term outcomes) of different intensities of glycaemic control (for example, inpatient intravenous insulin management versus outpatient multiple daily dose insulin injection therapies)?

14. In adults with type 1 diabetes who have recently been diagnosed, what is the clinical and cost effectiveness (particularly in terms of preservation of residual insulin secretion and other long-term outcomes) of using basal–bolus insulin regimens?

15. In adults with type 1 diabetes, what modifications of rapid-acting insulin use (including but not limited to timing of administration, and the nature of the insulin) could be employed to improve glycaemic control around different meal compositions?

16. In adults with type 1 diabetes, what modifications of rapid-acting insulin (including timing of administration and nature of the insulin) could be employed to improve glycaemic control around different modalities of exercise?

17. In adults with type 1 diabetes and a BMI of ≥25 kg/m^2, what is the clinical and cost effectiveness of metformin as an adjunct to insulin, particularly in terms of glycaemic control and weight loss (or reduction in weight gain)?

18. In adults with type 1 diabetes, what is the clinical and cost effectiveness of GLP-1 analogues and other potential pharmacological adjuncts to insulin therapy?

19. In adults with type 1 diabetes, what are the optimum needle length and type for administration of exogenous insulin in terms of clinical and cost effectiveness?

20. In adults with type 1 diabetes, what is the optimum injection site and injection site rotation regimen in terms of clinical and cost effectiveness?

21. For adults with type 1 diabetes, what are the optimum technologies (such as insulin pump therapy and/or continuous glucose monitoring, partially or fully automated insulin delivery, and behavioural, psychological and educational interventions) and how are they best used, in terms of clinical and cost effectiveness, forpreventing and treating impaired awareness of hypoglycaemia?

22. In adults with type 1 diabetes, what is the clinical and cost effectiveness (particularly in terms of morbidity, reduction in admission rates, and length of stay) of using blood capillary ketone strips compared to urine ketone strips for the management of DKA?

23. In adults with type 1 diabetes, what is the clinical and cost effectiveness (particularly in terms of morbidity, reduction in admission rates, and length of stay) of using blood capillary ketone strips compared to urine ketone strips for the prevention of DKA?

24. In adults with type 1 diabetes, what is the clinical and cost effectiveness (particularly in terms of pre-empting admissions) of self-monitoring blood ketones compared to urine ketones?

25. In adults with type 1 diabetes, what is the clinical and cost effectiveness of aspirin and other anti-platelet agents who are at high risk for vascular disease (for example, smokers, those with renal disease, those with other evidence of vascular disease)?

26. In adults with type 1 diabetes, what is the clinical and cost effectiveness (particularly in terms of optimal blood glucose control, patient-reported outcomes and experience, length of stay, and short-term complications) of closed loop insulin delivery systems and automated insulin dose advisors during in-hospital care, and could the development of new systems and technologies improve on current clinical outcomes?

27. In adults with type 1 diabetes, clinical and cost effective treatments for diabetic gastroparesis are needed, together with further evidence for the clinical and cost effectiveness of existing treatments such as dopamine antagonists, insulin pump therapy, and gastric electrical stimulation.

28. What is the clinical and cost-effectiveness of constructing a national database and centralising supervision of the management of adults with type 1 diabetes who have painful neuropathy of rapid glycaemic control?

4.5 Key research recommendations

1. What methods and interventions are effective in increasing the number of adults with type 1 diabetes who achieve the recommended HbA1c targets without risking severe hypoglycaemia or weight gain?

2. In adults with type 1 diabetes who have chronically poor control of blood glucose levels, what is the clinical and cost effectiveness of continuous glucose monitoring technologies?

3. In adults with type 1 diabetes, what methods can be used to increase the uptake of structured education programmesand to improve their clinical outcomes (particularly achieving and sustaining blood glucose control targets)?

4. Can a risk stratification tool be used to aid the setting of individualised HbA1c targets for adults with type 1 diabetes?

5. For adults with type 1 diabetes, what are the optimum technologies (such as insulin pump therapy and/or continuous glucose monitoring, partially or fully automated insulin delivery, and behavioural, psychological and educational interventions) and how are they best used, in terms of clinical and cost effectiveness, for preventing and treating impaired awareness of hypoglycaemia?

5 Diagnosis

This section was updated and replaced in 2022.

See www.nice.org.uk/guidance/ng17/evidence for the 2022 evidence review and guideline recommendations.

5.1 Economic evidence

This section was updated and replaced in 2022.

See www.nice.org.uk/guidance/ng17/evidence for the 2022 evidence review and guideline recommendations.

5.2 Evidence statements

This section was updated in 2022.

See www.nice.org.uk/guidance/ng17/evidence for the 2022 evidence review and guideline recommendations.

5.3 Recommendations and link to evidence

The current guideline recommendations can be found at

https://www.nice.org.uk/guidance/ng17

5.4 Research recommendation

See https://www.nice.org.uk/guidance/ng17 for the 2022 research recommendations.

1. **This research recommendation was deleted as part of the 2022 update.**

2. **This research recommendation was deleted as part of the 2022 update.**

6 Care process and support [2004]

This section was not updated by the 2015 GDG and is the work of the 2004 GDG, included from CG15, with the exception of recommendation 6, which was added to support equality.

6.1 Scope of this chapter [2004]

It is outside the scope of this guideline to consider service delivery issues.Accordingly no recommendations are made regarding site of care; the emphasis is on the process of care necessary for the individual person with Type 1 diabetes to achieve optimal yet cost-effective outcomes.For example, while it is evidence-based that multidisciplinary team care leads to a reduced rate of complications, and it is known that no health professional alone possess all the necessary skills, no recommendation is made about the membership of such teams, or where they are sited.Nevertheless, where an evidence base exists for an activity associated with a health professional this has been appraised (because it influences the skillmix required), even if it is not used directly in the recommendations.

Equally, a term such as 'diabetes centres' should be read as a group of people working together as a resource with access to appropriate healthcare equipment and supporting all those in the local area providing diabetes care.This should not be interpreted as buildings sited in a primary or secondary care environment, or to sole sites of care.Some items of equipment (telephones, structured records, diabetes recall registers) are necessary components of the process of care (for example retinopathy screening) discussed in other parts of this guideline.

6.2 Optimal healthcare processes [2004]

6.2.1 Rationale

The management of diabetes is multidimensional, and each dimension multifaceted.Notable dimensions include diagnosis and associated management, preventative long-term care, hospital and emergency management, and detection and management of late-developing complications.With each of these dimensions a number of care areas are found (for example in long-term prevention, glucose control, blood pressure control, risk factor surveillance, blood lipid control and smoking), and for each care area a number of deliverables addressed (for example in blood glucose control: knowledge and basis of targets, injection skills, self-monitoring, dose adjustment, dietary matching, hypoglycaemia management, sick day management) by a number of different members of a multidisciplinary team.This multidimensional care delivery requirement has spawned diverse attempts aimed at ensuring optimal care is available to all those with diabetes. This section of the guideline seeks to examine what evidence is available to support some of those approaches.

6.2.2 Evidence review

It was recognised that the systems underlying structured organisation of care (for example diabetes centres) do not easily lend themselves to comparison by higher level studies (RCTs and cohort studies).Some technologies within such systems (for example a foot care information initiative) may on occasion be so approachable, but for the most part such technologies are offered and may only be applicable as part of an integrated care package.Accordingly, for the purposes of evidence review, no limits to study type were placed on the papers sought.Of 348 titles identified, 58 were selected as relevant for critical appraisal.

Additionally the major national and international guidelines were reviewed for consistency of recommendations.As the current question was considered at the end of the guideline process, a

review of generic structures of care already inherent or explicit in agreed recommendations within the current guideline was also made.

Only rarely did the ascertained primary literature distinguish type of diabetes.On occasion, insulin-treated people from both major types of diabetes were considered separately from people with Type 2 diabetes managed without insulin injections.Historically, people using insulin have been managed in specialist care; papers addressing issues of delivery of care by family doctors without reference to insulin-treated diabetes were also excluded from consideration, except in regards of complications surveillance.

6.2.3 Evidence statements

Multidisciplinary care

The Diabetes Control and Complications Trial (DCCT),[176] and smaller RCTs using improved management to judge the effect on patient outcomes, used multidisciplinary team input (in particular from specialist nurses and dietitians) as part of an integrated package to improve metabolic intermediate outcomes.A Cochrane review[466] of diabetes specialist nurse input identified six heterogeneous studies unsuitable for meta-analysis, and found little evidence of longer term impact on intermediate outcomes.An RCT[641] of the impact of structured team care as compared to usual care showed improved satisfaction and blood glucose control at 6 months. An RCT[725] of the use of diabetes specialist nurses to adjust insulin doses over the telephone showed improved blood glucose control (**Ib**).

A nurse specialist approach has been justified by a number of before and after studies and case series with such input (**II**).[98,304,408,435,793]

A number of studies of variable quality address the impact of inclusion of podiatrists compared to normal care within what is then usually called a diabetes foot care team.These studies included one RCT showing more patient knowledge and less callosities at 1 year, and a controlled study[164] (it is unclear whether that study is randomised) showing less foot ulceration (**Ib**).

A number of historically-controlled or descriptive studies support this approach, mainly reporting on patient preference outcomes (**IV**).[41,146,242,435]

The current guideline and all examined guidelines advise the use of members of a multidisciplinary team or more specifically nurses with training in teaching skills and adult education in a number of aspects of patient education, and formally trained dietitians and podiatrists within the specifically relevant areas of diabetes care (**IV**).

Annual review

No RCTs address the concept of integrated annual review.Newly- implemented structured annual review has been subject to a descriptive review,[617] suggesting improved satisfaction with care and improved patient motivation.Few full-length descriptions of the review process are available,[93] most references being editorials and letters (**IV**).

The current guideline suggests annual surveillance of a number of potentially developing late complications (as do all other guidelines for the most complications).The International Diabetes Federation's European guideline recommends integration of these activities into one patient visit.[361]Annual review also is the basis of many quality control structures proposed for diabetes care,[279] including (implicitly) that of the UK Audit Commission (**IV**).

Diabetes registers

A series of descriptive papers appear to demonstrate the feasibility of establishing population-based and clinic-based diabetes registers, with varying densities of information.[55,106,107,206,297,352,391,399,405,413,751]A system of database-driven recall for complications surveillance is implicit in the recommendations for annual complications surveillance of this and published guidelines.Issues of data security and confidentiality are not reported to have proved to be problematic obstructions to the deployment of diabetes registers (**IV**).

Diabetes centres and structured care

Most papers in this area are descriptive, and there is inevitable overlap with deployment of multidisciplinary teams and provision of diabetes information and foot care.Using historical controls a study[172] suggests improved blood glucose control, while another non-randomised study which suggests improved survival (presumably mainly in people with Type 2 diabetes (**IIb**).

Structured records and care cards

Although papers were ascertained addressing these areas, the papers were descriptive with no useful analysis of patient-related outcomes (**IV**).[96,169,207-210,227]

Electronic patient records and computer data analysis

A number of descriptive papers were identified,[123,277,588,691] suggesting such approaches can be feasible and have utility, but not demonstrating comparative advantage to traditional approaches (**IV**). However when such records were used to send judgmental letters to people with diabetes,[704] randomising sites of care, intermediate outcomes were significantly improved (probably mainly in people with Type 2 diabetes) (**Ib**).

Telemedicine

A number of approaches to medical care without direct patient contact are described in the literature.One RCT of a telecare system for insulin[74] provided equivalent control at reduced cost, while another study[725] using nurses resulted in improved blood glucose control (**Ib**).

In more rural and remote situations telemedicine can similarly provide apparent time and cost savings where images of foot problems[498] and eye photographs[156] need to be reviewed by specialists (**Ib**).

Inpatient care

Three papers using historical controls or randomised controls address the value of multidisciplinary teams with a specialist interest in diabetes management in the care of inpatients on non-diabetes wards.[414,453,494]Reduced length of inpatient stay is consistently reported.One study suggests improved

glucose control.[414]One study, also using historical controls, addresses length of stay in a developing country in newly-diagnosed people with diabetes, showing much reduced stays with multidisciplinary team input (**Ib**/**IIa**).

Guidelines

No literature on the deployment or impact of diabetes guidelines was identified.

6.2.4 Health economic evidence

Two potentially useful papers consider the type of treatment facility used to deliver care to those with Type 1 diabetes.[591,696]One German study[591] found that the treatment facility (polyclinics, specialist clinics or general practitioners) makes no difference to diabetes-specific knowledge when this was controlled for age, sex and education. One UK study[696] found no difference between hospital- and general practice-based care on a range of outcome measures for metabolic control, satisfaction with treatment or beliefs about diabetic control for a mixed diabetic population. Some differences were observed in the surveillance for complications, with more frequent testing in integrated care. Whilst costly, it is worth noting that fewer patients defaulted from general practice-based care than conventional care, although this cannot be established on the basis of this study.

One UK-based study[167] suggested that the provision of a hospital-based diabetes specialist nurse lowered the cost per patient admission without producing a significant difference in readmission, quality of life, or patient satisfaction.

Consideration

The group endorsed the approaches suggested by the evidence, but noted that attempts to implement some of the recommendations in the past had been inhibited by funding difficulties. This, however, was not felt to be a barrier to reiterating the health gains to be obtained.It was noted that recent publications (beyond the cut-off date of the searches) supported some of the recommendations further, including those relating to specialist nurses.The UK's national service framework for diabetes was noted to have endorsed diabetes registers.The group recognised the lack of any kind of formal evidence relating to walk-in, telephone-request, and out-of-hours services.

6.2.5 Recommendations

The current guideline recommendations can be found at

https://www.nice.org.uk/guidance/ng17

6.3 Support groups [2004]

6.3.1 Rationale

As having type 1 diabetes can have a major impact on lifestyle and self-esteem, it would appear that support groups could have a role in providing for some needs outside the professional environment and even separately from immediate carers.The range of such potential input is large and might

stretch from simply fulfilling a need for belonging, through to helping with diabetes-related financial problems (such as insurance), and even providing a further source of diabetes related information.

Coping with diabetes, or any other condition, is influenced not only by psychological characteristics of the individual but also by social relationships (e.g. support and communication by healthcare team, family and friends). Informal interpersonal variables, such as social resources and support, have been found to be associated with better diabetes self-management,[316,386] family environment,[231,295,653] and marital interaction.[56] A medical condition is only one aspect that affects the make-up of an individual's personal identity, and for some may be perceived as a minor factor compared to their environmental and social circumstances.

A 'support group' is defined in this guideline as a group of people with type 1 diabetes that comes together to provide support to themselves and others in their locality.Members are usually unpaid and many will be supported under the auspices of national (or local) voluntary organisations.Support groups have become commonplace throughout health and social care.

Patients and carers may choose to contact or be involved with support groups to gain information and support to benefit their own needs, or with a wider altruistic aim of helping other people within the local community. It was not possible to find specific research identifying patient and carer preferences for support groups, or indeed to identify specific groups or types of people who may benefit more than others. Some people attend meetings of groups regularly whilst other individuals are reassured by being aware of a group's existence and the opportunity to contact the group at a later date if problems arise and/or support is required. Preferences are dependent on what stage people are at in their lives and what information is taken (or needs to be taken) on board.

6.3.2 Evidence statements

The Diabetes Attitudes, Wishes and Needs (DAWN) questionnaire study[8] highlighted that emotional support, along with family support, was a key factor in how well people with diabetes manage their condition, with support networks being considered at least as important as the medication they take in helping them manage their diabetes.Interim results also indicate that people who do not have access to a community of support, especially the young or elderly living alone, may be less likely to be concordant with their medication regimen, putting them at risk of inadequate control of their diabetes (**III**).

There are still significant numbers of people emerging from the confirmation of a diagnosis who are under informed and unsupported.[186] Qualitative research of various designs examining the views and experiences of people with diabetes and carers has identified that many perceived benefits exist from meeting other people with diabetes. It has helped many to overcome the feelings of isolation and is seen as an opportunity to talk to others going through the same experience (**IV**).[333]

Research evaluating the effectiveness of support groups for patients and carers, across numerous conditions and groups (not necessarily diabetes) has shown specific benefits including:

- psychological and emotional benefits[6] including lower pain perception, and improved ability to cope with stress[186,407,731]
- reduction of carers' burdens and stresses[427,560]
- improvement in quality of life[292,488]
- improved self-care through health promotion strategies which have been helpful in smoking cessation and management of chronic conditions[228,513]
- improved access to health service provision[551]
- reduced isolation, overcoming depression and loss of self-esteem[333]
- better understanding of conditions, symptoms and healthcare systems through education and information[731] (**III**).

The Diabetes UK network of support groups recorded 175,426 members in July 2003, with around 7% under the age of 20 years and around 30% aged 70 years or over. Around 40% had paid for annual adult membership, 50% had a reduced rate membership (including children), and 10% had chosen life membership. The Diabetes UK Careline is, at the time of writing, one of the busiest sources of information for all people with Type 1 diabetes in the UK. In 2002, Careline were contacted 40,747 times (81% telephone, 13% e-mail, 6% post). The five most frequent topics of enquiry recorded were[142,243]:

- diet
- insulin
- medicines other than insulin
- new diagnosis
- travel (**III**).

Health economic evidence

Two studies were identified as potentially useful in this area.[37,323] As neither paper included cost information, the cost-effectiveness of support interventions cannot be ascertained.

6.3.3 Recommendations

The current guideline recommendations can be found at

https://www.nice.org.uk/guidance/ng17

6.4 Quality audit and monitoring [2004]

6.4.1 Rationale

It is generally accepted now that any system delivering a product, including healthcare systems, can benefit from review of its performance.The diabetes care espoused by this guideline is both complex and systematic, and thus lends itself to the kind of data collection needed for quality development. That very complexity, however, means that monitoring the structures, process and outcomes of all sectors can seem overwhelming, necessitating consideration of how limited monitoring activity can be undertaken without distorting the areas gaining attention for improvement.Monitoring of quality of life would seem *a priori* to be of particular importance in diabetes care, but presents its own difficulties of data acquisition and of analysis of temporally different outcomes.

Audit criteria are suggested in Section 3.3 of this guideline to assist local users in promoting implementation and monitoring ongoing improvements in process and outcome. They have been informed where possible by existing validated measures, principally those of the National Centre for Health Outcome Development. [339]

7 Education programmes and self-care

The 2015 GDG updated the evidence and recommendations for structured education programmes (Section 7.2). Evidence reviews and recommendations for carbohydrate counting and glycaemic index (GI) diets evidence reviews have been added to the dietary management section (Section7.3). Other aspects of education and self-care were not updated (dietary management other than carbohydrate counting and GI diets, physical activity and cultural and individual lifestyle). The content from the 2004guideline that has been replaced by the new evidence reviews can be found in Appendix S.

7.1 Rationale [2004]

Having diabetes involves acquiring a great range of new skills and knowledge, including insulin therapy, dietary changes, self-monitoring, hypoglycaemia, jobs, travel, physical exercise, coping with concurrent illness, foot care, arterial risk control, avoiding complications. The history of education and information giving in diabetes care goes back to the earliest dietary interventions several centuries ago, and the use of education professionals to impart skills associated with insulin therapy dates from the time of discovery and isolation of insulin. Accordingly patient education is a true cornerstone that enables self-management of diabetes, and most diabetes management is self-management. Review of other parts of this NICE guideline will reveal that education and information giving are parts of nearly all of them, from enabling patient choice in determining features of self-management, to acquisition of skills needed to perform tasks and make judgements, to self-care where high risk complications have developed, and to skills in handling healthcare professionals to ensure that issues of importance to the person with type 1 diabetes are addressed.

7.2 Structured education programmes [updated 2015]

This section was updated in 2015.

7.2.1 Introduction

People with type 1 diabetes have an absolute need for insulin replacement therapy. The body's requirement for insulin varies greatly by time of day, food eaten, energy expended, state of health and other factors. Historically, people with type 1 diabetes were prescribed specific insulin regimens and a lifestyle to match it, with times of eating and quantities of food eaten made as reproducible as possible. Modern management aims to support a more flexible lifestyle with minimal restrictions as a route to optimal biomedical outcomes and good quality of life. In order to achieve these aims, the person with diabetes needs knowledge and skills traditionally taught to healthcare professionals.

Therapeutic education aims to help people with long-term conditions better manage their treatment and, in the case of diabetes, adapt the diabetes control to the constant changes in daily life.[53] "Structured education" is a method of therapeutic education defined as "a planned and graded process that facilitates the knowledge, skills and ability for diabetes self-management and empowers individuals to live healthily, to maintain and improve their quality of life, and assume an active role in their diabetes care team".[233]The essential requirements of a structured education programme are that it has a philosophy that guides its delivery; a formal, written curriculum; appropriately trained educators to deliver it; and that it is both quality assured and regularly audited.[233] The Department of Health and the Diabetes UK Patient Education Working Group stated that any programme should be evidence-based, should suit the needs of the individual with specific aims and learning objectives, and be able to support the patient plus his or her family and carers in developing attitudes, beliefs, knowledge and skills to self-manage diabetes.[377] Programmes for people with type 1 diabetes should empower individuals to make day-to-day decisions about their diabetes treatment and lifestyle, with

the best outcomes for their health.[528]It is recommended that structured patient education is made available to all people with diabetes at the time of initial diagnosis and then, as required on an ongoing basis, based on formal, regular assessment.[528]

Multiple packages offer structured education for adults with type 1 diabetes in the UK.[280] The question addressed in this chapter is "In adults with type 1 diabetes, what is the most effective structured education programme?"

7.2.2 Review question: In adults with type 1 diabetes, what is the most effective structured education programme?

For full details see review protocol in Appendix C.

Table 7: PICO characteristics of review question

Population	Adults with type 1 diabetes
Intervention(s)	Structured education programme
Comparison(s)	• Other education programmes • Usual care/no treatment • SMBG
Outcomes	• HbA1c • Hypoglycaemia - preferably severe hypoglycaemia if reported • Hospital admissions • Hypoglycaemia unawareness • Quality of life – measured by DQoL, DSQoL, PAID, HADS, fear of hypoglycaemia, anxiety, depression • Adverse events • Knowledge • Adherence
Study design	RCTs

7.2.3 Clinical evidence

We searched for randomised trials comparing the effectiveness of structured education programmes versus other education programmes or usual care/no treatment in adults with type 1 diabetes. Studies cited in the original 2004 type 1 diabetes guideline[529] were also assessed and included where appropriate.

The original 2004 NICE guideline based the main bulk of its review of the evidence for education on the 2002 unpublished report[603] of the HTA published in 2003[466] that looked at structured education in diabetes. Therefore, any RCTs in the HTA that were type 1 diabetes-specific and looked at structured education programmes were included in our review. The 2004 NICE guideline also included three additional RCTs which assessed education programmes [173,415,450] and these were therefore included in our review.

In 2003, NICE published a TA (TA60)[528] on the use of patient education models for people with type 1 and type 2 diabetes. As for the 2004 NICE type 1 diabetes guideline, this was based on the 2002 unpublished report[603] of the HTA published in 2003[466], as well as some additional studies. Of the additional studies found, only 2 RCTs were reported that assessed education in type 1 diabetes. One of these RCTs was not suitable for our review and thus, would have been excluded because it looked at intensive insulin treatment in combination with an educational component (SDIS study)[612] rather than the effects of an intensive/structured education programme. The second RCT[718] met our inclusion criteria and was therefore included in our review

From our updated literature search, we found 10 relevant RCTs that had been published since the original 2004 guideline and these were included in our review.

Overall, fifteen RCTs were included in our review(DAFNE study[31], BGATTIII study[652], BITES study[260], [173]HAATT study[150], HYPOS study[318], [415,450]BGAT study[693], Rossi 2010[630], Terent 1985[718], Trento 2005[734],Trento 2011[735]PRIMAS,[319] Rossi 2013[631]). Evidence from the included studies are summarised in Table 8. See also the study selection flow chart in Appendix D, forest plots in Appendix J, study evidence in Appendix G.

Table 8: Summary of studies included in the review

Study	Intervention	Content	Delivered by	Comparison	CHO counting component	Population	Inclusion: with IAHor frequent severe hypoglycaemia only	Follow-up
BGAT (Snoek 2008) [693]	BGAT Psychoeducational programme	Prevent and correct in a timely fashion, extreme blood glucose excursions Done by improving symptom discrimination and understanding of the interaction between insulin, food intake and physical activity	Diabetes nurse educators and clinical psychologist	CBT	X	n=86 Type 1 diabetes 18 years duration	X	6 week course (1/week) 3, 6 and 12 months follow-up
BGAT III study 2005[652]	BGATIII Psychoeducational programme	Using signals to accurately recognise when blood glucose is too high or low Signals: physical symptoms, disruptions in cognitive and motor performance, mood changes Predicting when blood glucose likely to rise or fall based on - previous insulin injections, food consumption, physical exercise	Physician-psychologist team	Self-help group	X	n=138 Type 1 diabetes on intensified insulin regimen 23 years duration	Mostly patients with frequent hypoglycaemic episodes	8 week course (1 hour/week) 6 and 12 months follow-up
BITES study 2008[260]	BITES Psychoeducational programme	Problem solving; psychoeducational. Fictitious individual with type 1 diabetes throughout the course who they mentored throughout and discussed helping them with change. Specific content details not given	DSN and SDD	Usual care	X	n=114 Type 1 diabetes 19.5 years duration	X	6 week course (2.5 days total) 3, 6 and 12 months follow-up

Study	Intervention	Content	Delivered by	Comparison	CHO counting component	Population	Inclusion: with IAHor frequent severe hypoglycaemia only	Follow-up
DAFNE study 2002[31]	Immediate DAFNE Educational training course	CHO intake and matching insulin Adjusting insulin to suit lifestyle Confidence and autonomy	DSNs and dietitians	Delayed DAFNE (waiting list/usual care)	Yes - in intervention group	n=169 Type 1 diabetes 16 years duration	X	5 day course 6 months follow-up
deWeerdt 1991[173]	Education Included motivational aspects	Highly structured Video film, a book, and some practice materials were used as part of the programme. The lessons also had a motivational function Content details not given	Trained nurse, dietitian or patient with diabetes	Usual care	X	n=558 Insulin-treated diabetics 13 years duration	X	4 week course (3 hours/ week) 6 months follow-up
HAATT study 2004[150]	HAATT + SMBG Psychoeducational programme	Anticipation, prevention, recognition and treatment of hypoglycaemia Insulin kinetics and how to anticipate when their insulin action is at its peaks and nadir CHO counting and matching insulin and exercise Demands of physical activity/insulin adjustment	Physician	SMBG	X	n=60 Type 1 diabetes and ≥2 severe hypo episodes in past year 14 years duration	Yes	7 week/2 months course (once/week) 6, 13 and 18 months follow-up
HYPOS study 2007[318]	HyPOS Bio-psychosocial training/education programme	Causes and correct treatment of hypoglycaemia Unawareness Avoiding hypoglycaemia. Symptoms of hypoglycaemia. Detection of hypoglycaemia Coping with activities that may	Diabetologist and diabetes educators	Standard education	Yes - in comparison group only	n=164 Type 1 diabetes and hypoglycaemia	Yes	5 week course (90 minutes/week) 6 months follow-up

Study	Intervention	Content	Delivered by	Comparison	CHO counting component	Population	Inclusion: with IAHor frequent severe hypoglycaemia only	Follow-up
		pose risk of hypoglycaemia				20 years duration		
Korhonen 1983[415]	Intensive education Group and individual	Education programme Details not given Instructed to adjust insulin dose during sick days and in other special situations and call the nurse whenever had problems from diabetes.	physician, dietitian, and teaching nurse	Traditional education	X	n=77 Type 1 diabetes (insulin-dependent) 8 years duration	X	5 day intense course 1 year follow-up
Lennon 1990[450]	Education Motivational and behavioural features	aspects of diabetes treatment and technical skills diet, insulin, hypoglycaemia, diabetic control, exercise and illness, ketones, hyperglycaemia, new diet, complications of diabetes, new developments in research, practical problems in self-management	Not given – individual and group sessions	Usual care	X	n=74 Insulin treated Type 1 diabetes 13.7 years duration	X	1 year course (once a month meeting) No additional follow-up
PRIMAS study (Hermanns 2013) [319]	PRIMAS education programme Group education	CHO counting. Self-management/empowerment approach. Detection and treatment of acute complications	Diabetes educators	DTTP education programme	Yes – in both groups	n=160 Type 1 diabetes 19 years duration	X	6 weeks course 6 months follow-up
Rossi 2010[630]	CHO counting education	CHO counting programme - further details not given	Not mentioned	Diabetes interactive	Yes – in both groups	n=130 Type 1	X	3 month course

Study	Intervention	Content	Delivered by	Comparison	CHO counting component	Population	Inclusion: with IAHor frequent severe hypoglycaemia only	Follow-up
	programme Standard educational approach			diary telemedicine		diabetes 16 years duration		(days/week not mentioned) 6 months follow-up
Rossi 2013 [631]	Standard educational approach	Standard education programme - further details not given	Not mentioned	Diabetes interactive diary telemedicine	Yes – in DID unclear in educated (but likely as for Rossi 2010 study)	n=127 Type 1 diabetes 15.5 years duration	X	Length of course not stated. 6 months follow-up
Terent 1985[718]	Education Formal education	Explain interplay between food consumption, blood glucose levels, insulin and urinary glucose. Excretion hypo- and hyperglycaemia, footcare, injections, and urine testing techniques Social aspects Encouraged to test urine for glucose and ketone bodies	physicians and dietitian	Standard therapy	X	n=19[a] Type 1a diabetes 9 years duration	X	6 month course (days/week not mentioned) 6, 12 and 18 months follow-up
Trento 2005[734]	Structured education programme (group care) Group education	differences between type 1 diabetes and type 2 diabetes principles of nutrition and classification of nutrients; composition of food and food exchanges physical exercise and adjusting	Pyschopaedagogist	Usual care (1:1 consultations every 2-3 months)	X	n=62 Type 1 diabetes 16 years duration	X	18-27 months (9 education sessions; one every 2-3 months)

Study	Intervention	Content	Delivered by	Comparison	CHO counting component	Population	Inclusion: with IAHor frequent severe hypoglycaemia only	Follow-up
		insulin hypoglycaemia and hyperglycaemia – causes, recognition, management and informing relatives and friends areas of insulin injection and their rotation retinopathy, neuropathy, low-level (micro) albuminuria and nephropathy (self-care, when and how to screen); hypertension and CV aspects. HbA1c day-to-day problems						6 additional visits over the remainder of the 3 years) 3 years follow-up
Trento 2011[735]	CHO counting programme Programme included cognitive and psychomotor abilities	CHO counting Hypoglycaemia, recognition and treatment motivational aspects, acceptance of diabetes, psychosocial problems, and coping strategies included cognitive and psychomotor abilities	Doctor, psychopedagogist, dietitian and nurse	Continuing education programme	Yes - in intervention group	n=56 Type 1 diabetes 22 years duration	X	8 sessions every 3-4 months 30 months follow-up

Abbreviations: IAH, impaired awareness of hypoglycaemia.

Note: This study had 2 levels of randomisation of n=37 patients. First randomisation: education versus standard therapy; second randomisation: education plus SMBG versus education, versus SMBG versus Standard therapy. Data used in this review are for the n=19 patients who remained in the education versus standard therapy groups throughout the entire study period.

Outcomes

Conference abstracts were excluded for this review question because there were sufficient RCT data found for the critical outcomes. However, there were no data reported in any of the studies for the following outcomes:

- HADS score
- Adverse events

Outcomes were grouped into the following categories based on time-points:

- less than or equal to 6 months (or the one nearest to 6 months if multiple time-points are given in the study)
- more than 6 months (or the longest one if multiple time-points are given in the study).

Heterogeneity – HbA1c

For the outcomes of HbA1c(%), at both 6 and 12 months, when data were pooled into the meta-analysis, there was significant heterogeneity ($p<0.1$ and I^2 more than 50%) between the trials (see GRADE profiles in Appendix I and the forest plots in Appendix J). Three pre-specified subgroup analyses were conducted in order to try to explain the heterogeneity, based on:

1. The type of comparison used in the studies - because the studies varied in the type of comparison group that was used (see forest plots Figure 2 and Figure 29 in Appendix J).
1. Whether the structured education programme included a carbohydrate counting component (see forest plots Figure 3 and Figure 30 in Appendix J).
2. Whether the patients recruited in the trials included those with impaired awareness of hypoglycaemia (IAH) and/or severe hypoglycaemia or not (see forest plots Figure 4 and Figure 31 in Appendix J).

Less than or equal to 6 months

At less than or equal to 6 months (see Figure 2 in Appendix J) the heterogeneity could be partlyexplained by the type of comparison used (test for subgroup differences shows p=0.005). The analysis showed that structured education was favoured in lowering HbA1c when compared with usual care, but there was no difference in HbA1c when structured education was compared with other education groups or types of support.

Additionally, when using the pre-specified subgroup analysis of whether the structured education included a carbohydrate counting component (see Figure 3 in Appendix J), the heterogeneity could be partly explained (test for subgroup differences shows p=0.0002). The analysis showed that structured education programmes that included carbohydrate counting were favoured in lowering HbA1c when compared with usual care, but there was no difference between structured education and the control group in HbA1c when only the control group had carbohydrate counting, when both the groups included carbohydrate counting, and when neither of the groups included carbohydrate counting.

An additional subgroup analysis was also performed to determine whether trials that included only people with problematic hypoglycaemia (impaired awareness and/or a history of severe hypoglycaemia versus trials with unselected type 1 diabetes patients or from which people with problematic hypoglycaemia were excluded could explain the heterogeneity (see Figure 4 in Appendix J). This analysis showed that heterogeneity could not be explained by the inclusion of only hypoglycaemic patients in the study (test for subgroup differences shows p=0.05 and I^2 =74.8%).

More than or equal to 12 months

At more than or equal to 12 months (see Figure 29 in Appendix J) the heterogeneity could be explained by the type of comparison used (test for subgroup differences shows $p<0.00001$). The analysis showed that structured education was favoured in lowering HbA1c when compared with usual care, but was worse when compared with other education groups or types of support (that is, other education groups or types of support were better for lowering HbA1c).

Additionally, when using the pre-specified subgroup analysis of whether the structured education included a carbohydrate counting component (see Figure 30 in Appendix J), the heterogeneity could be explained (test for subgroup differences shows $p<0.00001$). The analysis showed that structured education programmes that included carbohydrate counting were worse in lowering HbA1c when compared with usual care (but this was due to a single study, Trento 2011, of only 56 patients), but when there was no carbohydrate counting in either the structured education programmes or the control groups, structured education was favoured in lowering HbA1c.

The subgroup analysis to see whether trials that included only patients with problematic hypoglycaemia explained the heterogeneity was not conducted, as all the trials at 12 months were in unselected type 1 diabetes patients.

Heterogeneity – Severe hypoglycaemia (episodes/patient/year)

For the outcomes of severe hypoglycaemia (episodes/patient/year), when data were pooled into the meta-analysis, there was significant heterogeneity ($p<0.1$ and I^2 more than 50%) between the trials (see GRADE profiles in Appendix I and the forest plots in Appendix J). Subgroup analyses were conducted (using the same subgroups as mentioned above for HbA1c). The type of comparison subgroup analysis could not be conducted as this was the same in both studies. When the remaining two subgroup analyses were preformed (carbohydrate counting and hypoglycaemic patients), neither of these analyses could explain the heterogeneity between the groups.

Table 9: Structured education programme versus control - usual care or other type of education (less than or equal to 6 months)

Outcomes	Number of studies	Imprecision	GRADE rating	Absolute difference Structured education	Control event rate (per 1000 patients) or final value in control group Control
HbA1c, %	8 studies (n=1396)	Not serious	VERY LOW	MD 0.15 lower (0.27 to 0.03 lower)	8.0 final value in control group
HbA1c, % - MD only given	1 study (n=114)	Serious	VERY LOW	MD 0.06 lower (0.32 lower to 0.2 higher)	Not given
HbA1c, % - SD not given	1 study (n=60)	Very serious	VERY LOW	Data provided: HAATT 8.0% and SMBG 8.1%	
Severe hypoglycaemia (episodes/study)	2 studies (n=269)	Very serious	VERY LOW	14 more per 1000 (from 36 fewer to 121 more)	81
Severe hypoglycaemia (episodes/6 months)	1 study (n=111)	Not serious	LOW	MD 0.94 lower (1.7 to 0.18 lower)	1.07
Severe hypoglycaemia (episodes/month)	1 study (n=558)	Not serious	LOW	MD 0.05 higher (0.04 lower to 0.14 higher)	-0.1
Severe hypoglycaemia (episodes/patient/year)	3 studies (n=433)	Not serious	HIGH	MD 0.22 lower (0.94 lower to 0.51 higher)	1.2
Severe hypoglycaemia (episodes/person) - SD not given	1 study (n=60)	Very serious	VERY LOW	Data provided: HAATT 0.4 and SMBG 1.7; p=0.03	
ADDQoL - impact	1 study (n=139)	Not serious	LOW	MD 0.4 higher (0.34 lower to 0.46 higher)	0
ADDQoL - impact and importance	1 study (n=146)	Not serious	LOW	MD 0.1 lower (0.36 lower to 0.16 higher)	1.1
DTSQ - total satisfaction	1 study (n=139)	Not serious	LOW	MD 8.76 higher (7.09 to 10.43 higher)	22.8
SF-36 physical	1 study (n=130)	Not serious	MODERATE	MD 0.4 lower (2.53 lower to 1.73 higher)	1.0
SF-36 physical health - MD only given	1 study (n=60)	Very serious	VERY LOW	MD 2.2 higher (0.7 lower to 5 higher); p=0.14	
SF-36 mental	1 study (n=130)	Not serious	MODERATE	MD 5 higher (1.09 to 8.91 higher)	-0.8

Outcomes	Number of studies	Imprecision	GRADE rating	Absolute difference Structured education	Control event rate (per 1000 patients) or final value in control group Control
Hospital admissions	1 study (n=130)	Not serious	MODERATE	0 admissions in both groups	
Symptomatic hypoglycaemia (perceived frequency, scale 0-6)	1 study (n=139)	Serious	VERY LOW	MD 0.24 lower (0.67 lower to 0.19 higher)	2.4
Hypo unawareness (more recognition of low blood glucose, % of patients)	1 study (n=111)	Serious	VERY LOW	MD 12.40 higher (2.41 to 22.39 higher)	45.8
Hypo unawareness (HAQ)	1 study (n=146)	Serious	VERY LOW	MD 0.3 lower (0.67 lower to 0.07 higher)	0.6
Hypo unawareness (change in Clarke score, max 7)	1 study (n=160)	Not serious	HIGH	MD 0.1 lower (0.52 lower to 0.32 higher)	1.2
Hypo unawareness (VAS) – SD not given	1 study (n=146)	Very serious	VERY LOW	MD 0.8 higher (0.2 to 1.4 higher); p=0.05	5.3
Hypoglycaemia unawareness (%detection of low blood glucose) – no SD given	1 study (n=60)	Very serious	VERY LOW	Data provided: HAATT 70% and SMBG 55%, p=0.005	
Fear of hypo (Hypo fear survey) - Worry	1 study (n=111)	Not serious	LOW	MD 0.60 higher (3.42 lower to 5.12 higher)	14.6
Fear of hypo (Hypo fear survey) - Behaviour	1 study (n=111)	Serious	VERY LOW	MD 2.10 higher (0.63 lower to 4.83 higher)	11.6
Fear of hypo (change in DSQoL)	1 study (n=127)	Not serious	MODERATE	MD 5.34 lower (12.11 lower to 0.23 higher)	-3.91
Fear of hypo (Hypo fear survey) – Worry – MD only given	1 study (n=111)	Very serious	VERY LOW	MD 2.4 lower (7.2 lower to 2.4 higher); p=0.33	
Fear of hypo (Hypo fear survey) – Behaviour – MD only given	1 study (n=111)	Very serious	VERY LOW	MD 0.01 lower (2.9 lower to 2.9 higher); p=0.99	
Depression (CES-D)	2 studies (n=306)	Not serious	MODERATE	MD 0.2 lower (0.85 lower to 1.45 higher)	6.2
Depression (CES-D) - no SD given	1 study (n=86)	Very serious	VERY LOW	Data provided: BGAT 15.8 and Control 13.5, p=0.74	

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Outcomes	Number of studies	Imprecision	GRADE rating	Absolute difference Structured education	Control event rate (per 1000 patients) or final value in control group Control
Anxiety (STAI)	1 study (n=146)	Not serious	LOW	MD 0.50 higher (1.54 lower to 2.54 higher)	37.1
PAID	1 study (n=146)	Not serious	LOW	MD 0.70 lower (4.45 lower to 3.05 higher)	24
PAID - no SD given	1 study (n=86)	Very serious	VERY LOW	MD 0 higher (0 to 0 higher)	38.7
Knowledge, % correct answers	1 study (n=77)	Not serious	LOW	MD 7.50 higher (6.63 to 8.37 higher)	72
Knowledge (change score out of 11)	1 study (n=160)	Not serious	HIGH	MD 0.10 higher (0.4 lower to 0.6 higher)	0.6
Adherence	1 study (n=160)	Very serious	LOW	13 fewer per 1000 (from 24 fewer to 108 more)	250

Table 10: Structured education programme versus control - usual care or other type of education (more than or equal to 12 months)

Outcomes	Number of studies	Imprecision	GRADE rating	Absolute difference Structured education	Control event rate (per 1000 patients) Control
HbA1c, % pooled	5 studies (n=300)	No serious	VERY LOW	MD 0.08 higher (0.01 lower to 0.17 higher)	10.4
HbA1c, % (between 6 and 12 months)	1 study (n=86)	Very serious	VERY LOW	Study reported that there was NS change in either of the groups	
HbA1c, % - MD only given	1 study (n=114)	Serious	VERY LOW	MD 0.01 higher (0.3 lower to 0.32 higher); p=0.94	
Severe hypoglycaemia (episodes/study)	1 study (n=56)	Very serious	VERY LOW	21 fewer per 1000 (from 143 fewer to 331 more)	207
Severe hypoglycaemia (episodes/6 months)	1 study (n=111)	Serious	VERY LOW	MD 1.65 lower (2.86 to 0.44 lower)	1.78
Severe hypoglycaemia (episodes/12 months) - SD not given	1 study (n=114)	Very serious	VERY LOW	MD 0.05 lower (0.61 lower to 0.5 higher); p=0.94	
Severe hypoglycaemia (episodes/person) - SD not given	1 study (n=60)	Very serious	VERY LOW	Data provided: HAAT 1.76 and SMBG 3.65; p<0.023	
DQoL	2 studies (n=114)	Not serious	LOW	MD 2.40 lower (3.13 to 1.67 lower)	4.27
SF-36 physical health - MD only given	1 study (n=60)	Very serious	VERY LOW	MD 1.9 higher (0.8 lower to 4.6 higher); p=0.17	
Hypo unawareness (more recognition of low blood glucose, % of patients)	1 study (n=111)	Serious	VERY LOW	MD 17.2 higher (7.77 to 26.63 higher)	48.0
Fear of hypoglycaemia (Hypo fear survey) - Worry	1 study (n=111)	Serious	VERY LOW	MD 1.50 lower (5.78 lower to 2.78 higher)	14.7
Fear of hypoglycaemia (Hypo fear survey) - Behaviour	1 study (n=111)	Not serious	LOW	MD 0.60 lower (3.48 lower to 2.28 higher)	12.2
Fear of hypoglycaemia (Hypo fear survey) – Worry – MD only given	1 study (n=102)	Very serious	VERY LOW	MD 1.4 lower (6.2 lower to 3.4 higher); p=0.57	
Fear of hypoglycaemia (Hypo fear survey) – Behaviour – MD only given	1 study (n=102)	Very serious	VERY LOW	MD 1.2 lower (4.2 lower to 1.9 higher) ;p=0.45	

Outcomes	Number of studies	Imprecision	GRADE rating	Absolute difference Structured education	Control event rate (per 1000 patients) Control
Depression (CES-D) - no SD given	1 study (n=86)	Very serious	VERY LOW	Data provided: BGAT 15.5 and Control 15.4, p=0.19	
PAID - no SD given	1 study (n=86)	Very serious	VERY LOW	Data provided: BGAT 45.4 and Control 38.3, p=0.68	
Knowledge, % of correct answers	1 study (n=77)	Not serious	LOW	MD 15.8 higher (2.17 to 29.42 higher)	64.9
Knowledge of diabetes (GISED)	1 study (n=56)	Not serious	LOW	MD 1.81 higher (0.15 to 3.46 higher)	1.59

7.2.4 Economic evidence

Published literature

One study was included with the relevant comparison.[422] This is summarised in the economic evidence profile below (Table 11). See also the study selection flow chart in Appendix E and study evidence tables in Appendix H.

In addition, NICE Technology Appraisal 60[528] recommends that "structured patient education is made available to all people with type 1 diabetes at the time of initial diagnosis and then as required on an on-going basis, based on a formal, regular assessment of need of which the DAFNE programme may be a suitable option for individuals with type 1 diabetes". It also concludes that "given the relatively small costs associated with education programmes, only small improvements in terms of morbidity or health-related quality of life are needed to make educational interventions cost effective".

In the previous version of this guideline, one Health Technology Assessment identified only one study on type 1 diabetes and this has been selectively excluded.[267] Three new studies that met the inclusion criteria were selectively excluded due to the availability of a UK CUA.[173,203,734] One study[677] that met the inclusion criteria was selectively excluded as the included study[422] was its updated version. The excluded studies are listed in Appendix L.

Table 11: Economic evidence profile: Structured training and treatment programme (STTP) (DAFNE) versus current practice

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Kruger 2013[422] (UK)	Directly applicable[a]	Potentially serious[b]	DAFNE vs. current practice HbA1c was the key surrogate outcome influencing long-term diabetes-related complications modelled through the Sheffield Type 1 Diabetes Policy Model.	£426	0.0294 QALYs	£14,475 per QALY	Probability DAFNE is cost-effective at £20,000 per QALY threshold: 54%. DAFNE was dominant or still cost-effective when: 6-month HbA1c was predicted from RCT as 12-month, 4-year HbA1c maintained for lifetime, 6-month HbA1c predicted from RCT as 12-month and 4-year HbA1c maintained to 7 years, 12 month HbA1c maintained to year 7, 6-month HbA1c predicted from RCT as 12-month and maintained to year 7, 4-year HbA1c maintained to 7 years, 6-month HbA1c predicted from RCT as 12-month and HbA1c returns to baseline levels after 1 year, probabilities of severe hypoglycaemia and ketoacidosis differ between arms and linked to HbA1c based on research database. If HbA1c returns to baseline levels after 1 year: ICER £78,227 per QALY gained

(a) CUA from the UK, NHS perspective. However the Sheffield Type 1 Diabetes Policy Model used published data from non-UK settings to define risk of long-term complications, some of which are now very old (for example DCCT). Old and non-UK data may not accurately represent the incidence of complications in the UK DAFNE population.

(b) It is possible not all the costs were included as PSS costs were not included. The study was only conducted over ten years where the full benefits of structured educational programmes are unlikely to be realised within ten years. The analysis used only HbA1cchange to represent the clinical effectiveness of DAFNE. HbA1cwas assumed to be equivalent between those individuals who had and had not received training. Health related quality of life data was unavailable for type 1 diabetes and so outcomes were estimated using multivariate statistical models developed for type 2 diabetes. In addition authors assumed that macro vascular complications have no impact on morbidity.

7.2.5 Evidence statements

Clinical

Overall summary

- Programmes examined were:
  - BGAT
  - BGAT-III
  - HyPOS
  - HAATT
  - DAFNE
  - BITES
  - de Weert et al.
  - Korhonen et al.
  - PRIMAS
  - Rossi et al., 2010
  - Rossi et al., 2013
  - Terent et al.
  - Trento et al., 2005
  - Trento et al., 2011
- Evidence was graded as moderate, low or very low for all the outcomes considered in the review.
- In a meta-analysis of RCTs comparing various programmes of structured education, there was no overall impact on HbA1c at 6 or 12 months of follow-up. The exception to this is DAFNE and PRIMAS, DAFNE resulted in a reduction in HbA1c difference of 1% (-1.42 to – 0.58%) at 6 months, and PRIMAS resulted in a reduction of 0.4% (-0.65 to -0.15), also at 6 months.
- Several programmes had a positive impact on severe hypoglycaemia when analysed individually. BGAT III, HAATT, Rossi 2013 and HyPOS showed a reduction in severe hypoglycaemia at 6 months, and BGAT and HAATT showed benefit also at 12months.
  - Of these three programmes, BGAT III encouraged the recruitment of people with severe hypoglycaemia (64% at baseline versus 47% in controls) while a history of severe hypoglycaemia was required of recruits to HAATT and HyPOS.
  - ~~o~~ DAFNE, which did not recruit people specifically with problematic hypoglycaemia, did not demonstrate a significant reduction in severe hypoglycaemia in its RCT, although there was no significant increase despite the fall in HbA1c.
  - BGAT III was also associated with improved hypoglycaemia awareness at 6 and 12 months, as did HyPOS at 6 months.
- Improved quality of life was demonstrated in DAFNE (ADDQoL- impact; DTSQ).
- When all the programmes are pooled together in meta-analysis, the studies showed no clinically significant benefit of structured education programmes versus control groups on all clinical and psychological outcomes except for:
  - At less than or equal to 6 months:
    - Severe hypoglycaemia – episodes every 6 months (favours structured education – evidence-based on BGATT III).
    - Severe hypoglycaemia – episodes per person, SD not given (favours structured education - evidence based on HAATT).

  - DTSQ total satisfaction (favours structured education – evidence based on ROSSI 2010)
  - ADDQoL- impact (favours structured education – evidence based on ROSSI 2010
  - Hypoglycaemia unawareness - % of patients with a greater recognition of low blood sugar (favours structured education – evidence based on BGATT III and HAATT)
  - Hypoglycaemia unawareness - HAQ (favours structured education - evidence based on HYPOS)
  - Knowledge - % of correct answers (favours structured education - evidence based on Korhonen)
- At 12 months:
  - Severe hypoglycaemia – episodes every 6 months (favours structured education – evidence based on BGATT III)
  - Severe hypoglycaemia – episodes per person, SD not given (favours structured education – evidence based on HAATT)
  - Hypoglycaemia unawareness - % of patients with a greater recognition of low blood sugar (favours structured education – evidence based on BGATT III)
  - Knowledge - % of correct answers (favours structured education – evidence based on Korhonen and Lennon)
  - Knowledge - GISED (favours structured education – evidence based on Trento 2005 and Trento 2011)

- However, the quality of evidence for all of these outcomes (at both 6 and 12 months), wasLow or Very low.
- However, when looking at the programmes individually, DAFNE and PRIMAS were the only programmes that showed some benefit on clinical outcome (HbA1c) which is clinically important versus a usual care control group DAFNE and PRIMAS show a difference, but the difference is lost when data from all the education programmes are pooled together.
  - Subgroup analyses at 6 months and 12 months:
    - When looking at the subgroup analyses of carbohydrate counting, the studies show that carbohydrate counting when combined with education is better for HbA1cat 6 months, but not at 12 months (the 12 months data was based on a small single study).
    - Studies with CHO counting in education versus no CHO counting showed benefit of education on HbA1c
    - Studies of education versus usual care showed benefit of education on HbA1c
    - Studies recruiting not solely hypoglycaemic patients showed benefit of education on HbA1c, but there is significant heterogeneity.

Economic

One cost-utility analysis found that DAFNE was cost effective compared with no DAFNE (ICER: £14,475 per QALY gained). This analysis was assessed as directly applicable with potentially serious limitations.

7.2.6 Recommendations and link to evidence

The current guideline recommendations can be found at

https://www.nice.org.uk/guidance/ng17

Relative values of different outcomes	The GDG were aware that in type 1 diabetes, as in many chronic diseases, education programmes can be shown to improve knowledge. They were particularly concerned with measures that produce benefit in terms of improved disease control. Not all of the educational programmes were designed with exactly the same aim in mind; for example, BGAT was designed specifically to combat major fluctuations in blood glucose, particularly episodes of hypoglycaemia, and did not incorporate some of the wider aspects of patient education which are featured in other programmes. The GDG felt that this had to be allowed for assessing the outcome measures. Overall, the GDG were interested in HbA1c as an objective measure of continuing glucose control and in improvements in quality of life. It was noted that single outcome measures could not be taken in isolation. For example, an intervention which lowers HbA1c levels is valuable, but if there is a simultaneous increase in hypoglycaemia, there may also be harm. Heterogeneity was noted in the outcome measures, which is readily apparent in the forest plots (Appendix J). Both the DAFNE and PRIMAS programmes produced statistically and clinically significant benefits in HbA1c which were not shown in any other individual study (except for Lennon 1990[450], which the GDG did not consider strongly because it was a very old study in only 74 people with an unusually high HbA1c of nearly 12%). This was apparent at the 6 month time point (and after 12 months in DAFNE when all patients in both arms of the trial continued on DAFNE - 12 month data only available for one arm). The DAFNE programme also showed benefits in some, but not all, components of the quality of life analysis. The BGAT programme was shown to improve hypoglycaemia unawareness. In a meta-analysis of RCTs comparing various programmes of structured education, there was no overall impact on HbA1c at the 6 or 12 month follow-up. The exception to this is DAFNE, which resulted in a reduction in HbA1c difference of 1% (-1.42 to 0.58%) at 6 months. Several programmes had a positive impact on severe hypoglycaemia when analysed individually. BGAT III, HAATT, [631] and HyPOS showed a reduction in severe hypoglycaemia at 6 months, and BGAT and HAATT showed benefit also at 12 months. Of these three programmes, BGAT III encouraged the recruitment of people with severe hypoglycaemia (64% at baseline versus 47% in controls) while a history of severe hypoglycaemia was required of recruits to HAATT and HyPOS. DAFNE, which did not recruit people specifically with problematic hypoglycaemia, did not demonstrate a significant reduction insevere hypoglycaemia in its RCT. BGAT III is also associated with improved hypoglycaemia awareness at 6 and 12 months, as well as HyPOS at 6 months. Improved quality of life was demonstrated in DAFNE (ADDQoL- impact; DTSQ).
Trade-off between clinical benefits and harms	The studies did not report any direct harms of educational programmes, nor is it expected that there would be any. The GDG discussed whether the programmes might increase anxiety levels in some patients with type 1 diabetes, but there was no evidence of this.
Economic considerations	The GDG considered the cost-effectiveness analysis of an education programme based on the DAFNE programme. This was an update of a previous analysis which showed that the DAFNE programme was highly cost effective. Although the ICER is much higher in the more recent ScHARR analysis, this analysis is based on national audit outcome data rather than data from an RCT which informed the earlier analysis, and the HbA1c reductions have been less in the audit than had been

	anticipated from the RCT results. Nonetheless, the ICER is still below the conventional NICE threshold of £20,000 per QALY and the GDG could therefore conclude that the DAFNE programme is a cost effective intervention. The ScHARR analysis assumed no impact of DAFNE on hypoglycaemia, although the DAFNE audit showed a reduction in severe hypoglycaemia.. Although there is no evidence for other education programmes, or for short or long courses, the GDG acknowledge that other courses of similar content, structure and criteria may also have the potential to be cost-effective.
Quality of evidence	GRADE analysis suggested that the data on structured education programmes is generally of low or very low quality. The main reasons for this were imprecision and also the heterogeneity between studies, but to some extent, this is understandable since the education programmes are all different, and in some cases have a particular primary focus, albeit there is overlap between the components. It was noted that the studies were typically performed with people who have had diabetes for a number of years. In general, the GDG felt that education should be offered to patients at a much earlier stage of diagnosis (and indeed, this is now what happens in practice). There are surprisingly few data on the use of the intervention at this time-point.
Other considerations	There is a strong impression amongst healthcare professionals that education is of value in type I diabetes, and people with type 1 diabetes naturally have a strong desire to be able to control the condition, so it was disappointing that results across the range of educational programmes were not unequivocally positive. In the broader educational programmes, the results of the DAFNE and PRIMAS studies were superior to others. The GDG were aware that DAFNE was a programme already used widely in the UK, whereas PRIMAS was a specific programme in Germany, and thus, DAFNE (along with its greater improvement in HbA1ccompared with PRIMAS) was considered to be the education programme of choice. The GDG debated whether their recommendation should specify that DAFNE alone could be employed. They were aware that there are other educational packages which appear to be useful but have not been formally studied. Educational programmes devised in research studies need to be examined for their outcomes in routine clinical practice. An audit of the DAFNE programme inclinical practice showed benefits on HbA1c, severe hypoglycaemia, hypoglycaemia awareness, well-being and psychological stress.[347] The GDG were also aware of evidence pertaining to follow-up education programmes and the importance of sustaining and providing ongoing support to patients, although, this was not the remit of this review. However, such studies show sustained improvement in outcomes (for example the DAFNE programme.[192]) Taking all of this into consideration, as well as the RCT evidence, the GDG decided that they should stipulate that structured education programmes had to fulfil the criteria of the NICE quality standards.[533] There was also a debate about when the programme should be offered. As already noted, the formal studies have been performed in patients with a relatively long duration of diabetes, but all members of the GDG felt that the programme should be offered earlier on. It was felt that the first few months post diagnosis are a period of considerable adjustment and that trying intensive education at this stage would be less worthwhile and even counter-productive. The overriding principal is that the programme should be undertaken when the person with diabetes feels ready to engage fully, but the consensus was that for most people it would be worthwhile enrolling in DAFNE (or similar) from a time point of 6-12 months post diagnosis.

1. **Carry out more formal review of self-care and needs annually in all adults with type 1 diabetes. Vary the agenda addressed each year according to the priorities agreed between the healthcare professional and the adult with type 1 diabetes. [2004, amended 2015]**

Specific recommendations on patient education and information-giving in particular aspects of care are given in individual sections of this guideline.

7.2.7 Research recommendations

3. **In adults with type 1 diabetes, what methods can be used to increase the uptake of structured education programmes and to improve their clinical outcomes (particularly achieving and sustaining blood glucose control targets)?**

Why this is important

Structured education programmes in flexible insulin therapy have been shown to improve diabetes control (lower HbA1c and less hypoglycaemia), but achieving and sustaining optimal diabetes control for avoidance of complications remains challenging. Some people do not achieve ideal targets for glycaemic control, others achieve but are not able tomaintain them, and still others are not offered or do not access structured education at all. There is therefore a need to develop and test (1) more effective ways of engaging adults with type 1 diabetes in education; (2) improvements in the delivery of education to increase the number of people achieving targets for diabetic control and (3) enhanced support for adults with type 1 diabetes to sustain good diabetic control over time. If the uptake and delivery of clinically and cost effective education and support for adults with type 1 diabetes can be improved, it should be possible to achieve a reduction in the short-term and long-term complications of the condition.

4. **In adults with newly diagnosed type 1 diabetes, what is the optimal timing and method of delivering structured education in terms of clinical and cost-effectiveness?**

7.3 Dietary management

This section was updated in 2015.

The 2015 GDG reviewed evidence in two areas that were not covered in 2004: Carbohydrate counting and GI diets. All other recommendations on dietary management from 2004 have been retained. The dietary management content from 2004 can be found in Appendix S.

7.3.1 Introduction to new evidence reviews on carbohydrate counting and GI diets [2015]

Carbohydrate is the macronutrient that has the greatest impact on glycaemic control. Carbohydrates include starches and sugars which are converted during the digestive process to glucose, the main purpose of which is to provide energy for the body. Starches are either oligosaccharides or polysaccharides, and are found in foods, such as bread, pasta, rice and potato. Sugars are either monosaccharides, such as glucose and fructose, or disaccharides, such as sucrose and lactose.

In the past it was largely assumed that sucrose-based carbohydrate foods had the largest impact on post-prandial blood glucose. It is now well established that the total carbohydrate or the glycaemic load is the main predictor of the rise in blood glucose levels postprandially.[390] Traditionally, people with diabetes were taught to estimate the carbohydrate content of food to be eaten, so that carbohydrate quantities could be prescribed for each meal to match insulin doses.

In modern diabetes management, insulin regimens, such as multiple daily insulin injections (MDI) or continuous subcutaneous insulin infusion (CSII), deliver basal (to control the body's own glucose production) and meal-related insulin replacement. For the latter, people with type 1 diabetes are taught to estimate or 'count'the carbohydrate in food to be eaten and adjust the insulin dose for the proposed meal accordingly, using individual insulin-to-carbohydrate ratios to estimate the insulin dose.[185]Accurate carbohydrate counting is key to the success of such flexible regimens, while for patients who are on fixed meal doses in a MDI regimen or still using twice-daily pre-mixed insulin, it is important to have consistent quantities of carbohydrate at every meal time. For the latter, it is also

advantageous to keep the timings of meals consistent. In all these circumstances, people with diabetes need to be trained in carbohydrate counting. This is often incorporated into structured education programmes that aim to cover many aspects of insulin self-management, however, carbohydrate counting skills are often taught as a stand-alone topic. Carbohydrate counting can be taught in a one-to-one consultation by a Diabetes Specialist dietitian, by e-learning[184,185] or by attending a structured education course (see Section7.2).

Almost all current meal-related insulin regimens are based on matching insulin dose to quantities of carbohydrate eaten. It follows that, if less carbohydrate is consumed, with a larger part of the diet coming from protein and fat, less insulin will be required. There have been suggestions that even in today's era of "normalising", the diet for the adult with type 1 diabetes, restricting but not omitting carbohydrate intake may improve diabetic control, particularly if the person with type 1 diabetes is overweight.

Prandial insulin doses are given to maximise the match between the rise of insulin in the circulation and the rise in blood glucose after the meal. The blood glucose profile from carbohydrate consumed is influenced by the nature of the carbohydrate containing food to be eaten. The 'glycaemic index' or GI of a food describes the area under the blood glucose curve after its consumption in comparison to a standard unit, such as one slice of white bread. Foods with a low GI are thought to facilitate diabetes control as the blood glucose response is slower to rise and fall, and in theory, easier to control with injected insulin. However, the GI of a food varies with method of preparation and with other foods consumed at the same time in a mixed meal, making the value of GI estimation as a major dietary intervention less easy to predict.

This chapter aims to address these questions:

- In adults with type 1 diabetes, what is the clinical and cost-effectiveness of carbohydrate counting or restriction for optimal diabetic control?
- In adults with type 1 diabetes, what is the clinical and cost-effectiveness of a diet based on the GI for optimal diabetic control?

7.3.2 Review question: In adults with type 1 diabetes, what is the clinical and cost-effectiveness of carbohydrate counting or restriction for optimal diabetic control?

For full details see review protocol in Appendix C.

Table 12: PICO characteristics of review question

Population	Adults with type 1 diabetes
Intervention/s	Carbohydrate counting/restriction (this may involve technology, such as a bolus calculator)
Comparison/s	• Placebo • Usual care/no carbohydrate counting • Manual carbohydrate counting (if the intervention is carbohydrate counting using a technology)
Outcomes	• HbA1c • Hypoglycaemia • Severe hypoglycaemia • Nocturnal hypoglycaemia • Quality of life (continuous) • Adverse events
Study design	RCTs, observational studies • Unit of randomisation: individual patient

7.3.3 Clinical evidence

This review was divided into studies that compared:

- Carbohydrate counting versus no carbohydrate counting
- Carbohydrate counting using technology (such as a bolus calculator) versus manual carbohydrate counting

Four studies were included in the first part of this review [189,436,651,656]. Three of the studies[436,651,656] were RCTs comparing patient carbohydrate counting with no carbohydrate counting. The fourth study[189] was an observational study (prospective case-series) of a prescribed diet and prescribed insulin doses and regime based on carbohydrate counting. Evidence from all the studies is summarised in Appendix G. Evidence from the three RCTs is summarised in the clinical GRADE evidence in Appendix I. See also the study selection flow chart in Appendix D, forest plots in Appendix J, study evidence tables in Appendix G and exclusion list in Appendix K.

There were no data reported in any of the studies for the following outcomes:

- Nocturnal hypoglycaemia
- Adverse events.

Eight studies[58,95,235,397,406,487,656,805] were identified and included for the second part of the review which compared carbohydrate counting using technology (such as a bolus calculator) versus manual carbohydrate counting. Three of the studies[487,656,805] were RCTs comparing carbohydrate counting with the use of a bolus calculator with manual carbohydrate counting. Evidence from these three RCTs is summarised in the clinical GRADE evidence in Appendix I. See also the forest plots in Appendix J. The remaining 5 studies[58,95,235,397,406] were observational studies, and therefore were not able to be combined in a meta-analysis or GRADE profile, and were graded as Low quality (due to their study design). However, a summary of the quality and limitations of these studies can be found in Appendix G. The study details and the full results have been summarised in tables below.

For the comparison of bolus calculators versus manual carbohydrate counting there were no data reported in any of the studies for the following outcomes:

- Nocturnal hypoglycaemia
- Adverse events.

Table 13: Summary of studies included in the review: Carbohydrate counting versus no carbohydrate counting

Study	Intervention	Comparison	Population	Follow-up	Outcomes
RCTs					
SCHMIDT 2012 RCT	CarbCount	CarbCount Automated Bolus Calculator (CarbCount ABC) and control (no carb count)	Type 1 diabetes n=63 (n=8 control, n=21, CarbCount; n=22, CarbCount Automated Bolus Calculator)	16 weeks	ABC CarbCount and CarbCount were SS better than no carb counting for: HbA1c (final values; ABC: 8.1±0.4%; CC: 8.4±0.9%; CHO alone 8.9±1.1%; ANOVA P=0.029) DTSQ There was NS difference between the groups for: • Severe hypoglycaemia • HFS score • PAID score • ADDQOL score
LAURENZI 2011 RCT	CHO counting	No CHO counting	n=61 Adults aged 18-65 years with Type 1 diabetes SCII for >3 months No previous training in CHO counting **SCII (Glulisine, Lispro or Aspart)** **SMBG 6-times daily**	24 weeks (training during first 12 weeks in intervention group)	CHO counting group was SS better than no CHO counting group for: DSQOLS diet restrictions score (change score; median 5.5 vs. 0) There was NS difference between the groups for: HbA1c (change from baseline; P=0.252) using ACA (Note: not enough data reported for forest plot). Severe hypoglycaemia (no events observed during the study) Frequency of mild hypoglycaemic events (BG 2.8 mmol/litre) using ACA (Note: not enough data reported for forest plot) DSQOLS (social relations score, leisure-time score, physical complaints score, future worries score, daily hassles score, hypoglycaemia fears score)
SCAVONE 2010 RCT	CHO counting	No carb counting	n=256 Type 1 diabetes duration >5 years No subjects had followed any dietetic or educational programme previously	9 months (nutritional education programme and CHO count training 4 weeks	CHO counting group was SS better than no CHO counting group for: HbA1c (change from baseline) using ACA CHO: Baseline 7.8±1.3%; 9 months 7.4±0.9% Control: Baseline 7.5±0.8%; 9 months 7.5±1.1% Note: not enough data reported to present as change scores, presented as final values on forest plot.

Study	Intervention	Comparison	Population	Follow-up	Outcomes
			Evening basal insulin and SA insulin at meal times **SMBG 6-times daily**	preceding in intervention group)	Frequency of mild hypoglycaemic events (BG <3.9 mmol/litre; CHO: 4%; control: 7%) using ACA
Non-randomised trials					
DIAS 2010 Observational: prospective case-series	Diet and insulin doses prescribed based on CHO counting	Baseline	n=55 Mainly adults (10-60 years) Type 1 diabetes (ADA criteria) Evening basal NPH insulin and SA insulin at meal times **No SMBG during study**	3 months	3 month follow-up was SS better than baseline for: HbA1c (baseline 10.40±0.33%; 3 months 9.52±0.32%; P=0.0009) 38/51 patients had a reduction in HbA1c from baseline; 11/51 patients had an increase in HbA1c from baseline and 2/51 patients had no change. Note: patients not SMBG or carb counting themselves during study

Table 14: Carbohydrate counting using bolus calculator or other technology versus manual carbohydrate counting

Study	Intervention	Comparison	Population	Follow-up	Outcomes
Carbohydrate counting with bolus calculator					
MAURIZI 2011 RCT	Calsulin bolus calculator	CHO counting	n=40 Adults aged 16-65 Type 1 diabetes (ADA definition) Type 1 diabetes duration ≥1 year	6 months	Calsulin group was SS better than CHO counting alone group for: HbA1c (6 months; change scores; calsulin -0.85%; CHO alone -0.07%) There was NS difference between the groups for: HbA1c (3 months; final values; calsulin 7.3±0.5%; CHO alone 7.7±1.0%) Frequency of hypoglycaemic events (Not enough data reported for forest plot and GRADE – only stated no SS difference between groups)
SCHMIDT 2012 (same as above) RCT	CarbCount Automated Bolus Calculator (CarbCountABC)	CarbCount and control (no carb count)	Type 1 diabetes n=63 (n= n=8 control, n=21, CarbCount; n=22, CarbCount Automated Bolus Calculator)	16 weeks	ABC CarbCount and CarbCount were SS better than no carb counting for: HbA1c (final values; ABC: 8.1±0.4%; CC: 8.4±0.9%; CHO alone 8.9±1.1%; ANOVA P=0.029) DTSQ There was NS difference between the groups for: • Severe hypoglycaemia • HFS score • PAID score

					• ADDQOL score
ZIEGLER 2013 RCT	Carb counting (BG meter with bolus calculator)	Manual carb count (standard BG meter with manual bolus calculation)	Type 1 diabetes and type 2 diabetes (93% Type 1 diabetes) on MDI treatment n=218	26 weeks	Bolus calculator was SS better than manual CHO counting group for: QOL (DTSQ; 8 questions of 7-point scale; BC 11.4±6.0; CHO alone 9.0±6.3) Manual CHO counting group was SS better than bolus calculator group for: Mild Hypoglycaemia (no. of patients <70 mg/dl; BC 43/105, CHO alone 31/113) There was NS difference between the groups for: HbA1c (change scores; BC -0.7±0.7%; CHO alone -0.5±0.7%) Severe hypoglycaemia (no. of patients <36 mg/dl or 3rd party; BC 11/105, CHO alone 7/113)
KLUPA 2008 Observational retrospective cohort study	Bolus calculator	No BC (trained in CC)	n=18 Type 1 diabetes Treated with CSII Trained in food counting (including carb, protein and lipid counting and GI estimation)	Bolus calculator provided 9 months previously	There was NS difference between the groups for: HbA1c (final values; BC 6.8%; CHO alone 7.0%). Hypoglycaemic episodes/day (CMBG n=3 in each group; BC 1.4; CHO alone 1.6)
FRANC 2009 Observational prospective case-series	Phone bolus calculator for FIT CHO counting	CHO counting using FIT	n=35 Type 1 diabetes duration ≥1 year Use of CHO counting using flexible intensive insulin therapy (FIT) for at least 6 months **SCII or MDI**	4 months	Use of bolus calculator was SS better than baseline (CHO counting alone) for: HbA1c(change scores; baseline 7.8±0.9%; 4 months 7.3±0.6%) There was NS difference from baseline for: Mild hypoglycaemic events at 12 weeks (BG<3 mmol/litre; events/individual/week; Baseline 1.4; 12 weeks 0.8) Patients reported to vary CHO content from one day to the next and enjoy dietary freedom
Carbohydrate counting using other technologies					
BAO 2011 RCT crossover	FII algorithm + CHO counting to calculate insulin dose (lab test meal)	CHO counting alone to calculate insulin dose (lab test meal)	• n=31 • Adults aged ≥18 and ≤70 • Type 1 diabetes duration ≥1 year • HbA1c ≤9%	3 hours after each test meal	• FII group was SS better than CHO counting alone group for: ○ Time within normal BG (4-10mmol/l) in 3 hour post-prandial period • There was NS differencebetween the groups for: ○ Severe hypoglycaemia (3 hour post-prandial period; no events in either group) ○ Mild hypoglycaemic episodes (3 hour post-prandial period; FII 6 episodes;

			Use of SCII (including bolus calculator) for ≥2 months and reliable SMBG 4-times daily		CHO alone 1 episode)
KILBRIDE 2011 Cohort study (prospective)	CHO counting algorithm developed considering exercise (lab test exercise session)	self-management (patients experienced in CHO counting; lab test exercise session)	• n=14 • Adults (20-50 years) • Type 1 diabetes duration > 2 years • HbA1c<10% • Experienced in CHO counting by education **Basal–bolus insulin regime**	2 weeks (week 1: self-management; week 2: CHO/exercise algorithm	• Exercise algorithm + CHO counting was SS better than CHO counting alone for: ○ Duration of hypoglycaemia during 40 exercise session (<4mmol/l) ○ Duration of hypoglycaemia during 6-hour post exercise period (<4mmol/l) • Mild hypoglycaemic episodes (episodes/week; self-reported) ○ Algorithm: 2; CHO counting alone: 18 (on exercise days) ○ Algorithm: 27; CHO counting alone: 34 (on non-exercise days) • There was NS differencebetween the treatments for: Severe hypoglycaemic episodes (no events during either treatment)
BRAZEAU 2013 Cross-sectional study (accuracy of patient CHO estimates in CHO counting)	Patient estimate of CHO	Dietitian assessment of CHO	• n=50 • Adults ≥18 years • Type 1 diabetes duration >6 months • Had worn a CGM for 72 hours and had concomitantly assessed CHO content in food diary in >75% meals • SCII (n=10), basal insulin and MDI (n=39), intermediate NPH bedtime insulin (n=1) SA insulin at meal times	72 hours (patient estimates of CHO content and dietitian assessment of CHO content from food diary compared over 72 hours)	• Lower accuracy of patient CHO content estimates was a predictor of shorter time spent within normal BG range (4-10 mmol/litre) and longer time spent in hyperglycaemia (>10 mmol/litre).

Table 15: Clinical evidence summary: Carbohydrate counting versus no carbohydrate counting

Outcome	No. of studies	Imprecision	GRADE rating	Absolute difference	Control event rate (per 1000)	Control group mean
HbA1c						
>6 months	1	None	LOW	MD 0.1 lower (0.41 lower to 0.21 higher) MD 0.4 lower (change score[a])	-	7.5±1.1% (final value) 0% change score[a]
≤6 months	1	Serious	MODERATE	MD 0.5 lower (1.35 lower to 0.35 higher)[b]	-	8.9±1.1%
Mild hypoglycaemia						
>6 months	1	Very serious	VERY LOW	30 fewer per 1000 (from 59 fewer to 73 more)	71 per 1000	-
Severe hypoglycaemia						
≤6 months	2	Very serious	LOW	15 fewer per 1000 (from 58 fewer to 393 more)	63 per 1000	-
DSQOLS ≤6 months						
Diet restrictions	1	Serious	LOW	SS higher (p=0.008 reported; median change score 5.5 vs. 0)	-	Median change score (IQR) 0 (-2 to 3.5)
Social relations; Leisure-time flexibility; Physical complaints; Worries about future; Daily hassles	1	Serious	LOW	NS difference between groups	-	
Hypoglycaemia fear survey (transformed onto 0-100 scale; higher scores indicate more fear)						
≤6 months	1	Very serious	VERY LOW	MD 1.7 lower (15.62 lower to 12.22 higher)	-	24.5±18.2
Problem areas in diabetes questionnaire (transformed onto 0-100 scale; higher scores indicate more problems)						
≤6 months	1	Very serious	VERY LOW	MD 0.8 higher (14.6 lower to 16.2 higher)	-	27.2±18.8
Audit of Diabetes Dependent QOL questionnaire (range of scores -9 to 9; higher values indicate better QOL)						
≤6 months	1	Very serious	VERY LOW	MD 0.4 lower (1.33 lower to 0.53 higher)	-	-1.4±0.9
Diabetes Treatment Satisfaction Questionnaire (range of scores: 0-36; Better indicated by higher values)						
≤ 6 months	1	Serious	LOW	MD 2.1 lower (6.47 lower to 2.27 higher)	-	28.5±5.1

(a) Reported as SS difference (p<0.01) between groups for change score (not enough data provided to report change score and CI in meta-analysis and GRADE)

(b) HbA1c change scores reported as NS different between groups for Laurenzi 2011 but not enough data reported from Laurenzi 2011 to include data in meta-analysis. Observational before and after study (Dias 2010) 3 month follow-up was SS better than baseline (baseline 10.40±0.33%; 3 months 9.52±0.32%; p=0.0009)

Table 16: Clinical evidence summary: Bolus calculator versus manual carbohydrate counting

Outcome	No. of studies	Imprecision	GRADE rating	Absolute difference	Control event rate (per 1000)	Control group mean
HbA1c						
≤6 months	3	No serious imprecision	MODERATE	MD 0.25 lower (0.41 to 0.08 lower)[(a)]	-	8.1%
Mild hypoglycaemia						
≤6 months	1	Serious	LOW	134 more per 1000 (from 5 more to 323 more)	274 per 1000	-
Severe hypoglycaemia						
≤6 months	2	Very serious	VERY LOW	41 more per 1000 (from 26 fewer to 192 more)	79 per 1000	-
Hypoglycaemia fear survey(transformed onto 0-100 scale; higher scores indicate more fear)						
≤6 months	1	Very serious	VERY LOW	MD 0.2 lower (9.34 lower to 8.94 higher)	-	22.8
Problem areas in diabetes questionnaire (transformed onto 0-100 scale; higher scores indicate more problems)						
≤6 months	1	Serious	LOW	MD 2.4 lower (12.81 lower to 8.01 higher)	-	28.0
Audit of Diabetes Dependent QOL questionnaire (range of scores -9 to 9; higher values indicate better QOL						
≤6 months	1	Very serious	VERY LOW	MD 0 higher (0.96 lower to 0.96 higher)	-	-1.8
Diabetes Treatment Satisfaction Questionnaire (range of scores: 0-36; Better indicated by higher values)						
≤6 months	1	Serious	LOW	MD 5.10 higher (2.19 to 8.01 higher)	-	26.4

(a) Klupa 2008 observational cohort study reported a NS difference between groups for HbA1c. Franc 2009 observational before and after study reported HbA1cwas SS lower at 4 months after using bolus calculator (baseline 7.8±0.9%; 4 months 7.3±0.6%)

7.3.4 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow diagram in Appendix C.

Unit costs

Table 17: Cost of hospital dietitians

Cost	Band 5	Band 6	Band 7
Cost per hour[a]	£34[b]	£43[c]	£55[c]

(a) Including qualification costs
(b) From PSSRU 2012[159]
(c) Calculated using NHS Staff Earning Estimates in PSSRU 2012[159]

Table 18: Cost of 'stand-alone carbohydrate counting' course

Staff costs[a]	Number of patients on course	Incremental cost per patient[b]	Incremental QALY gain required[b,c]
£343	4	£86	0.00429
	8	£43	0.00214
	12	£29	0.00143

(a) Assuming 3.5 hours (3 hours to deliver course; 0.5 hours of preparation, set up and take down) of a band 6 and a band 7 dietitian.
(b) Compared with no carbohydrate counting course.
(c) To be cost-effective at a £20k per QALY threshold.

7.3.5 Evidence statements

Clinical

Carbohydrate counting versus no carbohydrate counting

Moderate, low and very low quality evidence, mainly from single studies, showed a clinical benefit of carbohydrate counting for HbA1c(change from baseline) at up to 6 months and over 6 months, and mild hypoglycaemia at over 6 months. There was also a clinical benefit for severe hypoglycaemia and the DSQOLs domain of diet restrictions both at up to 6 months.

Low and very low quality evidence from single studies showed no clinical benefit of carbohydrate counting for HbA1c(final values) at over 6 months, and for the QoL scores of DSQOLs (other domains), PAID, ADDQOL, Hypoglycaemia fear survey, and DTSQ all up to 6 months

Low quality evidence from a single observational study (case-series/before and after study) showed that compared with baseline, there were improvements in HbA1c after patients used carbohydrate counting.

Carbohydrate counting using a bolus calculator versus manual carbohydrate counting

Low quality evidence from a single study showed a clinical benefit of bolus calculators for DTSQ at up to 6 months.

Moderate quality evidence from three studies showed a borderline clinical benefit of bolus calculators for HbA1c at up to 6 months.

Low and very low quality evidence from a single study and from two studies showed clinical harm of bolus calculators for mild hypoglycaemia, and severe hypoglycaemia at up to 6 months.

Low and very low quality evidence from single studies showed no clinical benefit of bolus calculators for mild hypoglycaemia, and severe hypoglycaemia at up to 6 months; and for the QoL scores of Hypoglycaemia fear survey, PAID, ADDQOL, and DTSQ at up to 6 months.

Low quality evidence from a single observational study (retrospective cohort) showed no difference between using a bolus calculator to assist carbohydrate counting and manual counting for HbA1c, and number of hypoglycaemic episodes/day (at more than 6 months).

Low quality evidence from an observational study (a case-series/before and after study) which showed that compared with baseline (manual carbohydrate counting), using a bolus calculator to assist with carbohydrate counting led to improvements at 12 weeks in HbA1c, but no improvement in the number of mild hypoglycaemic events experienced /individual/week.

Economic

No relevant economic evaluations were identified.

7.3.6 Recommendations and link to evidence

The current guideline recommendations can be found at

https://www.nice.org.uk/guidance/ng17

Relative values of different outcomes	The GDG determined the impact of carbohydrate counting regimens and bolus calculators on clinical outcomes in adults with type 1 diabetes, by assessing their impact on the following clinical outcomes: • Improvement in glycaemic control; assessed by reduction in HbA1c. • Incidence of hypoglycaemia, with particular focus given to: • Incidence of severe hypoglycaemia (hypoglycaemia event requiring help from a third party for correction), an event which has been recognised as having a significant impact on quality of life in patients with type 1 diabetes. • Incidence of nocturnal hypoglycaemia. • Quality of life: the evidence was reviewed to look at the impact of carbohydrate counting and bolus calculator use on quality of life outcomes. • Adverse events: the literature was reviewed for any adverse events related to teaching and use of carbohydrate counting and bolus calculators.
Trade-off between clinical benefits and harms	**Carbohydrate counting regimens** The evidence for the use of carbohydrate counting regimens outside of structured education courses was reviewed. **Impact on glycaemic control** One study [651] reported a 0.4% reduction in HbA1c at >6 months with the intervention of carbohydrate counting, but it was noted that the HbA1c of the control group was lower at the start of the study compared with the intervention group (7.5 % versus 7.8 %). A second study with <6 months follow-up did report a significant reduction in HbA1c with carbohydrate counting .[656]

Impact on frequency of hypoglycaemia

One study showed that mild hypoglycaemic episodes were reduced with the introduction of carbohydrate counting.[651] For severe hypoglycaemic episodes, an absolute difference of 15 fewer episodes per 1000 patient-years was thought to be of clinical significance, although, statistical significance was not attained and numbers within the individual studies were small. One small study reported that the frequency of severe hypoglycaemia episodes was reduced in the carbohydrate counting group. [656]A third study[436] reported no episodes of severe hypoglycaemia in both the educated and non-educated groups. There were no data available from any of the studies about the impact of carbohydrate counting regimens on the incidence of nocturnal hypoglycaemia.

Impact on quality of life

One study reported that individuals with the ability to carbohydrate count felt less restricted in their daily dietary intake [436], but other studies indicated no impact of carbohydrate counting on the Hypoglycaemia Fear Survey (HFS), Problems Areas In Diabetes (PAID), Audit of Diabetes-Dependent Quality of Life (ADDQoL) and Diabetes Treatment Satisfaction Questionnaire (DTSQ) scores.

Impact on adverse events

There were no data available for non-hypoglycaemia adverse events from any of the studies assessing the impact of carbohydrate counting regimens on clinical outcomes.

Use of bolus calculators:

The evidence for the use of bolus calculators used withself-monitoring of blood glucose levels was reviewed.

Impact on glycaemic control

Three studies reported a reduction in HbA1c with use of a bolus calculator in place of manual counting[487,656,805]. However, the mean reduction in HbA1c achieved at <6 months (0.25 %) was <0.3 % and not felt to be significant by the GDG.

Impact on frequency of hypoglycaemia

For studies assessing the impact of bolus calculator use on the incidence of hypoglycaemia, the mean incidence of mild and severe hypoglycaemia was higher with bolus calculator use compared with manual counting. There were no data available from any of the studies about the impact of bolus calculators on the incidence of nocturnal hypoglycaemia.

Impact on quality of life

One study reported that bolus calculator use improved DTSQ scores.[656] However, other studies indicated no impact of bolus calculator use on HFS, PAID and ADDQoL scores.

Impact on adverse events

There were no data available for non-hypoglycaemia adverse events from any of the studies assessing the impact of bolus calculators on clinical outcomes.

From a review of all of the available evidence, the GDG concluded that there was evidence to suggest a benefit of carbohydrate counting regimens taught outside of structured education courses for the management of type 1 diabetes. However, the GDG also recognised that evidence available from structured education programme reviews indicated that the effectiveness of carbohydrate counting teaching was likely to be improved when incorporated into structured education courses for the

	management of type 1 diabetes, with greater and more sustained improvements in glycaemic control, incidence of hypoglycaemia and quality of life. The use of bolus calculators was associated with an improvement in glycaemic control, but an increased incidence of hypoglycaemia. The GDG recognised that the current evidence base for bolus calculators referred to trials where participant numbers were small; therefore a research recommendation was made requesting further evidence for the assessment of bolus calculators in adults with type 1 diabetes.
Economic considerations	No economic evaluations about the use of carbohydrate counting regimens outside of structured education courses or bolus calculators in the management of adults with type 1 diabetes was available for review. Consultation amongst healthcare professionals within the GDG concluded that a three and a half hour education session from a dietitian could be reasonably recognised as sufficient time to educate adults with type 1 diabetes on carbohydrate counting regimens (half an hour for course set-up followed by three hours education). Dietitian costs for a three and a half hour education session were calculated to be £343 per session, based on a band 6 and a band 7 dietitian. Cost per patient per session was reduced with increasing numbers of patient per session (£86 for 4 adults, £43 for 8 adults and £29 for 12 adults). The GDG believed that education could be reasonably delivered to 8 adults at a single session; groups larger than this could result in a detriment in the quality of the education and time available for each course attendee. Cost per attendee per session was therefore calculated at £43 per individual: at this level of cost, the improvement in quality of life per individual achieved by the education session would only have to be small to be cost-beneficial. The GDG concluded that carbohydrate-counting courses were cost-beneficial for adults with type 1 diabetes.
Quality of evidence	The impact of carbohydrate counting regimens used outside of structured education courses for adults with type 1 diabetes were assessed in the evidence review. Three studies ([656,436,651]) were randomised controlled trials (RCTs) comparing the impact of carbohydrate counting on outcomes versus no carbohydrate counting, and one study was a before and after observational study ([189]) assessing the clinical impact of a prescribed diet and prescribed insulin doses regimen based on carbohydrate counting. Eight studies[95,235,487,805,656,58,397,235,406]) did not compare carbohydrate counting with a control group but reported methodologies (technologies or additional algorithms) to assist patient carbohydrate counting and they were therefore included in the evidence review for carbohydrate counting. Three of these studies[487,805,656] were RCTs comparing carbohydrate counting with the use of technology (a bolus calculator) vs. manual carbohydrate counting (without technology). This evidence was also used to assess the impact of bolus calculators on clinical outcomes in adults with type 1 diabetes. The GRADE quality of the assessed studies ranged from moderate to very low, and the potential for risk of bias was considered to be serious to very serious. The GDG noted that many of the available studies were small in size (largest study [651]; 256 participants) and of short duration (longest follow-up [651]; 9 months).
Other considerations	The available evidence for the use of bolus calculators in the management of type 1 diabetes had a substantial overlap with that of the use of carbohydrate counting, and therefore the GDG considered the impact of each in a single set of recommendations, as the evidence for bolus calculators was inextricably linked with that of carbohydrate counting outcomes. The GDG also recognised that correct use of bolus calculators was likely to be highly dependent on the level of education delivered to an individual from a preceding carbohydrate counting course.

	The evidence reviewed by the GDG for the use of bolus calculators did not include evidence for their use in conjunction with insulin pump therapies, and only considered their impact on clinical outcomes when used with self-monitoring of blood glucose levels in adults with type 1 diabetes using multiple daily injections of insulin. The GDG noted that any recommendations made about the use of bolus calculators should not stop individuals on continuous subcutaneous insulin infusions using bolus calculators built into insulin pump devices. The GDG found no evidence about when carbohydrate counting education should occur in individuals with type 1 diabetes. Members of the GDG recognised that ideally some carbohydrate-counting education should be provided soon after a diagnosis of type 1 diabetes, so that the individual understand the relationship between bolus insulin and carbohydrate intake. However, the GDG also recognised that some individuals may be overwhelmed by carbohydrate-counting education whilst coming to terms with a new diagnosis of type 1 diabetes. In addition, some of the benefits of carbohydrate counting education may not be fully realised if education was provided during the honeymoon period, when good glucose control might be achieved even without accurate carbohydrate counting. The GDG concluded that there was insufficient evidence to make a recommendation as to when carbohydrate counting education should take place, and that timing and depth of education was likely to be based on an individual's personality and needs. The GDG recommended that carbohydrate counting be given as part of a structured education course, as carbohydrate counting education delivered in this way was more likely to have greater benefit to an individual with diabetes than carbohydrate counting education on its own. However, the GDG also recognised that there may be circumstances where access to a structured education course might be limited or delayed, and that early carbohydrate counting education alone could be of benefit to adults with type 1 diabetes willing to make lifestyle changes. The GDG therefore made an additional recommendation to provide guidance on providing carbohydrate counting education outside of structured education courses in these circumstances. Bolus calculators can be a useful addition to a patient's own carbohydrate-counting. They remove much of the burden of dose and correction calculation, especially for patients using more varied or more precise ratios. Additionally bolus calculators can assist patients who have difficulty with mental arithmetic. However the GDG felt that it is important to recognise that a bolus calculator's effectiveness relies on carefully adjusted settings, ratios and blood glucose targets, and ability to carbohydrate count accurately. These are usually established with the help of skills learned in structured education, or in intensive one-to-one consultation with a suitably trained healthcare professional. It is also important for patients to realise that these settings should be regularly reviewed and updated to take account of changing circumstances.

7.3.7 Research recommendation

5. In adults with type 1 diabetes, what is clinical and cost effectiveness of bolus calculators used in conjunction with self-monitoring blood glucose meters?

7.3.8 Review question: In adults with type 1 diabetes, what is the clinical effectiveness of a diet based on the glycaemic index for optimal diabetic control?

For full details see review protocol in Appendix C.

Table 19: PICO characteristics of review question

Population	Adults with type 1 diabetes
Intervention(s)	High GI diet

Population	Adults with type 1 diabetes
Comparison(s)	Low GI diet
Outcomes	• HbA1c • Severe hypoglycaemia • Nocturnal hypoglycaemia • Quality of life • Patient satisfaction • Adherence
Study design	RCTs

7.3.9 Clinical evidence

Five studies (one non-randomised crossover study and four crossover randomised controlled trials) were included in the review[112,232,431,495,753] and these are summarised in Table 20 below. Evidence from these studies is summarised as a GRADE table in Appendix I. See also the study selection flow chart in Appendix D, forest plots in Appendix J, study evidence tables in Appendix G, and excluded studies list in Appendix K.

Table 20: Summary of studies included in the review

Study	Intervention versus comparison	Study design; Population	Critical outcomes reported	Comments
Calle-Pascual 1988[112]	Low GI diet (GI range: 29 – 36) vs. High GI diet (GI range: 50 – 02)	Non-randomised crossover study 4 weeks treatment Type 1 diabetes mean age = 25.6 ± 4.3 years Type 1 diabetes (n=16) and type 2 diabetes (n=18) Baseline insulin regimen: 2 daily doses (fast and delayed action) Mean insulin dose - unit per day (SD): 40 ± 16	HbA1c	The results for type 1 diabetes participants were reported separately from those of type 2 diabetes participants. The relatively low mean age implies that the population may include children and young people (<18 years old) but this is not stated.
Fontvieille[232] 1992	Low GI diet (GI mean ± SD: 38 ± 5) vs. High GI diet (GI mean ± SD: 64 ± 3)	Crossover RCT 5 weeks treatment Type 1 diabetes mean age = 42.7 ± 10.3 years Type 1 diabetes (n=12) and type 2 diabetes (n=6) Baseline insulin regimen: 2 – 3 injections per day (type 1 diabetes only) Mean insulin dose - unit per day (SD): 40.9 ± 12.8	HbA1c	The results were of both the type 1 diabetes and type 2 diabetes participants combined, but it is noted that there were no statistically significant differences between the two groups for any of the outcomes.
Lafrance[431] 1998	Low GI (GI <60) vs. Intermediate GI (GI 60 – 90) vs. High GI	Crossover RCT 12 days treatment Mean age not reported Type 1 diabetes only (n=9) Baseline insulin regimen: Intensive insulin therapy for ≥3 months with either multiple subcutaneous insulin injections (n=5) or continuous subcutaneous insulin infusion	Severe hypoglycaemia	The participants are said to be highly motivated and had well-controlled diabetes.

Study	Intervention versus comparison	Study design; Population	Critical outcomes reported	Comments
	(GI >90) vs. High fibre (GI 60 – 90 + ≥40 g fibre/day)	with multiple basal rates and pre-meal boluses (n=4) Mean insulin dose – unit per day (SD): not reported		
McCulloch[495] 1985	New diet (ND) (high carb + high fibre + low fat) vs. Continuation of current diet (CD)	RCT >6 months treatment Mean age = 35 years (Range 17 – 64) Type 1 diabetes only (n=40) Baseline insulin regimen: short and intermediate acting insulin given 30 minutes before breakfast and 30 minutes before the evening meal Mean insulin dose – unit per kg per day: ND 0.67 ± 0.03 vs. CD 0.88 ± 0.08	HbA1c Adherence to treatment	The final values were measured at different time points (intervention group at 10 months and control group at 6 months) and therefore caution should be taken when comparing the outcomes.
Venhaus[753] 1998	Unrefined carbohydrate diet (fibre-rich = low GI) vs. Refined carbohydrate diet (fibre-depleted = high GI)	Crossover RCT 6 weeks treatment Mean age = 27 ± 9 years Type 1 diabetes only (n=10) Baseline insulin regimen: continuous subcutaneous insulin infusion for >1 year Mean insulin dose – unit per day: 41.7 ± 6.9	HbA1c Severe hypoglycaemia	It was reported that the overall intake of carbohydrate and hence, energy was lower in the intervention group than in the comparison group. The difference in daily energy intake between the two groups was significant (p=0.04). The mean age is also relatively low, and there may have been children or young people, but this is not clearly stated.

Table 21: Evidence summary table: Low GI diet versus high GI diet

Outcomes	Number of studies	Imprecision	GRADE rating	Absolute difference Low GI diet	Final value for control group High GI diet
HbA1c at ≤6 months (Non-RCT)	1 study (n=24)	Serious	VERY LOW	MD 0.25 higher (from 0.09 to 0.59 higher)	9.02
HbA1c at ≤6 months (RCT)	2 studies (n=56)	No serious imprecision	LOW	MD 0.36 higher (from 0.14 lower to 0.86 higher)	Study 1 = 8.3 Study 2 = 5.8
HbA1c at >6 months (follow-up at different time points)	1 study (n=22)	Serious	VERY LOW	MD 0.5 higher (from 0.08 to 0.92 higher)	9.5
Severe hypoglycaemia ≤6 months	2 studies (n=38)	No serious imprecision	VERY LOW	No difference	0 event
Adherence to treatment at >6 months (Coefficient of variation based on patient's food diary)	1 study (n=22)	Not applicable	VERY LOW	1.7% higher	28.1%

7.3.10 Economic evidence [2015]

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix E.

7.3.11 Evidence statements

7.3.11.1 Clinical evidence statements [2015]

- Low and very low quality evidence from RCTs showed a clinically important harm in terms of HbA1c at less than or equal to 6 months and at more than 6 months for a low GI diet compared with a high GI diet.
- Very low quality evidence mostly from single studies showed no clinically important difference between low GI diet and high GI diet for HbA1c and severe hypoglycaemia at less than or equal to 6 months, and for adherence to treatment at more than 6 months. The HbA1c data in this case was from a non-randomised controlled trial.

7.3.11.2 Economic [2015]

No relevant economic evaluations were identified.

7.3.12 Recommendations and link to evidence

The current guideline recommendations can be found at

https://www.nice.org.uk/guidance/ng17

Relative values of different outcomes	The GDG determined the impact of high GI diets in comparison to low GI diets on clinical outcomes in adults with type 1 diabetes by assessing the impact of each intervention on the following outcomes: **Improvement in glycaemic control -** Assessed by reduction in HbA1c. Extensive previous research has shown that an improvement in glycaemic control is associated with a reduction in microvascular and macrovascular complications. A diet comprising low GI foods, which are individually associated with a low post-prandial blood glucose peak, may be associated with better overall glycaemic control than a diet of high GI foods, which are associated with a more rapid release of glucose into the circulation **Hypoglycaemia, including severe hypoglycaemia -** A low GI diet might theoretically reduce the incidence of hypoglycaemia in an individual with type 1 diabetes by providing a more sustained release of glucose into the bloodstream over a longer period of time in comparison to a high GI diet. Particular focus was given to: Incidence of severe hypoglycaemia (hypoglycaemia event requiring help from a third party for correction), an event which has been recognised as having a significant impact on quality of life in patients with type 1 diabetes. Incidence of nocturnal hypoglycaemia.

	Quality of life – The evidence was reviewed to look at the impact of each diet on quality of life outcomes. An intervention that reduces the frequency of severe hypoglycaemia episodes and improves glycaemic control should increase quality of life. However, the need to adhere to a strict diet may also impact on quality of life. **Adverse events** – A diet aiming to achieve a GI target may produce gastro-intestinal side-effects; the evidence was reviewed to assess any reported adverse events associated with adherence to diets.
Trade-off between clinical benefits and harms	The GDG considered evidence from available randomised controlled trials (RCTs) and observational studies assessing the impact of high and low GI diets on clinical outcomes in adults with type 1 diabetes. **Impact on glycaemic control** The GDG reviewed the impact of GI diets on glycaemic control, with glycaemic control assessed by HbA1c (%) at <6 months in three studies[112,232,753]), and at >6 months in one study[495]. Overall, no difference in HbA1c outcome was noted with low or high GI diets at <6 months or >6 months. I**mpact on incidence of hypoglycaemia** One study[431] reported no significant difference in frequency of hypoglycaemia in nine participants who were alternated between low, medium and high GI diets; none of the participants experienced severe hypoglycaemia events during the study, which lasted a total of 48 days. A second crossover study[753] compared 10 participants on a high GI diet with 10 participants on a low GI diet, with participants switching over diets after six weeks. No difference in incidence of hypoglycaemia was reported when outcomes were compared for high and low GI diets. None of the other studies reported outcomes on incidence of hypoglycaemia. I**mpact on quality of life** None of the reviewed studies commented on the impact of high and low GI diets on quality of life. **Adverse events** None of the available evidence reviewed by the GDG reported any adverse events as a consequence of adhering to a diet aimed at maintaining a fixed GI at mealtimes, with no adverse side-effects and no instances of diabetic ketoacidosis reported in the studies.
Economic considerations	No cost effectiveness studies assessing the impact of GI diets on clinical outcomes in adults with type 1 diabetes were available for review. As GI diets did not show any significant impact on clinical outcomes, they are unlikely to be cost effective in the management of adults with type 1 diabetes.
Quality of evidence	Five studies met the inclusion criteria for review by the GDG: one non-randomised crossover study [112] and four crossover RCTs [232,431,495,753]. The GDG noted that the available evidence for review was from more than a decade ago, that the number of participants in each study was small (the largest study was undertaken in 40 adults with type 1 diabetes[495], and that the duration of the trials was short (the longest duration of a dietary intervention in the studies was four months[495]making it difficult to assess the impact on glycaemic control by

	HbA1c measurement). The quality of the evidence was GRADE assessed, and ranged from Low to Very low, with a serious to very serious risk of bias.
Other considerations	The GDG noted that there were no recent studies assessing the impact of GI diets on clinical outcomes in adults with type 1 diabetes. Many of the previous studies used only small numbers of participants over a short duration of time and few used modern insulin treatment regimens. The GDG recognised that there are theoretical reasons why a low GI diet might lead to improved blood glucose control, and that post-prandial glucose levels might be reduced with a low GI diet. There are currently no long-term trials assessing the impact of low GI diets which is low in fat (low GI foods can be those which are high in fat, such as, chocolate and cakes) on the incidence of microvascular complications. Given that no adverse events were reported from adherence to a diet aimed at achieving a target GI, the GDG decided that a research recommendation be made for further assessment of following a low GI diets (also low in fat) in adults with type 1 diabetes.

7.3.13 Research Recommendations

6. **In adults with type 1 diabetes, what is the clinical and cost effectiveness of different types of diet and dietary constituents, particularly in terms of the effect on insulin requirement and blood glucose control?**

7.4 Physical activity [2004]

Physical activity was not within the scope of the 2015 update. The content presented here is from 2004.

7.4.1 Rationale

Many people wish to perform varying amounts of physical exercise, but this can interact to disturb blood glucose levels in people on insulin therapy. Physical exercise is usually recommended to the general population as part of a package of lifestyle measures to improve future health, in particular reduction of arterial risk, which is markedly elevated in people with Type 1 diabetes.

7.4.2 Evidence statements

Aerobic exercise

One small randomised controlled trial was identified that assessed the effect of a 16-week aerobic exercise programme on fitness and lipid profile in young men with Type 1 diabetes.[426]There were significant differences in VO_{2max} and serum total cholesterol compared with no training. There were no significant changes in outcomes of HbA1c and plasma glucose. The study was not blinded due to the nature of the intervention (**Ib**).

A small cross-sectional study evaluating the effect of three months of individualised aerobic exercise in altering blood pressure and lipid profile found that HbA1c, fructosamine, and total blood glucose

did not change significantly from baseline levels.[458]The design of the study would not represent a sound basis for supporting a recommendation for advocating exercise as therapy (**IIa**) .

Another study with a similar intervention found that four months of aerobic training provided no changes in terms of HbA1c or total cholesterol, although there were benefits of exercise compared to control in terms of peak oxygen uptake (**IIb**).[426]

A prospective non-randomised study with a before and after design found that steady-state plasma glucose was significantly decreased compared to baseline as was plasma insulin with supervised exercise programme (at least 135 minutes/week) for three months compared to no exercise.[447] Also cholesterol decreased significantly, however there were no reported significant changes in fasting blood glucose, HbA1c and microalbuminuria (**IIb**).

Education and exercise

A medium-sized randomised controlled trial of intensive advice and lifestyle programme with specified diet and exercise prescriptions compared to conventional care found that HbA1c decreased from baseline measurements significantly over six months in the control group but remained relatively stable in the intervention group, but no between-group comparison was made.[578] Also HDL cholesterol and triglycerides were not significantly different between groups at any phase of the study. However exercise sessions were not standardised in the study and a lack of blinding limited the validity of the trial (**Ib**).

A small before and after study found that an intervention of 10 hours of education and physical training three or four times a week produced no metabolic response at three months with fasting plasma glucose levels and serum cholesterol not changing significantly.[657] Without blinding or randomisation this evidence is not sufficient to support the use of a mixed education and exercise intervention for people with type 1 diabetes (**IIb**).

Other exercise

A non-randomised prospective controlled study to assess whether exercise is related to better diabetes control was reviewed.[458]There was no significant correlation between the exercise expenditure and HbA1c in all Type 1 diabetes patients, nor was there any relationship to the frequency of mild hypoglycaemic events (**IIa**).

Guidelines on exercise

The ADA guidelines present recommendations based on a good evidence-based review.[29]They recommend that a thorough evaluation be undertaken of patients before exercise is initiated. General recommendations for how to exercise safely include:

- metabolic control before activity
- blood glucose monitoring before and after physical activity
- food intake to be considered with added carbohydrate as necessary (**Ia**).

7.4.3 Health economic evidence

No evidence was found on the cost-effectiveness of programmes encouraging physical activity for Type 1 diabetes.

7.4.4 Consideration

The group noted that the evidence for an improved arterial risk profile in people with Type 1 diabetes was consistent with that for other diabetic and non-diabetic people. Evidence of a consistent effect in improving blood glucose control was absent, although by analogy with people with Type 2 diabetes the overweight/insulin-resistant person might benefit form an exercise programme as part of a lifestyle improvement initiative. Some people will undertake significant exercise by choice and would benefit from support in so doing.

7.4.5 Recommendations

The current guideline recommendations can be found at

https://www.nice.org.uk/guidance/ng17

7.5 Cultural and individual lifestyle[2004]

Cultural and individual lifestyle was not within the scope of the 2015 update. The content presented here is from 2004.

7.5.1 Rationale

Cultural and genetic differences between ethnic groups are known to affect health and response to healthcare for many diseases. In regard of Type 1 diabetes this is particularly true of eating habits, while arterial risk is known to differ for the general population and people with Type 2 diabetes. Other care issues seem likely.

7.5.2 Consideration

The group were aware of a systematic review designed to detect issues of relevance (rather than trials of interventions) identified papers concerning differences in incidence, attitudes to complications, degree of response to education programmes, blood glucose control, religious fasting and feasting, and hospitalisation.

The group noted that cultural and genetic issues affected diabetes healthcare delivery in the areas of:

- patient education and self-care
- nutritional advice
- insulin therapy (including religious feasts and fasts)
- arterial risk
- blood pressure management
- hospitalisation.

In some areas there was overlap with social/deprivation issues. The group's recommendations addressed cultural/religious issues in the appropriate sections of this guideline, emphasising the primacy of the individual in this regard.

7.5.3 Recommendations

The current guideline recommendations can be found at

https://www.nice.org.uk/guidance/ng17

8 Blood glucose control

This section was updated in 2015.

The evidence and text from the 2004 guideline, CG15, that has been superseded by this update is included in Appendix S.

8.1 Optimum target HbA1c level and frequency of HbA1c monitoring

8.1.1 Introduction

One of the main objectives of care for people with type 1 diabetes is to keep the risk of microvascular and macrovascular complications of diabetes to a minimum. Optimising glycaemic control is an obvious tool and one measure of glycaemic control is the glycated haemoglobin, or HbA1c, which is formed by an interaction between the red cell pigment, haemoglobin, and the circulating blood glucose. HbA1c measurements reflect time-averaged blood glucose concentrations during the previous 2 to 3 months and are used worldwide as the gold standard assessment of glycaemic control in people with type 1 diabetes. Lowering the HbA1c towards the non-diabetic range with intensified insulin therapy was proven to reduce the risk of microvascular complications in the randomised controlled Diabetes Control and Complications Trial (DCCT) [721] and was associated with a reduction in macrovascular disease in the DCCT follow-up studies ([521][428]). Of various measures of glucose control, only HbA1c was associated with risk of both microvascular and cardiovascular disease.[291]

The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) has standardised HbA1c measurements across the world, providing a reference method for calibration purposes. Local laboratories should report results that are reproducible in other laboratories, using the IFCC standards. The IFCC reference method reports HbA1c in mmol/mol. Previously, results were reported as a percentage of total haemoglobin (%) as in the DCCT assay standard and dual reporting of both values has been encouraged. [524]

In DCCT, the attainment of lower HbA1c was associated with a greater risk of severe hypoglycaemia (low blood glucose concentration that impaired function so that the person was unable to self-treat and required treatment from a third party). [1,721] Subsequently, many groups have been able to support adults with type 1 diabetes reduce risk of severe hypoglycaemia at the same time as lowering HbA1c, (for example, [644],[347]) but there remain concerns that targets for glycaemic control need to take into account individual ability to achieve them without increasing severe hypoglycaemia risk. Adults with type 1 diabetes need information on the blood glucose control targets they need to achieve if they wish to minimise vascular risk

The GDG therefore addressed the following questions:

- In adults with type 1 diabetes, what is the optimum target HbA1c level that should be achieved to reduce the risk of complications?
- In adults with type 1 diabetes, what is optimum frequency of HbA1c monitoring for effective diabetic control?

For full details see review protocol in Appendix C.

8.1.2 Review question: In adults with type 1 diabetes, what is the optimum target HbA1c level that should be achieved to reduce the risk of complications?

Table 22: PICO characteristics of review question

Population	Adults with type 1 diabetes • Adult is defined as aged ≥18 years
Intervention/s	HbA1c target values
Comparison/s	• Other target values (RCTs and comparative observational studies) • No targets (prognostic studies)
Outcomes	Outcomes • Number of people reaching target HbA1c(dichotomous) • Final HbA1cvalue (continuous) • Hypoglycaemia (dichotomous or continuous outcome at a particular target • Severe hypoglycaemia (dichotomous or continuous outcome, depending how it is reported) • Nocturnal hypoglycaemia (dichotomous or continuous outcome, depending how it is reported) • Complications/avoidance: ○ CV events (MI, IHD, Stroke, cardiac and peripheral revascularisation, major amputation) ○ Retinopathy ○ Low-level (micro) albuminuria/proteinuria ○ Renal replacement therapy/end-stage renal failure ○ Neuropathy ○ Sudden death • Quality of life – (dichotomous/continuous)
Study design	RCTs, observational studies

8.1.3 Review question: In adults with type 1 diabetes, what is optimum frequency of HbA1c monitoring for effective diabetic control?

For full details see review protocol in Appendix C.

Table 23: PICO characteristics of review question

Population	Adults with type 1 diabetes • Adult is defined as aged ≥18 years
Intervention/s	HbA1c monitoring
Comparison/s	• HbA1c monitoring (the same as the intervention but at a different frequency or delivery time) • Standard care • No comparison (non-comparative studies)
Outcomes	• Number of people reaching target HbA1c(dichotomous) • Final HbA1c value (continuous) • Hypoglycaemia (dichotomous or continuous outcome at a particular target • Severe hypoglycaemia (dichotomous or continuous outcome, depending how it is reported) • Nocturnal hypoglycaemia (dichotomous or continuous outcome, depending how it is reported) • Complications/avoidance:

	○ CV events (MI, IHD, Stroke, cardiac and peripheral revascularisation, major amputation) ○ Retinopathy ○ Low-level (micro) albuminuria/proteinuria ○ Renal replacement therapy/end-stage renal failure ○ Neuropathy ○ Sudden death • Quality of life – (dichotomous/continuous)
Study design	RCTs, observational studies

8.1.4 Clinical evidence

Forty three studies were identified for the optimum HbA1c target review.[2,3,5,21,24,42,97,187,198,234,287,325,334,365,400-403,424,443,448,460,471,515,516,521,550,556,557,576,611-613,632,673,709,721,749,768,772,777,778,806] Five studies reported from the Diabetes Control and Complications (DCCT) RCT.[3-5,24,721,773] Three studies were post-intervention follow-ups of DCCT (DCCT/EDIC).[365,521,772] Two studies reported from the Pittsburgh Epidemiology of Diabetes Complications study (Pittsburgh EDC).[556,557] Three studies reported from Stockholm Diabetes Intervention Study (SDIS)[611-613], two at 94 months [611,612], and one 3 years later[613] Seven studies reported from the Wisconsin Epidemiology Study of Retinopathy (WESDR).[400-403,443,515,516] Two studies reported from a Swedish cohort.[777,778]

Four studies reported glycated haemoglobin as HbA1, which includes non-enzymatic binding of several carbohydrate moieties to HbA) [400-402,515,516], while the remaining studies measured HbA1c (binding of glucose specifically).

Two studies were identified for the frequency of monitoring HbA1creview.[221,434]Both these studies measured HbA1c.

Most of the studies were observational studies, and therefore were not able to be combined in a meta-analysis or GRADE profile, and were graded as Low quality (due to their study design). However, a summary of the quality and limitations of these studies can be found in Appendix G. The study details and the full results have been summarised in tables below. A summary of the included studies is provided inTable 24, Table 25, Table 26 and Table 27. See also the study selection flow chart in Appendix D, forest plots in Appendix J, study evidence tables in Appendix G and exclusion list in Appendix K.

Table 24: Summary of studies included on optimum HbA1c target level

Study	Intervention/ comparison	Population	Follow-up	Outcomes	Comments
Agardh 1997[21]	Prospective case-series	n=442 with type 1 diabetes Sweden	5 years	Retinopathy Urinary albumin concentration Death MI CV disease	Regression analysis
Araskiewicz[42]	Prospective case series	n=88 with type 1 diabetes Poland	6 years	Retinopathy Low-level (micro) albuminuria Severe hypoglycaemia QoL	Regression analysis
Brinchmann-Hansen 1992[97]	Prospective case-series of patients originally enrolled in Oslo 1985 RCT[163]	n=45 with type 1 diabetes Norway	7 years	Retinopathy	Regression analysis Oslo 1985 RCT; insulin pumps versus multiple injections versus conventional retreatment treatment (regular insulin and isophane insulin twice daily)
DCCT 1993[281,721] DCCT 1995[3] DCCT 1996[4] DCCT 1997[5] DCCT end of follow-up[24]	RCT Intensive therapy; ≥3 insulin injections daily or external insulin pump use Conventional therapy 1-2 daily insulin injections	n=1441 IDDM USA	6.5 years	Progression to retinopathy Macular oedema Severe non-proliferative or proliferative retinopathy Nephropathy Neuropathy (5 years) Mortality Hypoglycaemia requiring assistance	Intensive therapy; glucose target of 70 to 120 mg/dl (3.9 to 6.7 mmol/litre) before meals Conventional therapy; no target Population <20% 13-18 year olds
DCCT/EDIC 2005[521] DCCT/EDIC	Prospective case-series	DCCT; n=1441 EDIC; n=1421 USA	17 years	CVD events; non-fatal MI, stroke, CVD death, angina Retinopathy	Proportional hazards model Prospective case series (EDIC ending 2004) from patients originally enrolled in DCCT (Baseline

Study	Intervention/ comparison	Population	Follow-up	Outcomes	Comments
2008[772] DCCT/EDIC 2013[365]				DQoL	1983–1989, end of DCCT 1993)
Diamante 1997[187]	Cross-sectional observational study	n=1822 Spain; 18 centres	NA	Nephropathy	Regression analysis
EEG-OLOFSSON 2010[198]	Retrospective case-series	n=7,454 with type 1 diabetes Sweden	5 years	Mortality CV outcomes	Regression analysis
FORREST 2000[234]	Prospective case-series	n=658 with type 1 diabetes USA	6 years	Mortality CHD LEAD (lower extremity arterial disease)	Regression analysis
GUERCI 1999[287]	Cross-sectional study	n=341 with type 1 diabetes France	n/a	Retinopathy Proliferative retinopathy	Regression analysis
HIETALA 2013[325]	Prospective case-series	n=2019 with type 1 diabetes Finland	Mean 5.2 years	Mortality Retinopathy Nephropathy	Regression analysis
Hislop 2008[334]	Prospective case series	n=92 Australia	6 months	Quality of life CES-D ASR	ANOVA statistical analyses
KULLBERG 1994[424]	Retrospective case series	n=90 with type 1 diabetes Sweden	9.2 years (average)	Retinopathy	Regression analysis
Lehto 1999[448]	Prospective case series	n=177 with type 1 diabetes Finland	7 years	CHD mortality Combined outcome; CHD mortality or non-fatal MI	Regression analysis

Study	Intervention/ comparison	Population	Follow-up	Outcomes	Comments
LIND 2011[460]	Prospective case series	n=20,985 with type 1 diabetes Sweden	9 years (mean)	Heart failure	Regression analysis
Lustman 2005[471]	Cross-sectional observational study	n=188 with type 1 diabetes USA	NA	Quality of life SCL-90 SDSCA	Regression analysis
NORDWALL 2009[550]	Case-series (retrospective and prospective elements)	n=269 with type 1 diabetes Sweden	Between 14 to 28 years	Retinopathy Nephropathy	Regression analysis
Pirez Mendez 2007[576]	Prospective case series	n=59 with type 1 diabetes Spain	7 years	HbA1c Severe hypoglycaemia Mild hypoglycaemia	Regression analysis Patient switched to multiple insulin dose regime with target of HbA1c<6.2% at start of study
Pittsburgh EDC 2002[556]	Prospective case series	n=586 with type 1 diabetes USA	10 years	Lower extremity arterial disease (claudication, foot ulceration or lower extremity amputation)	Regression analysis
Pittsburgh EDC 2003[557]	Prospective case series	n=603 with type 1 diabetes USA	10 years	CAD death, non-fatal MI, angina, revascularisation, ECG ischaemia	Regression analysis
ROSSING 1996[632]	Prospective case series	n=939 with type 1 diabetes Denmark	10 years	Mortality CV mortality	Regression analysis
SDIS 1995[611-613]	RCT/cohort follow-up	n=89 with type 1 diabetes Sweden	94 months/10 years	Retinopathy Nephropathy Neuropathy	Incidence of outcomes according to HbA1c levels Regression analysis Patients originally randomised to either intensified conventional insulin treatment (insulin with education to ensure constant monitoring and treatment) or standard therapy (2 to 3 insulin injections/day)
Shaban 2006[673]	Cross-sectional	n=273 with type	NA	Quality of life	Regression analysis

Study	Intervention/ comparison	Population	Follow-up	Outcomes	Comments
	observational study	1 diabetes UK		HADS	
Tabaei 2004[709]	Cross-sectional observational study USA	n=634 with type 1 diabetes USA	NA	Quality of life QWB-SA	Regression analysis
Van Tilburg 2001[749]	Cross-sectional observational study	n=30 with type 1 diabetes USA	NA	Quality of life BDI	Regression analysis
WDRS 2013[443]	Prospective case series	n=305 with type 1 diabetes USA	20 years	Retinopathy and proliferative retinopathy	Regression analysis
WEINSTOCK 2013[768]	Cross-sectional study/retrospective case-series	n=7012 with type 1 diabetes USA	n/a and previous 12 years data	Severe hypoglycaemia	Regression analysis
WESDR 1994[516]	Prospective case series	n=2990 with type 1 diabetes USA	10 years	CHD death	Regression analysis 2 subgroups of WESDR; n=1210 subjects with diabetes diagnosis <30 years n=1780 subjects with diabetes diagnosis ≥30 years
WESDR 1995[401,402]	Prospective case series	n=2990 with type 1 diabetes USA	10 years	Retinopathy Nephropathy Neuropathy	Nephropathy; incidence at 6 yearfollow-up 2 subgroups of WESDR; n=12101 subjects with diabetes diagnosis <30 years n=1780 subjects with diabetes diagnosis ≥30 years
WESDR 1998[400]	Cross-sectional observational study	n=987 with type 1 diabetes USA	14 years	Quality of life SF-36	Regression analysis 2 subgroups of WESDR; n=654 subjects with diabetes diagnosis <30 years

Study	Intervention/ comparison	Population	Follow-up	Outcomes	Comments
					n=333 subjects with diabetes diagnosis ≥30 years
WESDR 1998a [403]	Prospective case series	n=634 With type 1 diabetes USA	14 years	Retinopathy	Regression analysis 1 subgroup of WESDR; n=654 subjects with diabetes diagnosis <30 years
WESDR 1999[515]	Prospective case series	n=1890 with type 1 diabetes USA	14 years	Lower extremity amputations	Regression analysis Incidence of outcomes according HbA1c 2 subgroups of WESDR; n=906 subjects with diabetes diagnosis <30 years n=984 subjects with diabetes diagnosis ≥30 years
WESDR 2013[443]	Prospective case series	n=583 with type 1 diabetes USA	20 years	Retinopathy and proliferative retinopathy	Regression analysis
Wikblad 1991[778]	Retrospective case series	n=185 with type 1 diabetes Sweden	9 years	Retinopathy Nephropathy (proteinuria)	Incidence of outcomes according to HbA1c levels
Wikblad 1996[777]	Retrospective case series	n=108 with type 1 diabetes Sweden	10 years	Quality of life SWEDQUAL Hypoglycaemia	ANOVA statistical analyses
ZOFFMANN 2014[806]	Cross-sectional study	n=710 with type 1 diabetes Norway	n/a	PAID score	Regression analysis

Abbreviations: ANOVA, Analysis Of Variance; ASR, Adult-Self-Report Scale; BDI, Beck Depression Inventory; CAD, coronary artery disease; CES-D, Centre for Epidemiological Studies-Depression Scale; CHD, coronary heart disease; CVD, cardiovascular disease; DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Interventions and Complications; HADS, Hospital Anxiety and Depression Scale; MI, myocardial infarction; NA, not applicable; NR, not reported; Pittsburgh EDC, Pittsburgh Epidemiology of Diabetes Complications; QWB-SA, Quality of Well-Being Self-Administered; SDIS, Stockholm Diabetes Intervention Study; SCL-90, Symptom Checklist-90; SDSCA, Summary of Diabetes Self-Care Activities; SF-36, Short Form 36; SWEDQUAL, Swedish quality of life questionnaire; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy

Table 25: Summary of studies included on frequency of HbA1c monitoring

Study	Intervention/ comparison	Population	Follow-up	Outcomes	Comments
Eid Fares 2010[221]	Retrospective case series	n=117 with type 1 diabetes USA	5 years	Fluctuations in HbA1c Nephropathy	Regression analysis Age range; 9–33 years
Larsen 1990[434]	RCT Monitored group; HbA1clevels available to staff, used with blood or urine glucose values to adjust treatment, target NFBG <9mmol/(162 mg/dl) Control group; HbA1clevels (including the randomisation values) not entered into the patients' records during study period,staff treated patients on blood or urine glucose values, target NFBG <9 mmol/(162 mg/dl) Second year; HbA1clevels in both groups available to healthcare professionals	n=240 with IDDM Denmark	1 year (followed for 2nd year post intervention)	HbA1c	Analysis of HbA1clevels between groups Unclear if patients were type 1 diabetesor type 2 diabetes 8% patients lost to follow-up at 1 year, 22% patients lost to follow-up at 2 years

Abbreviations: IDDM, insulin dependent diabetes mellitus; NFBG, non-fasting blood glucose

Table 26: Study details and results for optimum HbA1c target

Study	Number of patients	Study type/ follow-up	Diabetes therapy	Baseline HbA1c level, mean %±SD	Frequency of HbA1cmonitoring	Measure of glycosylated haemoglobin and results
Agardh 1997[21]	442	Prospective case series 5 years	NR	8.5±1.6 (HbA1c)	Mean±SD; 16±5 times/patient	Measured; HbA1c Retinopathy (n=121 follow-up data available for patients without retinopathy at entry); Any retinopathy (n=64); HbA1c; 8.2±1.1% versus no retinopathy (n=57); HbA1c; 7.5±1.1%, p<0.0) Cumulative frequency for retinopathy at 5 years; 50% patients who still had no signs of retinopathy, the mean HbA1c levels were <7.5% during the observation period versus 50% patients who developed any type of retinopathy, the mean HbA1c levels were >8.3% (p<0.0002) 50% patients who progressed to severe retinopathy mean HbA1c levels were >8.9%, (p<0.001) compared with patients without retinopathy at follow-up or those who developed any type of retinopathy Increase UAC associated with mean HbA1c levels (p<0.01) MI, CV disease, death not associated with mean HbA1c levels
ARASKIEWICZ[42]	88	Prospective case series 6 years	Intensive functional insulin therapy	8.1 ± 1.9 (HbA1c)	Not reported	Measured; HbA1c • Patients with retinopathy had higher values of HbA1c (p=0.04) than those without • HbA1c<7.0% versus >7.0%: OR = 1.35 (95% CI 0.21 to 8.52), p = 1.0 • Patients with low-level (micro) albuminuria had higher values of HbA1c (p=0.04) than those without • HbA1c<7.0% versus >7.0%: OR = 4.25 (95% CI 0.50 to 35.5), p=0.27 • Final HbA1c value: ○8.8 ± 1.3 (with retinopathy) versus 8.1 ± 1.4 (without retinopathy) ○ 8.8 ± 1.3 (with low-level (micro) albuminuria) versus 8.8 ± 1.3

Study	Number of patients	Study type/ follow-up	Diabetes therapy	Baseline HbA1c level, mean %±SD	Frequency of HbA1cmonitoring	Measure of glycosylated haemoglobin and results
						(without low-level (micro) albuminuria)
Brinchmann-Hansen 1992[97]	45	Prospective case-series 7 years	10 patients; insulin pumps 29 patients; multiple injections delivered by an insulin pen 6 patients; conventional treatment (regular insulin and isophane insulin twice daily)	11.2±2.2 (HbA1)	Every 2 months	Measured; HbA1 Retinopathy Mean±SD; number of microaneurysms and haemorrhages according to mean HbA1; <9.0% (n=20); baseline 11.8(14.8), 7 years 25.5(43.1), change 13.8(39.5) 9.1 to 10.0% (n=13); baseline 24.7(40.8), 7 years 41.1(58.7), change; 16.4(56.6) >10.1%(n=12); baseline; 17.6(16.2), 7 years 80.5(66.7), change 62.8(65.8)* *p= 0.014 compared with patients with HbA1 <10.0% Multivariate regression analysis Severity of retinopathy not correlated to age, BP, or kidney function, patients with retinopathy at baseline were more likely to have more severe retinopathy at 7 years (r = 0.41; p=0.005) Independent variables; baseline HbA1, change HbA1, duration diabetes, baseline retinopathy Regression coefficient(95%CI); baseline HbA1 r=0.36(0.06 to 0.66) p=0.027, change Hb1A r=-0.35(-0.068 to -0.02) p=0.041 duration diabetes r=0.009(0 to 0.018) p=0.44, baseline retinopathy r=0.35(0.02 to 0.68) p=0.046
DCCT 1993[281,721] DCCT 1995[3] DCCT 1996[4] DCCT 1997A[5] DCCT end of follow-up[24]	1441 Primary cohort; n=726 Secondary cohort; n=715	RCT 6.5 years	Intensive therapy; ≥3 insulin injections daily or external insulin pump use	Primary cohort Intensive therapy; 8.8±1.6 Conventional therapy; 8.8±1.7	4 times/year	Measured; HbA1c Progression of retinopathy; Primary prevention cohort; intensive versus conventional RR (95%CI) 0.73 (0.62 to 0.85) Secondary prevention cohort; intensive versus conventional RR(95%CI) 0.54 (0.39 to 0.66) ARR per 100 patient-years (95%CI)

Study	Number of patients	Study type/ follow-up	Diabetes therapy	Baseline HbA1c level, mean %±SD	Frequency of HbA1cmonitoring	Measure of glycosylated haemoglobin and results
			Conventional therapy	Secondary cohort Intensive therapy; 8.9±3.8 Conventional therapy; 8.6±3.7 (HbA1c)		Progression of retinopathy Primary cohort; Conventional; 4.7 versus intensive; 1.2 risk reduction 76 (95%CI 62 to 85) Secondary cohort Conventional; 7.6 versus intensive; 3.7 risk reduction 54 (95%CI 39 to 66) Macular oedema Secondary cohort Conventional; 3.0 versus intensive; 2.0 risk reduction 54 (95%CI -13 to 48) Severe non-proliferative or proliferative retinopathy Secondary cohort Conventional; 2.4 intensive; 1.1 risk reduction 47 (95%CI 14 to 68) UAE ≥40 mg/24 hours Primary cohort Conventional; 3.4 versus intensive; 2.2 risk reduction 34 (95%CI 2 to 56) Secondary cohort Conventional; 5.7 versus intensive; 3.6 risk reduction 43 (95%CI 21 to 58) UAE ≥300 mg/24 hours Primary cohort Conventional; 0.3 versus intensive; 0.2 risk reduction 44 (95%CI -124 to 86) Secondary cohort Conventional; 1.4 versus intensive; 0.6

Study	Number of patients	Study type/ follow-up	Diabetes therapy	Baseline HbA1c level, mean %±SD	Frequency of HbA1cmonitoring	Measure of glycosylated haemoglobin and results
						risk reduction 56 (95%CI 18 to 76) Clinical neuropathy at 5 years Primary cohort Conventional; 9.8 versus intensive; 3.1 risk reduction 34 (95%CI 2 to 56) Secondary cohort Conventional; 16.1 versus intensive; 7.0 risk reduction 57 (95%CI 29 to 73) Mortality; conventional 7 patients died versus intensive 4 patients died Regressionmodel estimates of the effect of 10% higher mean HbA1c on the change in risk of other outcome Retinopathy; ≥3 microaneurysms (primary cohort only) Conventional therapy %change in risk; 56, 95%CI 39 to 74 Intensive therapy %change in risk; 66, 95%CI 39 to 96 Neuropathy at 5 years; confirmed Conventional therapy %change in risk; 41, 95%CI 19 to 66 Intensive therapy %change in risk; 43, 95%CI 9 to 87 Nephropathy; AER ≥300 mg/24 hours Conventional therapy %change in risk; 71, 95%CI 32 to 121

Study	Number of patients	Study type/ follow-up	Diabetes therapy	Baseline HbA1c level, mean %±SD	Frequency of HbA1cmonitoring	Measure of glycosylated haemoglobin and results
						Intensive therapy %change in risk; 57, 95%CI 7 to 133 Hypoglycaemia requiring assistance HbA1c at eligibility screening subgroups; intensive versus conventional therapy <7.825%; intensive n=189, conventional n=171 RR(95%CI) 2.098 (1.37 to 3.19) 7.825-8.819%; intensive n=185, conventional n=175 RR(95%CI) 3.12(2.15 to4.51) 8.820-10.099%; intensive n=166, conventional n=192 RR(95%CI) 4.13(2.79 to 6.13) >10.100%; intensive n=190, conventional n=173 RR(95%CI) 4.89 (3.05 to 7.83) Relative risk reductions associated with a 10% lower mean HbA1c among HbA1c values ≤8 versus values >8% estimated from a segmented (change point) model Sustained retinopathy progression, %risk reduction (95%CI) Intensive ≤8%; 49 (27 to 65) versus >8%; 37 (17 to 53), p=0.46 Conventional ≤8%; 69 (29 to 87) versus >8%; 37 (26 to 41), p=0.055 Sustained low-level (micro) albuminuria, %risk reduction (95%CI) Intensive ≤8%; 43 (2 to 67) versus >8%; 44 (17 to 62), p=0.97 Conventional ≤8%; 58 (-50 to 87) versus >8%; 33 (17 to 45), p=0.47 Confirmed clinical neuropathy, %risk reduction (95%CI) Intensive

Study	Number of patients	Study type/ follow-up	Diabetes therapy	Baseline HbA1c level, mean %±SD	Frequency of HbA1cmonitoring	Measure of glycosylated haemoglobin and results
						≤8%; 30 (-19 to 58) versus >8%; 35 (-17 to 64), p=0.87 Conventional ≤8%; 32 (-70 to 56) versus >8% ; 29 (13 to 42), p=0.90 • **Retinopathy:** Higher values of HbA1c were all associated with higher rate of retinopathy progression. For each 10% decrease in HbA1c (for example,9.0-8.1): 44% decreased risk of progression.
DCCT/EDIC 2005[521] DCCT/EDIC 2008[772] DCCT/EDIC 2013[365]	1441	Prospective case series study DCCT 17 years and 23 years = EDIC 10 years and 17 years	DCCT Intensive therapy3 insulin injections or external insulin pump Conventional therapy; 1-2 daily insulin injection EDIC follow-up, percentage on intensive; conventional group; 94% intensive group; 97%	DCCT; Intensive group (n=711); 27±7 Conventional group therapy (n=730); 27±7 Start of EDIC; Intensive group(n=698); 34±7 Conventional group (n=723); 33±7	DCCT 4 times/year EDIC; every year	Measured; HbA1c CVD event (non-fatal MI, stroke, CVD death, angina) at 17 years (DCCT/EDIC) (EDIC; 10 years); Intensive therapy; 0.38 events/100 patient-years Conventional therapy; 0.80 events/100 patient-years (p=0.007 versus intensive therapy) Cumulative incidence 1st CVD event Intensive versus conventional therapy ; RR (95%CI) 0.59 (0.9 to 0.63), p=0.02 Cumulative incidence 1st non-fatal MI, stroke or CVD death Intensive versus conventional therapy; RR (95%CI) 0.57 (0.12 to 0.79), p=0.02 HbA1c; per 10% increase (adjusted for HbA1c, age, cholesterol, smoking status at baseline); HR (95%CI) 1.25 (1.10 to 1.43) HbA1c; per 10% decrease (adjusted for HbA1c, age, cholesterol, smoking status at baseline); HR (95%CI) 0.8 (0.70 to 0.91) Higher HbA1c levels (9.5% versus 9.0%), at DCCT baseline associated with occurrence of the CV events independent of

Study	Number of patients	Study type/ follow-up	Diabetes therapy	Baseline HbA1c level, mean %±SD	Frequency of HbA1cmonitoring	Measure of glycosylated haemoglobin and results
						treatment assignment (p=0.014) Progression to retinopathy from DCCT closeout to EDIC at 10 years (n=1211) Risk reduction (95%CI) with intensive versus conventional therapy; 53% (43% to 61%), p<0.001 HbA1c intensive versus conventional therapy; 87.07% versus 7.98% p=ns • Higher values of HbA1c were all associated with a sustained drop of ≥5 points in DQOL score (multivariate: HR 1.12, 95% CI 1.06 to 1.19; p<0.01). • Higher values of HbA1c were all associated with a sustained drop of ≥5 points in DQOL score (multivariate: HR 1.12, 95% CI 1.06 to 1.19; p<0.01).
Diamante 1997[187]	1822	Cross-sectional observational study	Insulin treatment (%) 1 dose; 1.1 2 doses; 35.7 3 doses; 46.3 4 doses; 16.4	7.5±1.6 (HbA1c)	Not reported	Measured; HbA1c Logistic regression analysis HbA1c correlated with ESRF versus no ESRF (p<0.00005) HbA1c correlated with low-level (micro) albuminuria versus normoalbuminuria (p<0.00005) HbA1c levels Normoalbuminuria; 7.3±1.6% Low-level (micro) albuminuria; 8.0±1.6% Macroalbuminuria + ESRF; 7.7±1.9% HbA1c (diabetes <5 years evolution) Normoalbuminuria; 7.3±1.6% Low-level (micro) albuminuria; 8.0±1.6% Macroalbuminuria + ESRF; 7.7±1.9%
EEG-OLOFSSON	7,454	Retrospective	Not reported	8.0 (1.2 to	Not reported	• Mean HbA1c and baseline HbA1c were SS predictors of: all CVD,

Study	Number of patients	Study type/ follow-up	Diabetes therapy	Baseline HbA1c level, mean %±SD	Frequency of HbA1cmonitoring	Measure of glycosylated haemoglobin and results
2010[198]		case-series 5 years		0.01) (HbA1c)		and all CHD • Mean HbA1c and baseline HbA1c were not SS predictors of: all stroke, and all mortality. • The risk of all CVD with baseline HbA1c categories was: ○ HbA1c 5.0 to 7.9%: HR 1.0 ○ HbA1c 8.0 to 11.9%: HR = 1.59 [95% CI 1.13 to 2.24] • The risk of all CHD with baseline HbA1c categories was: ○ HbA1c 5.0 to 7.9%: HR 1.0 ○ HbA1c 8.0 to 11.9%: HR1.71 [95% CI 1.18 to 2.48] • The risk of all stroke with baseline HbA1c categories was: ○ HbA1c 5.0 to 7.9%: HR 1.0 ○ HbA1c 8.0 to 11.9%: HR = 1.40 [95% CI 0.70 to 2.79]
FORREST 2000[234]	658	Prospective case-series 6 years	Not reported	10.75 (HbA1c)	Not reported	• HbA1c level was not a SS predictor of CV mortality or of total CHD. • HbA1c was a SS predictor of LEAD (lower extremity arterial disease)
GUERCI 1999[287]	341	Cross-sectional study n/a	Intensive conventional insulin therapy (split and mixed insulin regimens)	7.57 (HbA1c)	Not reported	• HbA1c was a SS predictor of retinal status in all subjects, and in those who had had diabetes for ≥20 years
HIETALA 2013[325]	2019	Prospective case-series 5.2 years	Not reported	8.4±1.2 (HbA1c)	Not reported	• The estimated 5-year cumulative incidence of laser treatment for retinopathy increased significantly with increasing HbA1c quartile (p<0.0001) • Mean HbA1c was higher with worse severity of retinopathy: ○ No retinopathy = 8.2 ± 1.2

Study	Number of patients	Study type/ follow-up	Diabetes therapy	Baseline HbA1c level, mean %±SD	Frequency of HbA1cmonitoring	Measure of glycosylated haemoglobin and results
						○ Non-proliferative retinopathy = 8.5 ± 1.2 ○ Proliferative retinopathy = 8.7 ± 1.3 • Risk ofproliferative retinopathy increase with higher HbA1c quartile ○ 1st Q: HR = 1; p = 0.003 ○ 2nd Q: HR = 1.3 [0.97 to 1.8]; p = 0.07 ○ 3rd Q: HR = 1.5 [1.1 to 2.0]; p < 0.001 ○ 4th Q: HR = 1.7 [1.3 to 2.2]
Hislop 2008[334]	92	Prospective case series 6 months	17/92 patients on continuous subcutaneous insulin infusion	8.7±1.8 (HbA1c)	Not reported	Measured; HbA1c Quality of life CES-D Patients with worse quality of life (higher CES-D score ≥16) hadhigher HbA1c compared with those with normal CES-D (9.4% versus 8.4%, p=0.01) No correlation between HbA1c and CES-D in total cohort (r=0.2, p=0.14) Controlling for CSII use, higher CES-D score and HbA1c correlated (r=0.3, p=0.02) Patients on CSII versus patients not on CSII; lower HbA1c (7.9 versus 8.9%, p=0.03) ASR-T No difference in glycaemic control between patients with normal ASR-T scores (≤ 59) and psychologically distressed ASR-T scores (≥60)
KULLBERG 1994[424]	90	Retrospective case series 9.4 years	Not reported	7.2 ± 1.3 (HbA1c)	Mean 31.7 times/whole measurement	• Patients with mean HbA1c>8% had higher RRs for all kinds of background retinopathy compared with patients with HbA1c ≤ 7%

Study	Number of patients	Study type/ follow-up	Diabetes therapy	Baseline HbA1c level, mean %±SD	Frequency of HbA1cmonitoring	Measure of glycosylated haemoglobin and results
					period (mean of 9.4 years); measured regularly every 3-4 months at the clinic visit.	• Mean HbA1c for the preceding year did not contribute further to any regression model. • The impact of long-term HbA1c concentration was significant for all sets of retinopathy scores.
Lehto 1999[448]	177	Prospective case-series 7 years	Not reported	Men without CHD 9.5±0.21 Men with CHD 10.5±0.4 Women without CHD 10.1 ±0.2 Women with CHD 11.1±0.4 (HbA1)	Not reported	Measured; HbA1 CHD death Univariate Cox regression model; HbA1 associated with risk of CHD death (p<0.001) and all CHD events (p<0.01) Poor Glycaemic control (10.4% versus ≤10.4%) was associated with the incidence of CHD death (p<0.05) High HbA1 (>10.4%) associated with all CHD events Multivariate analysis (adjustment CV factors; age, gender, area of residence, previous MI, smoking, BMI, hypertension, total cholesterol, total triglycerides, and HDL cholesterol); High HbA1 (>10.4%), HR 5.4 [1.4 to 20.4]) associated with the incidence of CHD death (p=0.013) High HbA1 (>10.4%), HR 2.8 [1.2 to 6.9]) associated with the incidence of all CHD events (p=0.021) RR (95% CI) for HbA1 (per 1–percentage point increase) and incident coronary heart disease event (CHD death + non-fatal MI); 1.55 (1.05 to 2.30)
LIND 2011[460]	20,985	Prospective case series	Not reported	8.8±1.34	Not reported	**Incidence of HF** increased monotonically with HbA1c, with a range of 1.42 -5.20 per 1000 patient-years in the lowest (<6.5%) and highest (≥10.5%) categories of HbA1c **Risk of HF per 1% increase in HbA1c:** HR 1.30 (95% CI 1.21 to 1.40; p<0.0001).

Study	Number of patients	Study type/ follow-up	Diabetes therapy	Baseline HbA1c level, mean %±SD	Frequency of HbA1cmonitoring	Measure of glycosylated haemoglobin and results
						Risk of HF at intervals of HbA1c (multivariate*): • **6.5 to <7.5%:** HR 1.26 (0.76 – 2.07) • **7.5 to <8.5%:** HR 1.47 (0.91 – 2.38) • **8.5 to <9.5%:** HR 1.75 (1.07 – 2.85) • **9.5 to <10.5%:** HR 2.58 (1.54 – 4.34) • **≥10.5%:** HR 3.98 (2.23 – 7.14)
Lustman 2005 [471]	188	Cross-sectional observational study	Use of insulin pump; 55/188(29%) Total daily insulin dose, units mean(±SD); 37.2±20.9	7.7±1.3 (HbA1c)	NA	Measured; HbA1c Quality of life Multiple regression SDSA; HbA1c levels positively correlated with depression symptoms on SDSA (t=0.44, p<0.02) HbA1c levels were higher in the depressed than in the non-depressed patients (covariate-adjusted means±standard error of mean=8.8%±0.3% versus 7.6%±0.1%, F=10.1, p<0.0001) SDSCA composite score; Addition of SDSCA composite score to regression analysis, the parameter estimate for depression effect on HbA1c level was attenuated minimally (parameter estimate 0.50, t =3.3, p<0.001), SDSCA score had no effect within the model (p=0.40) SCL-90; Scores on SCL-90 depression subscale were 2.3±0.4 in the depressed group versus 0.6± 0.4 in the non-depressed group HbA1c levels correlatedto severity depression symptoms within depressed group (p<0.02, across subgroups)
NORDWALL 2009[550]	269	Case-series (retrospective and prospective	Not reported	8.55 (HbA1c)	3-4 times/year	• HbA1c showed a SS correlation to any retinopathy (OR 4.1 [95% CI 1.8 to 9.2]; p = 0.001). • Patients with low-level (micro) albuminuria had a mean HbA1c of 8.7 ± 0.9

Study	Number of patients	Study type/ follow-up	Diabetes therapy	Baseline HbA1c level, mean %±SD	Frequency of HbA1cmonitoring	Measure of glycosylated haemoglobin and results
		elements) 14-28 years				• Patients with severe laser-treated diabetic retinopathy had higher mean HbA1c levels versus those with background retinopathy, and those with no retinopathy (9.0 ± 1.0 versus 8.5 ± 0.8 versus 7.8 ± 0.8)
Pirez Mendez 2007[576]	59	Prospective case series 7 years	Multiple Dose Insulin (MDI); MID 2 or 3 daily injection of NPH insulin with short-acting analogue lispro as a pre-meal bolus The goal of HbA1c values was <6.2%.	Not reported	Every 3 months	Measured; HbA1c Mean values of HbA1c: 7.5±1.5%, 7.2±1.8%, 7.6±1.6%, 7.1±1.7%, 7±1.4,6.6,±1.6% and 6.8±1.4% for first, second, third, fourth, fifth, sixth and seventh year of follow-up, respectively Percentage of patients reaching target HbA1c<6.2% for the first, second, third, fourth, fifth, sixth and seventh year of follow-up: 16%, 27.5%, 15.7%, 33.3%, 28.6%, 42% and 33% Severe hypoglycaemic episodes (episodes/patient-year) Year before study; 0.32±0.2 During study; 0.28±0.1 (ns compared with before study) Mild/moderate hypoglycaemia episodes (episodes/patient-month) Year before study started; 17.7±6 During study; 16.5±4 to 21.7±5 (NS compared with before study value)
Pittsburgh EDC 2002[556]	586	Prospective case series	Not reported	Without LEAD; 10.3±1.8 With LEAD; 10.9±1.9 (HbA1)	Not reported	Measured; HbA1 HR(95%CI) for 10 year incident LEAD (men and women); 1.53(1.22 to 1.92), p<0.001 HR(95%CI) for 10 year incident LEAD (men); 1.70(1.27 to 2.29), p<0.001
Pittsburgh EDC 2003[557]	603	Prospective case series	Insulin dose/kg BW;	Patients without CAD;	Not reported	Measured; HbA1 HbA1 not association with subsequent CAD events

Study	Number of patients	Study type/ follow-up	Diabetes therapy	Baseline HbA1c level, mean %±SD	Frequency of HbA1cmonitoring	Measure of glycosylated haemoglobin and results
		10 years	Patients without CAD; 0.81±0.25 Patients with CAD; 0.75±0.31	10.4±1.8 Patients with CAD; 10.3±1.8 (HbA1)		RR (95% CI) for HbA1 (per 1–percentage point increase) and incident coronary heart disease event (CAD death, non-fatal MI, ECG ischaemia, revascularisation, angina); 0.97 (0.86 to 1.09)
ROSSING 1996[632]	939	Prospective case-series 10 years	Not reported	9.17 (HbA1c)	Not reported	HbA1c was a SS predictor of all-cause mortality:RR 1.11 (95% CI 1.03 to 1.20); p<0.02 HbA1c was not a SS predictor of CV mortality.
SDIS 1995[611-613]	89	Prospective cohort study 94 months	Intensified conventional insulin treatment (insulin with education to ensure constant monitoring and treatment) Standard therapy (2 to 3 insulin injections/day)	9.5±1.3 (HbA1)	Not reported	Measured; HbA1c Retinopathy Cumulative frequency of serious retinopathy; increased with higher HbA1c levels only in patients with mild retinopathy at baseline, no increase in patients with moderate retinopathy (shown graphically) Patients with mild retinopathywith HbA1c below 7% did not develop serious retinopathy Nephropathy; patients with HbA1c<9% did not develop nephropathy 5/10 patients with HbA1c ≥9% developed nephropathy 0/12 patients with mild initial retinopathy and HbA1c ≥9% during the study had nephropathy Urinary albumin excretion (microgram/minute), mean±SD; HbA1c<7%; 87±40 HbA1c 7%-7.99%; 21±5 HbA1c 8%-8.99%; 55±19 HbA1c 9%-0.9%; 308±123 HbA1c ≥9; 266±150 Neuropathy (patients without neuropathy at baseline)

Study	Number of patients	Study type/ follow-up	Diabetes therapy	Baseline HbA1c level, mean %±SD	Frequency of HbA1cmonitoring	Measure of glycosylated haemoglobin and results
						HbA1c<7% (6.5±0.1%); 2/20 patients HbA1c 7%-7.99% (7.5±0.1%); 8/24 patients HbA1c 8%-8.99% (8.4±0.1%); 7/18 patients HbA1c ≥9% (9.6±0.2%); 3/7 patients Multivariate analysis Development of serious retinopathy at any time during follow-up; Related to HbA1c at baseline [OR(95%CI) 1.70(1.0 to 2.8)] and during first 6 to 60 months of follow-up [OR(95%CI) 2.4(1.4 to 4.3)], not after 60 months OR for HbA1c during the study Serious retinopathy; 2.70 (1.55 to 4.69) Nephropathy; 3.33 (1.66 to 7.56) Neuropathy; 3.13 (1.56 to 6.28)
Shaban 2006[673]	273	Cross-sectional observational study	Not reported	8.8±1.5 (HbA1c)	NA	Measured; HbA1c Quality of life HADS (maximum score 21-higher scores indicate worse outcome); HbA1c positively correlated with HADS scores (anxiety r=0.2, p=0.001, depression r=0.14, p=0.02) Patients'moderate to severe levels' of anxiety demonstrated poorer glycaemic control than those reporting 'none to mild' Anxiety score ≥11: HbA1c 9.4%; anxiety score <8, HbA1c 8.5%, p=0.001) No difference in HbA1c for patients reporting different symptom severity for depression (depression ≥11: HbA1c 8.7%; depression <8, HbA1c 8.9% p=0.5)
Tabaei 2004[709]	634	Cross-sectional observational study	Not reported	Median (range); 8.3(4.7-14.1) (HbA1c)	NA	Measured; HbA1c Linear regression Quality of life HbA1c not associated with QWB-SA derived utility score

Study	Number of patients	Study type/ follow-up	Diabetes therapy	Baseline HbA1c level, mean %±SD	Frequency of HbA1cmonitoring	Measure of glycosylated haemoglobin and results
						Multivariable regression analysis (adjustments; hypoglycaemia, gender, complications) HbA1c not associated with QWB-SA derived utility score (partial R2= -0.05, p=0.25)
Van Tilburg 2001[749]	30	Cross-sectional observational study	Insulin pump; 9/30(30%) Insulin 1 to 2 injections per day; 5/30(17%) Insulin ≥3 injections per day; 16/30(53%)	8.3±1.2 (HbA1c)	NA	Measured; HbA1c Linear regression Quality of life; HbA1clevels positively correlated with BDI scores with (r=0 .44, p<0.02)
WDRS 2013[443]	305	Prospective case series 20 years	93% on intensive insulin management (MDI or CSII)	8.0 ± 1.5 (HbA1c)	Not reported	% of patients who had HbA1c<7% with diabetic retinopathy at different severity grades: • None to minimal =34% • Mild to moderate = 18.5% • Vision threatening = 18.2%
WEINSTOCK 2013[768]	7012	Cross-sectional study/retrospective case-series n/a and previous 12 years data	Not reported	7.7 ± 1.2 (HbA1c)	Not reported	Frequency of SH event, with HbA1c levels: • <6.5: OR 1.95 [1.40 to 2.72] • 6.5 - 6.9: OR 1.64 [1.18 to 2.72] • 7.0 - 7.4: OR 1.0 • 7.5 - 7.9: OR 1.47 [1.09 to 2.00] • 8.0 - 8.9: OR 1.62 [1.21 to 2.17] • 9.0 - 9.9: OR 1.01 [0.66 to 1.52] • ≥10.0: OR 1.25 [0.80 to 1.97]
WESDR 1994[516]	2990	Prospective case series	Not reported	Younger onset;	Not reported	Measured; states 'glycosylated hemoglobin' Younger onset;

Study	Number of patients	Study type/ follow-up	Diabetes therapy	Baseline HbA1c level, mean %±SD	Frequency of HbA1cmonitoring	Measure of glycosylated haemoglobin and results
		10 years		12.6±2.6 Older onset; 11.1±2.4 (GHb)		HR (95% CI) for ischaemic heart disease mortality for a 1–percentage point increase in GHb; 1.18 (1.00 to 1.40) Older onset; HR (95% CI) for ischaemic heart disease mortality for a 1–percentage point increase in GHb; 1.18 (1.04 to 1.17)
WESDR 1995[401,402]	2990	Prospective case series	Not reported	Younger onset; 10.8 Older onset; 10.2 (GHb)	Not reported	Measured; states 'glycosylated hemoglobin' Retinopathy Younger onset patients; <30 OR of (95%CI) 2% difference in GHb from baseline to 6 year follow-up on the incidence of progression to proliferative retinopathy; 0.58 (0.48 to 0.72) Older onset patients OR of (95%CI) 2% difference in HbA1c from baseline to 6 year follow-up on the incidence of progression to proliferative retinopathy; 0.69 (0.47 to 1.04) Younger onset patients; OR of (95%CI) 2% difference in GHb from baseline to 6 year follow-up on the incidence of macular oedema; 0.53 (0.43 to 0.66) Older onset patients OR of (95%CI) 2% difference in GHb from baseline to 6 year follow-up on the incidence of macular oedema; 1.06 (0.67 to 1.69) Nephropathy Younger onset patients; OR of (95%CI) 2% difference in GHb from baseline to 6 year follow-up on the incidence of gross proteinuria; 0.71 (0.59 to 0.86) Older onset patients OR of (95%CI) 2% difference in GHb from baseline to 6 year follow-up on the incidence of gross proteinuria; 0.81 (0.61 to 1.09)

Study	Number of patients	Study type/ follow-up	Diabetes therapy	Baseline HbA1c level, mean %±SD	Frequency of HbA1cmonitoring	Measure of glycosylated haemoglobin and results
						Neuropathy Younger onset patients; OR of (95%CI) 2% difference in GHb from baseline to 6 year follow-up on the incidence of self-reported loss of tactile sensation; 0.81 (0.67 to 0.98) Older onset patients; OR of (95%CI) 2% difference in GHb from baseline to 6 year follow-up on the incidence of self-reported loss of tactile sensation; 0.77 (0.54 to 1.06) Younger onset patients; OR of (95%CI) 2% difference in GHb from baseline to 6 year follow-up on the incidence of self-reported loss of self-reported loss of temperature sensitivity; 0.84 (0.67 to 1.04) Older onset patients; OR of (95%CI) 2% difference in GHb from baseline to 6 year follow-up on the incidence of self-reported loss of self-reported loss of temperature sensitivity; 0.84 (0.61 to 1.16) Younger onset; any retinopathy GHb 5.6-9.4% (n=52), incidence; 82.1%, RR 1.0 GHb 9.5-10.5% (n=61), incidence 86.4%, RR(95%CI)1.1 (0.8 to 1.4) GHb 10.6-12.0% (n=71) incidence 93.1%, RR(95%CI)1.3 (1.0 to 1.7) GHb 12.1-19.5% (n=64) incidence 96.9%, RR(95%CI)1.6 (1.3 to 2.1) Younger-onset; progression to proliferative retinopathy GHb 5.6-9.4% (n=52), incidence; 6.2%, RR 1.0 GHb 9.5-10.5% (n=61), incidence 11.6%, RR(95%CI)1.9 (0.8 to 4.5) GHb 10.6-12.0% (n=71) incidence 34.4, RR(95%CI)5.9 (3.0 to 11.6) GHb 12.1-19.5% (n=64) incidence 96.9, RR(95%CI)9.9 (5.4 to 18.0)

Study	Number of patients	Study type/ follow-up	Diabetes therapy	Baseline HbA1c level, mean %±SD	Frequency of HbA1cmonitoring	Measure of glycosylated haemoglobin and results
						Older onset; any retinopathy GHb 5.6-9.4% (n=40), incidence; 65.9%, RR 1.0 GHb 9.5-10.5% (n=40), incidence 85.0%, RR(95%CI)1.1 (0.9 to 2.1) GHb 10.6-12.0% (n=32) incidence 78.8%, RR(95%CI)1.2 (0.7 to 1.9) GHb 12.1-19.5% (n=23) incidence 100.0%, RR(95%CI)2.1 (1.4 to 3.2) Older onset; progression to proliferative retinopathy GHb 5.6-9.4% (n=40), incidence; 10.7%, , RR 1.0 GHb 9.5-10.5% (n=40), incidence 13.1%, RR(95%CI)1.1 (0.4 to 2.8) GHb 10.6-12.0% (n=32) incidence 27.6%, RR(95%CI)1.3 (1.2 to 5.5) GHb 12.1-19.5% (n=23) incidence 37.9%, RR(95%CI)1.6 (1.6 to 7.3)
WESDR 1998[400]	987	Retrospective case-series	Not reported	NA	NA	Measured; states 'glycosylated hemoglobin' Multiple linear regression age mean Younger onset subgroup; GHb variable for negatively associated general health coefficient (r= -1.6, p<0.005), no association with physical functioning or physical role Older onset subgroup; GHb variable no association with general health, physical functioning or physical role
WESDR 1998a[403]	634	Prospective case series	Not reported	10.6±2.0 (HbA1)	Not reported	Measured; HbA1 Retinopathy After controlling for baseline retinopathy, duration of diabetes and gender, each percentage point of lower glycosylated haemoglobin at baseline was associated with increased odds of improvement of retinopathy (OR;1.41; 95% CI 1.19, 1.67) Progression to retinopathy HbA1 5.1-9.4% (n=187); 75.4%, RR 1.00 HbA1 9.5 to 10.5% (n=153); 79.5%, RR (95%CI) 1.37 (1.12 to 1.68) HbA1 10.6 to 12.0%(n=174); 95.2%, RR (95%CI) 1.99 (1.67 to 2.38) HbA1 12.1 to 19.5% (n=168); 95.0%, RR (95%CI) 2.64 (2.18 to 3.20)

Study	Number of patients	Study type/ follow-up	Diabetes therapy	Baseline HbA1c level, mean %±SD	Frequency of HbA1cmonitoring	Measure of glycosylated haemoglobin and results
						Incidence of macular oedema HbA1 5.1-9.4% (n=187); 12.7%, RR 1.00 HbA1 9.5 to 10.5% (n=153); 22.6%, RR (95%CI) 1.90 (1.12 to 3.25) HbA1 10.6 to 12.0% (n=174); 33.9%, RR (95%CI) 3.11 (1.95 to 4.95) HbA1 12.1 to 19.5% (n=168); 36.8%, RR (95%CI) 3.37 (2.12 to 5.34)
WESDR 1999[515]	1890	Prospective case series 14 years	Not reported	Younger onset; 10.8±2.1 Older onset; 9.6±2.0 (GHb)	Not reported	Measured; states 'glycosylated hemoglobin' Univariate analysis; lower extremity amputation Younger onset GHb 5.6–9.4% (n=223); incidence=2.5%, RR 1.00 GHb 9.5–10.5% (n=206); incidence= 6.7%, RR (95%CI) 2.93 (1.10 to 7.83) GHb 10.6–12.0% (n=220); incidence=7.6%, RR (95%CI) 3.21 (1.24 to 8.33) GHb 12.1–19.5% (n=216); incidence=13.4%, RR (95%CI) 5.64 (2.43 to 13.10) Older onset GHb 5.4–8.1% (n=244); incidence= 4.4%, RR 1.00 GHb 8.2–9.4% (n=218); incidence=8.5%, RR (95%CI) 1.98 (0.78 to 4.99) GHb 9.5–10.8% (n=223); incidence=12.6%, RR (95%CI) 2.68 (1.15 to 6.24) GHb 10.9–20.8% (n=225); incidence=14.6%, RR (95%CI) 3.79 (1.72 to 8.35) Multivariable analyses (linear logistic model) Younger onset GHb associated with a higher incidence of amputations; OR 1.39 (1.21 to 1.59), p<0.0001 Older onset GHb associated with a higher incidence of amputations; OR 1.25

Study	Number of patients	Study type/ follow-up	Diabetes therapy	Baseline HbA1c level, mean %±SD	Frequency of HbA1cmonitoring	Measure of glycosylated haemoglobin and results
						(1.09 to1.43), p<0.005
WESDR 2013[443]	583	Prospective case series 20 years	21% on intensive insulin management (MDI or CSII)	9.3 ± 1.7 (HbA1c)	Not reported	• Odds of Diabetic retinopathy severity by HbA1c (per 1%): OR = 1.34 [1.23 to 1.47] • % of patients who had HbA1c<7% with diabetic retinopathy at different severity grades: ○ None to minimal =11.1% ○ Mild to moderate = 9.5% ○ Vision threatening = 4.2%
Wikblad 1991[778]	185	Retrospective case series 9 years	≥20 U insulin daily at recruitment	8.7±1.3 (HbA1c)	Not reported	Measured; HbA1c Patients without retinopathy changes HbA1c ≤7.5%; 53% HbA1c 7.6-8.4%; 28% HbA1c 8.5-9.4%; 30% HbA1c ≥9.5%; 29% Patients without proteinuria; HbA1c ≤7.5%; 88% HbA1c 7.6-8.4%; 77% HbA1c 8.5-9.4%; 58% HbA1c ≥9.5%; 47%
Wikblad 1996[777]	108	Retrospective case series	≥ 20 U insulin daily at recruitment	7.7±1.0 (HbA1c)	Not reported	Measured; HbA1c Patient grouping according to mean values for HbA1c (during 1 year); Good; HbA1c ≤7.0, n=35 Acceptable; HbA1c = 7.1–8.0%, n=23 Unsatisfactory; HbA1c = 8.1 – 9.0%, n=24 Quality of life; SWEQUAL (high score indicates better health/more favourable health state; scale 0 to 100) Physical functioning;

Study	Number of patients	Study type/ follow-up	Diabetes therapy	Baseline HbA1c level, mean %±SD	Frequency of HbA1cmonitoring	Measure of glycosylated haemoglobin and results
						Good; 88.1 ±2.9 Acceptable; 91.0±2.4 Unsatisfactory; 78.2±5.5 Satisfaction with physical health; Good; 71.5±4.8 Acceptable; 72.8±5.8 Unsatisfactory; 61.6±6.1 Role limitation due to emotional health; Good; 92.2±3.0 Acceptable; 89.4±5.8 Unsatisfactory; 85.9±4.6 Groups comparable for; Satisfaction with family life, Marital functioning, Sexual functioning, General health, Positive feelings, Negative feelings, Pain, Mobility Patients who reported episodes of hypoglycaemia had significantly lower HbA1c mean values when compared with patients without severe hypoglycaemia (6.9%±1.0 versus 7.9%±1.2; F= 5.7, p=0.01)
ZOFFMANN 2014[806]	710	Cross-sectional study n/a	13.3% on CSII	8.2 ± 1.5 (HbA1c)	Not reported	• **PAID score:** SS higher prevalence of diabetes distress (PAID ≥30) among patients with HbA1c ≥8% (Score 48.3, 95% CI 41.4-55.3) versus those with lower HbA1c(score 35.7, 95% CI 29.0 – 42.9), p<0.01. • **HbA1cwas positively correlated with:** lack of motivation, and the PAID score (both p<0.001). • **HbA1cwas negatively correlated with:** perceived competence, self-esteem, well-being, and autonomy index (all p<0.001).

Abbreviations: ARR, absolute rate reduction; ASR, Adult-Self-Report Scale; BDI, Beck Depression Inventory; CES-D, Centre for Epidemiological Studies-Depression Scale; CSII, continuous

subcutaneous insulin infusion; ESRF, end-stage renal failure; GHb, glycosylated haemoglobin; HADS, Hospital Anxiety and Depression Scale; HR, hazard ratio; CVD, cardiovascular disease; MI, myocardial infarction; NA, not applicable; NPH, neutral protamine Hagedorn; NR, not reported; LEAD, lower extremity arterial disease; OR, odds ratio; QWB-SA, Quality of Well-Being Self-Administered; RR, relative risk; SCL-90, Symptom checklist-90; SDSCA, Summary of Diabetes Self-Care Activities; UAC, urine albumin concentration

Table 27: Study details and results for frequency of HbA1c monitoring

Study	Number of patients	Study type/ follow-up	Diabetes therapy	Baseline HbA1c level, mean %±SD	Frequency of HbA1c monitoring	Result
Larsen 1990[434]	240	RCT	See results	Monitored group; 10.1±1.9 Control group; 9.9±1.8 (HbA1c)	Every 3 months for monitored group	Measured HbA1c 1 year follow-up; HbA1c mean(±SD) Monitored group; decreased 10.1 ± 1.8% to 9.5 ± 1.3%(p<0.005) Control group; no difference Mean(±)HbA1c in monitored (n=98) versus control group (n=99) Baseline; monitored group 10.1±1.9% versus control 9.9±1.8% 3 months; monitored group 9.9±1.9% versus control; 10.1±1.6% 6 months; monitored group 9.8±1.7% versus control; 10.2±1.7% 9 months; monitored group 9.9±1.6% versus control; 10.2±1.7% 12 months; monitored group 9.4±1.4% versus control; 10.0±1.7%, p<0.02 18 months; monitored group 9.6±1.4% versus control; 10.1±1.5% 24 months; monitored group 9.3±1.2% versus control; 9.5±1.5% At 12 months Proportion patients in monitored group with HbA1c>10.0% decreased (46% to 30%, p<0.01), proportion of patients with values above 9.0% fell from 69% to 56% (p <0.05), proportion patients in control group with HbA1c> 9.0% remained at 69% Treatment changes during 1 year Control group (n=107) 1 daily injection; at entry 14.0% versus 11.2% at 12 months 2 daily injections; at entry 80.4% versus 67.7% at 12 months 3 or 4 daily injections; at entry 5.6% versus 27.1% at 12 months Monitored group (n=115) 1 daily injection; at entry 10.4% versus 4.3% at 12 months 2 daily injections; at entry 80.0% versus 55.7% at 12 months or 4 daily injections; at entry 9.6% versus 40.0% at 12 months (p<0.05

Study	Number of patients	Study type/ follow-up	Diabetes therapy	Baseline HbA1c level, mean %±SD	Frequency of HbA1c monitoring	Result
						for comparison between groups) Significant improvement in glycaemic control was achieved after 12 months care if clinicians and patients had access to HbA1c results, rather than being blinded to the results at 3 monthly consultations
Eid Fares 2010[221]	117	Retrospective case-series 5 years	NR	NR	Every 3 months	Measured HbA1c Nephropathy 18/117 (15.4%) developed nephropathy HbA1c in patients with; Neuropathy; 9.4±1.6% No neuropathy; 8.5±1.1% Fluctuations in HbA1c; Present with nephropathy; 15/18(83%) Present without nephropathy; 54/117(54%) Absent with nephropathy; 3/18(17%) Absent without nephropathy; 45/117(45%) Fluctuations and incidence of nephropathy in 77 patients HbA_{1C} ≤8%; With nephropathy, fluctuations present; 15(26%) With nephropathy, fluctuations absent; 5(1%) Without nephropathy; fluctuations present; 42(74%) Without nephropathy, fluctuations absent 19(95%) Multivariate analysis Mean HbA1c only significant predictor for development of diabetic nephropathy (adjustment for fluctuations) Average mean of HbA1c; OR(95%CI) 1.66 (1.03 to 2.68) [Model 1], 1.55 (1.01; 2.38) [Model 2], 1.75 (1.18; 2.59) [Model 3] Model 1; all risk covariates (average mean of HbA1c, Fluctuations in HbA1c, gender, family history, age at onset, time between diabetes onset to clinic admission, baseline BMI) Model 2; mean and fluctuations HbA1c

Study	Number of patients	Study type/ follow-up	Diabetes therapy	Baseline HbA1c level, mean %±SD	Frequency of HbA1c monitoring	Result
						Model 3; mean HbA1c Model 4; fluctuations HbA1c

Abbreviations: NA, not applicable; NR, not reported; OR, odds ratio

8.1.5 Economic evidence for optimal HbA1c

Published literature

No relevant economic evaluations were identified.

New economic analysis

New economic analysis was prioritised for this question. A summary is included here. The full analysis can be found in Appendix O.

a) Model overview and methods

An HbA1c target of 6.5% was compared with 7.5% in the model; however we did not estimate an ICER as the outputs of the model were only the costs and QALYs accrued by a cohort of patients reaching the target level, that is, the model did not compare actual strategies or interventions aimed at obtaining the set HbA1c target. For this reason, it would have been incorrect to conclude that the difference in costs and QALYs estimated in the model represent the incremental cost and effectiveness of setting a lower target, as this could be achieved through different strategies which have a cost that was not included in the calculations. This model simply estimates the potential cost savings and QALY gain in a hypothetical cohort of patients achieving the same set target. Even if a threshold analysis was conducted to estimate the maximum cost that we would be willing to pay (based on the cost-effectiveness threshold of £20,000per QALY) this would rely on the assumption that interventions provided to achieve the lower threshold are 100% effective (that is, all the patients to whom the interventions are provided achieve a target of 6.5%). For this reasons it would be misleading to estimate an incremental cost effectiveness ratio or to conduct a threshold analysis. The analysis was undertaken using a validated, internet-based model (IMS CORE Diabetes Model (CDM). IMS CDM is an interactive computer model developed to determine the long-term health outcomes and economic consequences of interventions for type 1 or type 2 diabetes mellitus. Separate transition probabilities and management strategies are used for each type where data exist, facilitating running diabetes type-specific analysis. IMS CDM has been widely used and validated against real-life clinical and epidemiological data.

A cohort of type 1 diabetes patients with defined demographic characteristics reflecting the adult type 1 diabetes population in the UK was used in the base case analysis. A lifetime horizon was used in the analysis. Health outcomes and costs were discounted at an annual rate of 3.5%. The analysis was undertaken from the perspective of the UK NHS and PSS.

b) Results

The mean costs and health outcomes associated with each strategy are reported in Table 28 below. Achieving a target of 6.5% HbA1ccompared with a 7.5% target is associated with a gain of 0.554 quality adjusted life-years (QALYs) and a reduction in healthcare costs of £3,524, when only the consequences of the lower HbA1cin terms of reduction of complications are considered and a discount rate of 3.5% is applied. The actual costs of strategies that have to be implemented to achieve this target have not been considered and could in theory offset the cost savings.

Table 28: Probabilistic results (mean per patient)

	HbA1c 6.5%		HbA1c 7.5%		Difference
	Mean	SD (low – high 95% CI)	Mean	SD (low – high 95% CI)	
Life expectancy - undiscounted	31.627	12.669 (30.842 -	29.752	12.658 (28.967 -	1.875

	HbA1c 6.5%		HbA1c 7.5%		Difference
years		32.412)		30.536)	
Life expectancy - discounted years	16.952	4.305 (16.685 - 17.218)	16.308	4.472 (16.031 - 16.586)	0.644
QALYs undiscounted	22.799	9.367 (22.218 - 23.38)	21.314	9.359 (20.734 - 21.894)	1.485
QALYs discounted	12.429	3.335 (12.223 - 12.636)	11.875	3.462 (11.66 - 12.089)	0.554
Direct Costs discounted (£)	29,908	18,739 (28,746 – 31,069)	33,432	20,272 (32,176 – 34,689)	-3,524

The undiscounted outcome values are quite high compared with the discounted outcomes as many of the benefits of the 6.5% strategy are experienced later in the patient's life through averted diabetes-related complications and subsequent deaths.

The analysis has some major limitations: the cost of any additional intervention(s) used to achieve the lower target is not included. Therefore this analysis does not give information about which interventions would be cost-effective in the achievement of a lower HbA1c target, and it does not conclude whether the lower target is cost-effective at all.

This original economic analysis is based on many parameters that are not specific to a type 1 diabetes population but utilises data on the type 2 population as well. It also utilises reduction in HbA1c as one of two main clinical outcome measures which is an intermediate outcome measure; but this is considered to be a reliable proxy measure of disease progression and complications outcomes. Its link to the most important clinical outcomes for diabetes patients is already well established and validated.

Disutility due to fear of hypoglycaemia was not explicitly included in the model. However, it was believed that the utility value associated with suffering a major hypoglycaemic event already incorporates this disutility.[157] Also the potential increased risk of hypoglycaemic events associated with a lower target level has not been taken into account in the analysis. This could have led to an overestimation of the QALY gain and cost savings associated with the lower target.

8.1.6 Evidence statements

Clinical

Optimal HbA1c target

Overall, Low quality evidence from 43 studies (mostly observational and mostly case-series but including 3 randomised controlled trials), showed that with lower HbA1cvalues the risk and incidence of clinical outcomes was significantly reduced. The main outcomes assessed by the evidence included mortality, CVD, CHD, stroke, retinopathy, low-level (micro) albuminuria, severe hypoglycaemia,

nocturnal hypoglycaemia, and QoL).Of these outcomes, all but hypoglycaemia rates were improved with lower HbA1c and/or intensive insulin therapy.

Frequency of HbA1c monitoring

Two studies (one RCT and one case series) examined frequency of monitoring HbA1cand one RCT (Cagliero et al., 1999) examined the benefits of having the HbA1cavailable at the consultation which was done 3 monthly. The last mentioned study showed significantly lower HbA1cin the group where the HbA1cresult was available during the consultation.

Economic

Our analysis indicates that achieving a target of 6.5% HbA1ccompared with a 7.5% target is associated with a gain of 0.554 quality adjusted life-years (QALYs) and a reduction in healthcare costs of £3,524. The analysis was assessed as partially applicable with potentially serious limitations.

8.1.7 Recommendations and link to evidence

The current guideline recommendations can be found at

https://www.nice.org.uk/guidance/ng17

Relative values of different outcomes	**Optimal glycosylated haemoglobin (HbA1c) target** Inadequate glycaemic control has been linked to microvascular and macrovascular complications. The evidence was reviewed to look at the range of glycosylated haemoglobin values at which the following complications occurred, in order to determine the optimal glycosylated haemoglobin target: • Mortality and sudden death • Macrovascular complications, including Myocardial infarction/Ischaemic heart disease; Stroke; Cardiac and peripheral revascularisation; Major amputations • Microvascular complications, including Retinopathy; Nephropathy, including low-level (micro) albuminuria, macroalbuminuria, proteinuria, end-stage renal failure, and renal replacement therapy • Neuropathy Hypoglycaemia is a regular occurrence in the treatment of type 1 diabetes and has been associated with a reduction in quality of life for people with diabetes, and an obstacle to improved control. The benefits of a glycaemic target that achieves an improvement in glycaemic control must be weighed up against the risk of producing an increase in the frequency of hypoglycaemia events. The following outcomes were therefore considered: Incidence of severe hypoglycaemia (hypoglycaemia event requiring help from a third party for correction), an event which has been recognised as having a significant impact on quality of life in patients with type 1 diabetes. Incidence of nocturnal hypoglycaemia. Loss of awareness of hypoglycaemia (episodes detected only by co-incidental blood glucose testing or recognised by someone other than the patient), as this increases risk of severe hypoglycaemia six-fold loss of awareness of hypoglycaemia was reported in the study but not prioritised by the GDG as a main outcome).[258] The evidence was reviewed to look at the impact of different HbA1c targets on quality of life outcomes. Setting HbA1c targets high may result in decreased quality

	of life by producing an increase in the incidence of vascular complications and/or worry about such complications. However, low HbA1c targets may be associated with an increase in the incidence of hypoglycaemia, which may also impact on quality of life. **Optimal frequency of glycosylated haemoglobin (HbA1c) monitoring** The evidence for HbA1c monitoring was reviewed to determine the following: • The frequency of HbA1c measurement required to achieve improvement in blood glucose control • The cost of HbA1c monitoring • Patient quality of life issues as a consequence of HbA1c monitoring
Trade-off between clinical benefits and harms	**Mortality and macrovascular disease** The available evidence showed that the incidence of macrovascular disease increased with increasing HbA1c. Poor glycaemic control was associated with an increased incidence of coronary heart disease (fatal and non-fatal)[448],[515]. Outcomes from the Diabetes Control and Complications Trial (DCCT) and the Epidemiology of Diabetes Interventions and Complications (EDIC) study showed that intensive treatment (mean HbA1c achieved 7.4 %) compared with conventional treatment (mean HbA1c 9.1 %) over 6 years reduced the risk of any predefined cardiovascular disease outcome by 42 % over a 17 year follow-up; each 10 % reduction in HbA1c was associated with a 20 % reduction in the risk of a cardiovascular event.[521,772] A further report has shown improved surrogate markers in the intensively treated group and a risk reduction of cardiovascular events of 42% (95% CI 9 to 63%, p=0.016) [428] although epidemiological data on the risk at any given mean HbA1c are still awaited. Reduced glycosylated haemoglobin levels have been shown to be associated with a reduction in the incidence of lower limb extremity amputations[515]. However, not all cohort studies reported an association between glycaemic control and the incidence of macrovascular disease[557]. One observational study divided people with type 1 diabetes into quartiles of HbA1c at recruitment into the study and followed them for 30 years.[698]Mortality increased in each successive quartile, being lowest in the quartile with an initial HbA1c<6.5%. **Microvascular disease** **Retinopathy** The DCCT showed that intensive treatment and improved glycaemic control reduced the risk of developing retinopathy by 76 % in those without retinopathy; whilst in those with mild retinopathy, development of severe non-proliferative retinopathy was reduced by 47%[2,176,722]. Inspection of the plot of 3-step deterioration of retinopathy against achieved HbA1c in these data showed flattening of the relationship at lower HbA1c values, with minimal deterioration when HbA1c was 6.5% or less. Retinopathy was reported not to occur at a level <7.5% in one observational study[21], whilst in a randomised controlled trial, no serious retinopathy developed in individuals with an HbA1c<7 % over 94 months[611-613]. **Nephropathy** In the DCCT, intensive control reduced the risk of low-level (micro) albuminuria (>40 mg/day) by 39 %, and reduced the risk of albuminuria (>300 mg/day) by 54%[2,176,722]. An increase in glycosylated haemoglobin was associated with increases in the urine/albumin creatinine ratio and the incidence of proteinuria in other studies.[778],

WESDR 1995, [21] Individuals with a mean HbA1c of <9 % were shown not to develop nephropathy in one study,[586-58]whilst logistic regression analysis in another study showed that increased HbA1c correlated with the incidence of end-stage renal failure[187]. In the 30 year follow-up of patients divided into quartiles of HbA1c at enrolment, frequency of renal replacement therapy was significantly increased in each quartile, being lowest in the quartile with initial HbA1c<6.5%.[698]

Neuropathy

The DCCT showed that intensive therapy and improved HbA1c reduced the incidence of clinical neuropathy by 60 % and abnormal nerve conduction by 44%[2,176,722], a finding supported by outcomes from other studies[401,402,611-613]. One study showed that mean HbA1c was 8.5 +/- 1.1 % in those without neuropathy and 9.4 +/- 1.6 % in those with neuropathy.[221]

Hypoglycaemia

The DCCT reported that patients receiving intensive therapy for improved glycaemic control were two to three times as likely to experience severe hypoglycaemia in comparison to those receiving conventional therapy[5]. Another study reported that in a cohort of patients aiming to improve HbA1c to a target of 6.2%, no increase in the incidence of hypoglycaemia events was recorded with improvements in HbA1c[576]. There have been a series of studies of intensified insulin therapy in which HbA1c is reduced at the same time as severe hypoglycaemia rate falls (see Chapter 7on education).

Quality of life

Measures assessing quality of life were found to be negatively associated with glycaemic control, with individuals with a higher HbA1c more at risk of depression and anxiety[403,777,749, 471673334] Audit of structured education programmes such as DAFNE[347] show improved quality of life and/or reduced anxiety and depression after intensified insulin therapy associated with lower HbA1c, and the DCCT/EDIC follow-up[365] showed deterioration of HbA1c (as well as serious diabetes complications, their symptoms and development of psychiatric illness) to be associated with deterioration in quality of life measures. However, the GDG noted that the studies did not indicate whether having a good HbA1c resulted in an improvement in quality of life or whether reduced mood led to deterioration in glycaemic control.

Frequency of monitoring

The available evidence showed that a significant improvement in glycaemic control was achieved after 12 months care if clinicians and patients had access to HbA1c results, rather than being blinded to the results at 3 monthly consultations.[434]

A further study showed that immediate access to HbA1c results from a bench top analyser available in clinic led to an improvement in glycaemic control in comparison to groups where no immediate HbA1c result was available.[111]

Although the evidence available showed that a knowledge of HbA1c at clinic appointments led to improvements in clinical outcomes, no data were available on the optimal frequency of HbA1c monitoring. The GDG recognised that if an HbA1c was checked, patients should be informed of the result and that ideally the result should be discussed at a clinic appointment to optimise therapeutic interventions.

The GDG recognised that there was no new evidence to suggest a change in practice for the frequency of HbA1c monitoring originally suggested in the 2004 NICE Guideline. Patient members of the GDG expressed concern that increasing the frequency of HbA1c monitoring may result in difficulties making arrangements to attend appointments, particularly if a visit to a healthcare member was required for a blood test in the week preceding a clinic appointment. The GDG therefore decided to leave the recommendation for the routine frequency of HbA1c monitoring

	unchanged from the NICE 2004 recommendation of 3-6 monthly, advising that an increase in the frequency of HbA1c checks might be considered if an individual's therapies had been recently altered.
Economic considerations	**Economic considerations for optimal HbA1c target** No relevant economic evaluations regarding optimum HbA1c target were identified. An original economic analysis was conducted to estimate the consequences in terms of costs and health outcomes associated with achieving a HbA1c target of 6.5% compared with 7.5%. This analysis showed that achieving a target of 6.5% HbA1ccompared with a 7.5% target is associated with a gain of 0.554 quality adjusted life-years (QALYs) and a reduction in healthcare costs of £3,524 over a lifetime, when only the consequences of the HbA1c reduction in terms of reduction of complications are considered. The actual costs of strategies that have to be implemented to achieve this target have not been considered in the analysis. Interventions that could be used to achieve a lower target HbA1c would include the use of insulin pumps, higher doses of insulin but also education programmes and more frequent monitoring. Since different interventions could be provided to achieve the lower target, it would not be possible to estimate this cost. Even if a threshold analysis was conducted to estimate the maximum cost that we would be willing to pay (based on the cost-effectiveness threshold of £20,000per QALY) this would rely on the assumption that interventions provided to achieve the lower threshold are 100% effective (that is, all the patients to whom the interventions are provided achieve a target of 6.5%). For this reasons it would be misleading to estimate an incremental cost effectiveness ratio or to conduct a threshold analysis. The GDG believed that the cost of interventions required to reach the target could be offset by the estimated improvement in QALYs and cost savings from the reduced complications. This analysis, however, was limited as it does not explicitly identify the most cost effective threshold and it does not confirm whether providing an intervention or some interventions to achieve a lower target is cost effective. **Economic considerations for optimal frequency of HbA1c monitoring** No relevant economic evaluations regarding optimum frequency of HbA1c monitoring were identified, and again the GDG made a qualitative judgment on cost-effectiveness for frequency of monitoring. Whilst an availability of HbA1c results to clinicians and individuals with type 1 diabetes was shown to improve glycaemic control outcomes[434], there was no evidence to suggest an optimum frequency of HbA1c monitoring. The previous 2004 NICE Guideline had suggested that HbA1c should be monitored 3-6 monthly. The GDG recognised that increasing the frequency of monitoring would have cost implications (investigation costs, appointment costs for blood tests and subsequent clinic appointments for review) with no evidence to suggest that an increase in the frequency of monitoring was required. Additionally, patient representatives within the GDG expressed concern that an increase in the frequency of monitoring may have an impact on quality of life, and the possibility of an increase in the frequency of missed clinic appointments. The GDG therefore decided to leave the frequency of routine HbA1c monitoring unchanged from the NICE 2004 recommendation of 3-6 monthly, thus resulting in no increase in HbA1c monitoring costs.
Quality of evidence	The methodological quality of each study was assessed by the GDG. Studies assessing populations with type 1 diabetes where ≥50 % of study participants were >18 years were considered for review. Studies with mixed populations of type 1 and type 2 diabetes were only considered if data were reported for the subgroup of type 1 diabetes patients, or if the assessed population contained ≥70 % of type 1 diabetes patients Randomised controlled trial data evidence was insufficient when considered alone,

	and therefore evidence from prospective case series studies and cross-sectional observational studies were identified by the GDG and included in the evidence review. This meant that the available evidence could not be GRADE assessed, and the GDG evaluated the quality of each individual study before making recommendations. **Evidence for optimum HbA1c target** Randomised controlled trials, prospective case series studies and cross-sectional observational studies were identified by the GDG for the HbA1c target review: 29 studies were identified as suitable for review. Four studies were reported from the Diabetes Control and Complications randomised control Trial (DCCT), with two further prospective case series studies reporting post-intervention follow-up of DCCT participants (DCCT/EDIC). Six studies were reported from the Wisconsin Epidemiology Study of Retinopathy (WESDR), a cross-sectional observational study. Three studies reported from the Stockholm Diabetes Intervention Study (SDIS), a randomised controlled trial with outcomes were reported at 94 months and a further cohort follow-up study three years later. Two studies reported from the Pittsburgh Epidemiology of Diabetes Complications Study, a prospective case series study. Two studies reported from a Swedish cohort looking at retrospective and prospective case series[777,778]. Further prospective cohort studies from Norway[97], Sweden[21], Finland[448], Spain[576] and Australia[334] and two further cross-sectional observational studies from Spain[187] and the US[471]were also reviewed when determining optimum HbA1c target. **Evidence for optimum frequency of HbA1c monitoring** Two studies were available for review of the optimal frequency of monitoring of HbA1c. The first study was a Very low quality randomised controlled trial investigating whether HbA1c outcomes improved when clinicians and patients were made aware of HbA1c results, with the control group blinded to HbA1c results[434]. The second study was a Very low quality case series in adults with type 1 diabetes and nephropathy[221]. The economic evidence was based on an original economic analysis which was assessed as partially applicable and with minor limitations.
Other considerations	In selecting an HbA1c target for the management of individuals with type 1 diabetes, the GDG recognised that individuals should achieve a target that minimised the risk of developing complications from glycaemia. Retinopathy is often the first microvascular complication to develop from inadequate glycaemic control, and particular attention was paid to the risk of retinopathy at varying levels of glycaemia reported by the Diabetes Control and Complications Trial. The GDG selected an HbA1c target of 6.5 % on the grounds that a minimal risk of retinopathy was achieved at this level, with further improvements in HbA1c not achieving any further significant reduction in retinopathy risk. The GDG also acknowledged the importance of the DCCT data as a large RCT of intensified therapy. It noted that the study design was intended to compare the

	outcomes of intensive versus conventional therapy, rather than identify an HbA1c value associated with minimal complication risk and that the target for the intensive therapy group was an HbA1c of 6.05%. This was achieved at least once during the study by 44% of participants using intensive therapy; but sustained there by only 5%. The mean HbA1c achieved over the trial by the intensive therapy group was just under 7% and this achieved value has support from other studies as being associated with reduced microvascular risk. The GDG therefore selected a target HbA1c value that is lower than the achieved HbA1c of the DCCT, as the one the evidence supports as associated with meaningful reduction in risk of complications, recognising that achieving the value of 7%, as done in the DCCT, was more likely if the target was set lower than this. The GDG recognised that aiming for an HbA1c of 6.5 % might lead to an increase in the frequency of hypoglycaemia events. The GDG believed that recent advances in treatments for type 1 diabetes mean that improvements in HbA1c might be achieved without necessarily increasing the risk of hypoglycaemia. The GDG agreed that if diabetes care was optimised with currently available therapeutic interventions, then a target HbA1c of 6.5 % could be achieved by some people with minimally increased risk of hypoglycaemia frequency and that adults with type 1 diabetes should be supported in achieving such a target, where this could be done without problematic hypoglycaemia. The GDG recommended that where such tight glycaemic control might not be desired by certain individuals (for example, those working at heights, those required to drive for a living), then healthcare professionals should be allowed to agree individualised targets of glycaemic control with patients, so that a glycaemia target allowing desired daily activities could be achieved. When determining the optimal frequency of HbA1c monitoring, the GDG agreed that HbA1c results should be readily available at consultation for discussion with patients attending clinic. The GDG therefore discussed whether site of care testing for HbA1c should be used in preference to laboratory testing. It was recognised that laboratory testing was likely to provide the most accurate measurement of HbA1c, although this was likely to require a patient to attend a pre-clinic appointment to have bloods taken and sent to the laboratory so that results were available at the time of clinic attendance. Site of care testing might allow HbA1c results to be made available whilst a patient attended clinic, allowing testing and discussion of results within a single visit. The GDG recognised that there was no evidence available on comparison of laboratory analysis and site of care HbA1c testing to determine which might be the most cost-effective, and which might have the greatest impact on improvement in glycaemic control in adults with type 1 diabetes. The GDG therefore made the research recommendation that this be investigated to determine which form of testing should be employed in clinics to improve clinical outcomes in the type 1 diabetes population.

8.1.8 Research recommendations

7. What methods and interventions are effective in increasing the number of adults with type 1 diabetes who achieve the recommended HbA1c targets without risking severe hypoglycaemia or weight gain?

Why this is important

The evidence that sustained near-normoglycaemia substantially reduces the risk of long-term complications in adults with type 1 diabetes is unequivocal. Current methods for achieving such

blood glucose control require skills in glucose monitoring and insulin dose adjustment, injection technique and site management, and the ability to use such self-management skills on a day-to-day basis life-long. Fear of hypoglycaemia and of weight gain are major barriers to success, as is fitting diabetes self-management into busy lifestyles. Everyone struggles to meet optimised targets and some are more successful in achieving them than others. Research into new interventions ranging from more effective education and support, through improved technologies in terms of insulin replacement and glucose monitoring, and including use of cell-based therapies, is urgently needed. It is also important to ensure that adults with type 1 diabetes are able to engage with such methodologies.

8. **Can a risk stratification tool be used to aid the setting of individualised HbA1c targets for adults with type 1 diabetes?**

Why this is important

Strict blood glucose control early in the history of type 1 diabetes has been shown to reduce the development and progression of long-term complications, but it is not possible to determine who is at particular risk of glucose-driven poor outcomes. Furthermore, there is a dearth of evidence of the risk:benefit ratio of strict blood glucose control in people who already have diabetes complications. Since achieving and maintaining near-normal blood glucose concentrations is complicated, a risk stratification tool to calculate the modifiable individual risk of complications willallow blood glucose targets to be tailored for each person and appropriate support to be provided.

9. **In adults with type 1 diabetes, is HbA1c measurement by laboratory analysis more cost-effective compared to site of care HbA1c testing?**

8.2 Self-monitoring of blood glucose

This section was updated in 2015 and minor language changes were made to recommendations in 2022. The current recommendations can be found at www.nice.org.uk/guidance/ng17

8.2.1 Introduction

Self-monitoring of blood glucose (SMBG) is central to the self-management of type 1 diabetes. A small sample of capillary blood, achieved by skin puncture, is obtained by the person with diabetes and the plasma glucose concentration of the sample is measured using a glucose meter.People with diabetes may use SMBG to check their plasma glucose when they feel unwell, to detect or confirm hypo- or hyper-glycaemia, but the ability of the person with diabetes to use SMBG to optimise blood glucose control longer term is dependent on their skills at interpreting blood glucose data and responding to them. Helping people with diabetes develop these skills is fundamental to structured education programmes supporting insulin self-management with the aim of optimising outcomes (see Section7.2).

Self-monitoring of blood glucose can be used in different ways. A person with diabetes can use the result immediately to determine whether to take any action to change it, for example, to eat if the result is low or take additional insulin if high. This is something many patients, at least after structured education in insulin therapy, find useful and relatively easy to do. [438]Recording SMBG over a period of time, usually by writing in a diary either at the time of the test, and sometimes accompanied by notes on food eaten, insulin taken or other relevant activity, or downloaded from the meter memory later (see SMBG technology,Section 10) may inform a decision to change an insulin regimen prospectively, for example, increase bedtime background insulin if pre-breakfast SMBG readings are consistently over target.This is reported by patients to be less easy.[438]Records

may also be shown to healthcare professionals intermittently, who may use them to advise on treatment change, but the utility of this may be limited by the infrequency of the contacts.

The person with diabetes needs to know the range of blood glucose readings he or she should aim to achieve. In people with type 1 diabetes, the range of possible blood glucose concentrations is much greater than in health. Blood glucose will be affected by such factors as the nutritional state (fasted versus fed); the speed of absorption of glucose from food or drink ingested; the amount of exercise taken, both in absolute terms and relative to the individual's norm; other drugs and substances, including alcohol, being taken and levels of emotional and physical stress. In the largest randomised controlled trial of intensified insulintherapy conducted in people with type 1 diabetes, the Diabetes Control and Complications Trial (DCCT), the targets for pre-meal, post-meal and 3 am plasma glucose were chosen to reflect the non-diabetic state (3.9-6.7; less than 10 and more than 3.6 mmol/litre, respectively).[721] However, the values achieved by people in the trial associated with reduced diabetes complications are not clear and the impact of hyperglycaemia at different times of day (particularly comparing fasting and pre-meal with post-prandial glucose excursions) on risk for diabetes complications remains uncertain.Indeed, the evidence suggests that only glycated haemoglobin predicts both micro- and macro-vascular disease[523] and SMBG may best be considered as a tool to achieve target HbA1c.

There are down-sides to SMBG. Although there have been major advances in the technology, such as reduced blood volume required per test, allowing less traumatic skin pricking devices, and much faster results from the meters, there remain issues. Use of the finger tip for sampling, which is recommended as having the closest approximation to a formal blood sample,[205] can cause discomfort; the procedure is messy and obtaining a result that is outside target is distressing. Another issue is timing. Plasma glucose concentrations can change very rapidly after eating carbohydrate, and post-prandial testing may pick up avalue that is very high but which may be only transiently so. Applying algorithms designed to correct pre-meal insulin doses for a pre-meal plasma glucose that is over target increases the risk of hypoglycaemia. (Reference for post meal corrections associated with hypoglycaemia)

The GDG therefore considered the questions:

- In adults with type 1 diabetes, what is the optimum frequency and timing to self-monitor blood glucose for effective diabetic control?
- In adults with type 1 diabetes, what is the optimum glucose target or profile for self-monitoring of blood glucose for effective diabetic control?

8.2.2 Review question: In adults with type 1 diabetes, what is the optimum timing and frequency to self-monitor blood glucose for effective diabetic control?

For full details see review protocol in Appendix C.

Table 29: PICO characteristics of review question

Population	Adults with type 1 diabetes • Adult defined as aged >18 years
Intervention/s	SMBG (finger pricks)
Comparison/s	• SMBG (finger pricks) – the same as the intervention but at a different frequency or delivery time • No comparison (non-comparative study)
Outcomes	• Adherence • Adverse events • Diabetic ketoacidosis (DKA) • HbA1c

	• Hypoglycaemia • Nocturnal hypoglycaemia • Quality of life • Severe hypoglycaemia • Time within range (blood glucose) • Unscheduled care use
Study design	RCTs, observational studies

8.2.3 Review question: In adults with type 1 diabetes, what is the optimum glucose target or profile for self-monitoring of blood glucose for effective diabetic control?

Table 30: PICO characteristics of review question

Population	Adults with type 1 diabetes • Adult defined as aged >18 years
Intervention/s	SMBG (finger pricks) – blood glucose target/profile values/glucose variability
Comparison/s	• Other target values (RCTs and comparative observational studies) • No targets (prognostic studies)
Outcomes	• HbA1cvalue • Quality of life • Risk of complications • Risk of hypoglycaemia • Risk of nocturnal hypoglycaemia • Risk of severe hypoglycaemia
Study design	RCTs, observational studies

8.2.4 Clinical evidence

For the review on self-monitoring of blood glucose targets and timing in people with type 1 diabetes we searched for randomised control trials or observational studies that reported on one of the following three topics: 1) the relationship between frequency of self-monitoring of blood glucose (SMBG) levels and diabetic control 2) the timing of measuring blood glucose levels and diabetic control and 3) the optimal target blood glucose value to prevent hypoglycaemia.

For topic one (frequency) we found 35 relevant studies.These included 2 RCTs, 31observational studies, and 2 post-hoc analysis of RCTs.[11,43,67,69,86,92,97,103,119,149,214,275,276,299,388,404,465,493,503,506,507,522,538,655,663,687,688,721,728,749,769,783,802-804] Some of these studies were not an exact match to the review protocol, but considered useful by the GDG. A summary of these papers can be found in Table 11.

For topic two (timing) we found 4 relevant studies. These included 3 observational studies and one post-hoc analysis of an RCT. [327,672,679,779]

For topic three (targets) we found seven relevant studies all of which were observational.[148,418,518,671,755,767,773]

Most of the studies were non-comparative observational studies (mainly case-series), and therefore were not able to be combined in a meta-analysis or GRADE profile (as GRADE is not designed for this type of study), and were graded as Low quality (due to theirstudy design). However, a summary of the methodological limitations of each of these studies can be found in Appendix G. The study details and the full results have been summarised in tables below. A summary of the included studies is provided inTable 24,Table 25, Table 26 andTable 27. See also the study selection flow chart in

Appendix D, forest plots in Appendix J, study evidence tables in Appendix G and exclusion list in Appendix K.

Table 31: Summary of studies included in the review for frequency and timing

Study	Intervention/comparison	Population	Follow-up	Outcomes	Comments
Frequency					
ABDELGADIR2006 [11]	Cross-sectional study SMBG: Fasting blood glucose using portable glucose meters Accutrend sensor	n=193 consecutive type 2 diabetes (n=143 [74%]) and type 1 diabetes (n=50 [26%])	Cross-sectional	HbA1c Blood glucose (mmol/litre)	Included type 1 and type 2 diabetes. Data from only the type 1 diabetes patient subgroupwas used for the analysis in this review.
BOTT 1994 [86]	Prospective case-series. SMBG: Patients advised to measure blood glucose before main meals and at bed time and to inject NPH-insulin in the morning and at bedtime and regular insulin before meals	n=697 type 1 diabetes patients. Type 1 diabetes patients, age 15-40 years Free of advanced diabetic late complications	3 years	HbA1c Severe hypoglycaemia	type 1 diabetes taking part in an in-patient treatment and teaching programme (TTP) for intensified insulin treatment (IIT)
BRAGD 2003 [92]	No intervention Prospective case-series.	n=178 with type 1 diabetes	Same cohort followed up 14 years later	Severe hypoglycaemia	Prediction of severe hypoglycaemia based on SMBG
COX 2007 [149]	No intervention. Prospective case-series.	n=90 type 1 diabetes	4 months	Severe hypoglycaemia	Prediction of severe hypoglycaemia based on SMBG
EVANS 1999 [214]	Retrospective case-series. Registry data	n=258 with type 1 diabetes	2 years data	Frequency of SMBG and HbA1c	Regression analysis
GORDON 1991 [276]	Cross-over trial BG reading 3 times before each meal and at 22h on any two non-consecutive days per week. BG reading 3x before each	n=25 with type 1 diabetes	3x12 week periods	Patient preference Frequency of SMBG and HbA1c	Regression analysis

Study	Intervention/comparison	Population	Follow-up	Outcomes	Comments
	meal and at 22 hours on any day of the week Two blood glucose measurements on each day for 7 days per week				
KARTER 2001 [388]	Retrospective case-series.	n=1159 TIDM	1 year of data	Frequency of SMBG and HbA1c	Regression analysis
KLEIN 1992 [404]	Prospective case-series. SMBG: Self-monitoring of blood glucose at least once a day or more. Two or more insulin injections per day. Combination of intermediate and short-acting insulin	n=1210 eligible patients with IDDM n=996 participated in the baseline examination. n=891 participated in the follow-up examination.	Participants followed up over 4 years	HbA1c	
MINDER 2013[507]	Cross-sectional study	n=150 type 1 diabetes	n/a	Association between frequency of SMBG and HbA1c	Results show HbA1cdeclines by approximately 0.2% for each additional measurement of SMBG, up to 4 times per day. After 4 times per day each additional mmt leads to a 0.02% decrease in HbA1c. HbA1c graphs show there is a decline until approximately 10 times per day and then HbA1c slowly increases again.
NATHAN 1996 [522]	Prospective case-series data	n=94 IDDM and n=137	1 year	Association	Insulin dependent and

Study	Intervention/comparison	Population	Follow-up	Outcomes	Comments
	taken from a cohort study	NIDDM		between frequency of SMBG and HbA1c	non-insulin dependent patients
SCHIFFRIN 1982 [655]	Cross over trial of multiple daily injections (MDI) and continuous subcutaneous insulin infusion (CSII) CSII 4x/day CSII 2x/day MSI 4x/day MSI 2x/day	n=21 IDDM	21 months	HbA1c	
SCHUTT 2006 [663]	Prospective case-series SMBG 4.4 times a day • Intensified conventional (≥4 daily injections) or continuous subcutaneous insulin infusion therapy (CSIIT) • Conventional (1-3 daily injections) therapy (CT)	n=24,500 participants with 19,491(80%) type 1 diabetes. For each patient the most recent complete year of diabetes care was evaluated.	1 year	HbA1c	On average type 1 diabetes performed 4.4 blood glucose measurements per day. This number increased continuously with the following years (1995: 3.1 values/day and 2004: 4.9 values/day; p<0.0001).
SKEIE 2009 [688]	RCT SMBG: Focussed, structured 9-month SMBG regular care SMBG	n=134 adults with type 1 diabetes. n=65, control group; n=69, intervention	9 months	HbA1c	
TILDESLEY 2004 [728]	Prospective case-series SMBG: The majority of patients used 2 injections of insulin per day, with a treatment goal of	n=934 TID using insulin therapy	10-year observation period with an average of 4.7 visits	HbA1c Hypoglycaemia	The number of insulin injections per day increased during the 10-year observation period.

Study	Intervention/comparison	Population	Follow-up	Outcomes	Comments
	A1C<8.0% (normal range: 4.0% to 6.0%)				
WEITGASSER 1994 [769]	Prospective case-series. SMBG: At baseline (year one) and five years SMBG was done ≤2 per day by 51% versus 12%, >2 but <4/day in 20% versus 21%, and ≥4/day by 29% versus 67% of the patients.	n=57; on intensive insulin therapy (IIT) requiring SMBG	5 years	HbA1c Hypoglycaemia Retinopathy Neuropathy	
ZIEGLER1993[803]	Cross-sectional study SMBG: Blood glucose measured 4 times a day (1 + 1 + 2 in a 3-injection regimen, 2 + 2 in a 2-injection-split and mixed regimen) before each meal and at bed-time.	n=80 insulin dependent diabetic patients chosen at random among diabetic patients treated by intensive insulin therapy (IIT)	At least 6 months	HbA1c	Fewer than 2 daily blood glucose determination was considered as incompatible with proper use of SMBG

Table 32: Summary of papers that were not fully extracted but included in the evidence statements

Study	Intervention/ comparison	Population	Follow-up	Outcomes	Comments
Frequency					
ANON 1993[721]	RCT – conventional once a day SBMG versus intensive ≤4 times a day	n=1441 IDDM (<20% 13-18 year olds)	6.5 years	Mortality Hypoglycaemia Diabetic Ketoacidosis Quality of life	Included <20% adolescents.McCARTER2006 is post-hoc analysis
ARASZKIEWICZ 2008 [43]	Prospective case-series. No intervention. Only	n=86 Type 1 diabetic	7.1±1.5 years	Association between risk of retinopathy and SMBG	

Study	Intervention/ comparison	Population	Follow-up	Outcomes	Comments
	logistic regression model was used to estimate RR for diabetic retinopathy and low-level (micro) albuminuria events	patients			
BELL 1994 [67]	Prospective case-series.	n=211 Insulin dependent diabetes	Questionnaire	Severe hypoglycaemia and glucose tests and insulin injections	
BELL1984 [69]	Prospective case-series.	n=34 Diabetic patients	3-4 months.	Association between frequency of testing and HbA1c	
BRUTTOMESSO 1992 [103]	No intervention.Retrospective case-series.	n=17 Type 1 diabetes	23.6 months (3-83mo)	Association between frequency of testing and HbA1cand blood glucose level	
BRINCHMANN-HANSEN 1992 [97]	Prospective case-series. Insulin pumps (continuous subcutaneous insulin infusion) versus Multiple injections (4-6 times a day) and conventional insulin (2 times a day)	n=45 Insulin dependent diabetes	7 years	HbA1c readings	
CHAN 2009 [119]	Prospective case-series. No intervention.	n=1898 Type 1 diabetes	5 years, this includes a 2-week cross-sectional and a 9-month longitudinal survey.	Association between frequency of testing and achieving HbA1c of <7%	
GONDER 1988 [275]	Prospective case-series. Use of memory meters versus record test results in diaries	n=30 Adults with insulin dependent diabetes of at least 1 year	2 weeks	Association between frequency of SMBG and HbA	
HARTEMANN2001 [299]	Cross-sectional study	n=122	Cross-sectional study	Association between frequency of	

Study	Intervention/ comparison	Population	Follow-up	Outcomes	Comments
	Good glycaemic control. HbA <7.5% versus poor glycaemic control HbA >8.5%	Adults with type 1 diabetes		SMBG and complications	
LLOYD 1993 [465]	Cross-sectional No intervention. Multiple regression analysis to assess which factors are independent correlates of glycaemic control (as measured by GHb).	n=592 type 1 diabetes	Cross-sectional	Association between daily injections or tests and glycaemic control	
MERIMEE 1984 [503]	Prospective case-series. Glucose monitored initially daily, later 2 times a week	n=15 diabetic patients (unclear if type 1 or type 2 diabetes) with normal IGF-I and IGF-II values	6 months	Change in HbA1c	
MCCLEAN 2005 [493]	Cross-sectional study. No intervention.Logistic regression analysis was used to identify characteristics associated with the presence of complications.	n=290 Type 1 and type 2 diabetes	Cross-sectional	Association between HbA1c and risk of retinopathy and neuropathy	
MILLER 2013 [506]	Cross-sectional study. No intervention. General linear relationship between HbA1clevels and SMBG	n=8914 Type 1 diabetes (adult data only)	Cross-sectional registry study	Association between frequency of SMBG and HbA1c	
NAYAK 2011[538]	Cross-sectional study.	n=127 Type 1 diabetes	Cross-sectional study	Predictors of HbA1c.	

Study	Intervention/ comparison	Population	Follow-up	Outcomes	Comments
ABSTRACT	No Intervention.	61.4%			
SJOBERG 1988 [687]	Cross-sectional study. No intervention.Pearson correlation analysis.	n=44 Insulin dependent diabetes.Excretors of C-peptide versus non-excretors	Cross-sectional analysis	Association between frequency of SMBG and HbA1c	
VANTILBURG 2001[749]	Cross-sectional study. No intervention.Linear regression analysis.	n=30 Type 1 diabetes	Cross-sectional analysis	Association between frequency of SMBG and HbA1c	
WOO 2011 [783] ABSTRACT	Cross-sectional study. No intervention.	n=325 type 1 diabetes n=293 type 2 diabetes	Cross-sectional study	Association between frequency of home glucose monitoring and HbA1c	
ZIEGLER 2012 [804] ABSTRACT	Cross-sectional data from an RCT	n=202 type 1 diabetes n=17 type 2 diabetes	Post-hoc analysis	Association between clinical outcomes and SMBG frequency.	
ZIEGLER1989 [802]	Prospective case-series.	n=14	21 days	Association between frequency of SMBG and HbA1c	

Table 33: Studies included in review for the optimal time of day to measure blood glucose levels

Study	Intervention/comparison	Population	Follow-up	Outcomes	Comments
HILLMAN 2004 [327]	Retrospective case-series.Measured glucose levels at pre and post meal times.	n=146 type 1 diabetes	8 weeks	Predictors of HbA1c	
SERVICE 2007 [672]	Post-hoc analysis (prospective case-series data) of RCT SMBG: Intensive therapy Conventional therapy	n=565 volunteers. n=296 assigned to conventional therapy; n=269 assigned to intensive therapy	6.5 years	HbA1c	

Study	Intervention/comparison	Population	Follow-up	Outcomes	Comments
SHIMIZU 2008 [679]	Cross-sectional study. SMBG: 6 times a day pre and post each meal	n=15 type 1 diabetes	1 week	HbA1c	
WILLEY 1993 [779]	Prospective case-series. SMBG: Four times daily (4/day) HBGM. Once-daily HBGM at a variable time each day (Var1/day),	n=12 IDDM participants treated three to four times daily were asked by their clinicians to perform Home Blood Glucose Monitoring (HBGM)	4 weeks	Mean blood glucose	

Table 34: Summary of studies included in the review for glucose targets

Study	Intervention/comparison	Population	Follow-up	Outcomes	Comments
COX 1994 [148]	SMBG: 50 SMBG readings over a 2 to 3 week period with a hand held computer. Prospective case-series.	n=78 Insulin Dependent Diabetic Mellitus (IDDM)	Data collected during a 6 month baseline period	HbA1c Blood glucose	
KOVATCHEV 2000 [418]	SMBG: all participants were instructed to use blood glucose (BG) memory meters for 4-6 months and to measure their BG two to four times a day. During the same period of time 5 to 8 HbA1c assays were performed for each subject. Prospective case-series.	n=700 participants with IDDM Data for n=608 participants were completed with SMBG and HbA1c records.	6 months	HbA1c Blood glucose	
MUHLAUSER1998 [518]	Self-administered questionnaire used to assess patients' treatment goals.	n=669 with type 1 diabetes: 18 years or older	19 months	Severe hypoglycaemia	The questionnaire consisted of 10 items which were rated on a

Study	Intervention/comparison	Population	Follow-up	Outcomes	Comments
	Questions possibly relevant for the prediction of severe hypoglycaemia (SH) were used. Prospective case-series.	Initiation of insulin therapybefore 31 years of age			6-point Likert scale (1 = very important; 6 = totally unimportant).
SERVICE 2001 [671]	SMBG: Intensive therapy Conventional therapy Prospective case-series.	n=565 volunteers. n=296 assigned to conventional therapy; n=269 assigned to intensive therapy		HbA1c Blood glucose	
VERVOORT 1996 [755]	SMBG: All treated with short-acting insulin at least three times a day and intermediate-acting insulin at night. Prospective case-series.	n=31 type 1 diabetes randomly selected from the population of a diabetes outpatient clinic.	Overnight observation	Hypoglycaemia	
WEI 2014[767]	SMBG values and HbA1c values. Prospective case-series.	n=387 (237 type 1 diabetes – subgroup analysis has been done)	12 weeks	Blood glucose values at different HbA1c measurements	
WHITE1982 [773]	SMBG: Conventional therapy (CT) Intensive therapy (IT) Prospective cohort study.	n=36 participants with IDDM. 5.5% (2) of the population <18 years of age. n=25 assigned to CT; n=11 non-obese assigned to IT	4-6 months	HbA1c Retinopathy	

1 **Outcomes**

2 **Table 35: Results of studies investigating relationship between frequency of self-monitoring of blood glucose and glucose control.**

Study	Study design	Insulin regimen	Number of patients	Frequency of SMBG	Outcome
SMBG versus none					
ABDELGADIR2006 [11]	Cross-sectional	No detail	n=50	SMBG versus not	Lower HbA1c5.6±1.5% (SMBG) versus 9.4±2.1% (none)
SMBG 0 to ≥3 times per day					
BOTT 1994 [86]	Prospective case-series.	to inject NPH-insulin in the morning and at bedtime and regular insulin before meals	n=697	0 to ≥2 times a day	An increased frequency was associated with a lower HbA1c
HARTEMANN2001[299]	Cross-sectional. Good glycaemic control. HbA <7.5% versus Poor >8.5%	Daily injections 3.1± 0.9	n=122	Mean 2.7 to 3.6 times a day	Well controlled group carried out more home blood glucose tests and fewer complications (physical complaints, psychological distress, leisure restrictions, conscious experience and management of hypoglycaemia, diet, difficulties at work)
KLEIN 1992 [404]	Prospective case-series 4 years.	64% ≥2 insulin injections times a day; 68% combination of intermediate short-acting	n=1210	0 to ≥3 times a day	HbA1c decreased more from baseline with increased frequency of SMBG
KARTER 2001 [388]	Prospective case-series, registry cohort	Insulin injections <1 to 3 times a day	n=1159	0 to ≥3 times a day	An increased frequency was associated with a lower HbA1c
TILDESELEV	Prospective case-	The majority used 2 injections/day, with	n=934	<1 to 1.5 times a day	An increased frequency was associated with a lower HbA1c

Study	Study design	Insulin regimen	Number of patients	Frequency of SMBG	Outcome
2004 [728]	series. 10 years	a treatment goal of ACI <8% (normal 4-6%)			
ZIEGLER 2012 [804]	Post-hoc analysis (cross-sectional data) from an RCT	NA	n=202	≥3 times a day	An increased frequency was associated with a lower HbA1c
ZIEGLER1989 [802]	Prospective case-series. 21 days	NA	n=14	>3 times a day	An increased frequency was associated with a lower HbA1c (r=-0.85, p<0.001).
SMBG up to ≥4 times per day					
ANON 1993[721]	RCT 6.5 years	Insulin injections Intensive ≤3 times a day Conventional 1-2 times a day	n=1441	4 versus 1 times a day	NS difference in mortality Hypoglycaemic episodes per 100 patient-yearsIntensive 62 versus conventional 19 Diabetic ketoacidosis per 100 patient-years Intensive 2 versus 1.8 conventional Quality of life no difference
SCHIFFRIN [655]	Cross-over trial 21 months	Multiple sc. Injections or continuous sc. injections	n=21	4 versus 2 times a day	An increased frequency was associated with a lower HbA1c
ARASZKIEWICZ 2008 [43]	Prospective case-series 7.1 years	Multiple daily injections with adapting short-acting insulin for before meals	n=86	3.6 to 4.1 times a day	Subjects who developed retinopathy had higher HbA1c. Risk of retinopathy was associated with infrequent monitoring of blood glucose RR=5.5 (2-15.11) Risk of low-level (micro) albuminuria was associated with bad self-monitoring of glucose (RR=2.86 (1.1-7.24)
EVANS 1999 [214]	Retrospective case-series, registry database	No detail	n=258	1 to 4 times a day	HbA1c decreased 0.7% for every additional SMBG per day
GONDER1988 [275]	Prospective case-series 2 weeks	Fast and intermediate-acting insulin, except one	n=30	0.21 to 4.43 times a day	An increased frequency was associated with a lower HbA1c

Study	Study design	Insulin regimen	Number of patients	Frequency of SMBG	Outcome
		who used multiple injections of regular insulin			
MINDER 2013 [507]	Cross-sectional study	Flexible intensified insulin therapy (details not given)	n=150	1->4 times a day	Mean HbA1cdeclined with increasing number of SMBGs per day Decline continued up to at least 4 SMBGs/day before flattening No. of SMBGs/day per 1 mmt increase and difference in HbA1c(95% CI): • ≤4 SMBGs = -0.19% (-0.42 to 0.05) • >4 SMBGs = -0.02 (-0.10 to 0.06) • HbA1cgraphs show there is decline until approximately 10 times a day and then HbA1c slowly increases again.
NATHAN 1996[522]	Prospective case-series data from cohort study	70% injecting insulin 2 times a day	n=231	1 to 4 times a day	An increased frequency was associated with a lower HbA1c
SCHUTT 2006 [663]	Prospective case-series>6 months	Conventional (≥4 injections/ day) or continuous or 1-3 injections/day	n=24,500	Mean 3.1 to 4.9 times a day	One additional daily BG measurement improved HbA1cby 0.26%
WEITGASSER 1994 [769]	Prospective case-series 5 years	All except one received intermediate or intermediate and long-acting insulin 2 times a day and shorting acting before meal times. One was on pump	n=57	Subgroup analysis of <4 to >4 times a day	Decrease in HbA1c from 7.2±1.6 to 6.2±1.4%
ZIEGLER 1993	Cross-sectional	Target blood sugar	n=80	4 times a day	Greater compliance to 4 times a day was associated with

Study	Study design	Insulin regimen	Number of patients	Frequency of SMBG	Outcome
[803]		3.6 – 7.3 mmol/litre fastingor before each meal and 5.6-7.3 mmol/litre at bedtime.3 times a day for regular insulin; 2 times a day for intermediate-acting insulin			lower HbA1c
SMBG up to ≥10 times per day					
MILLER2013[506]	Cross-sectional registry data	NA	n=8914	0 to ≥10 times a day	A higher number of SMBG measurements per day was strongly associated with a lower HbA1c in all groups.
COX 2007 [149]	Prospective case-series	0.48±0.26 units/kg/day	n=90	3 to 5 times a day Mean 5.4±2.3 times a day	5 times a day better predicted severe hypoglycaemia than 3 times a day
SMBG: studies where measurements as times/day was not reported					
SKEIE 20009 [688]	RCT 9 months	Focused regimen aimed at enhancing focus on BG self-management versus usual daily 25% on insulin pump	n=134	Intensive (details not given) versus 1 times a day	Comparing the 2 groups, A1C was approximately 0.6% lower in the intervention group No increase in major or minor hypoglycaemia in both groups during the study period
VANTILBURG 2001 [749]	Cross-sectional	53% ≥3 injections/day 30% insulin pump 17% 1-2 injections/day	n=30	25.5 ± 9.9 times a week	An increased frequency was associated with a lower HbA1c
SJOBERG 1988 [687]	Cross-sectional	n=34 insulin 2 times a day, n=8 3 times a	n=44	0 to 120 months	An increased frequency was associated with a lower HbA1c

Study	Study design	Insulin regimen	Number of patients	Frequency of SMBG	Outcome
		day, n=1 4 times a day. 82% intermediate or long-acting insulin and soluble insulin..			
NAYAK 2011[538]	Cross-sectional	NA	n=127	NA	Blood glucose variability explained 39% of variance of HbA1c.
LLOYD 1993 [465]	Cross-sectional	NA	n=592	SMBG (no detail)	An increased frequency was associated with a lower HbA1cNumber of tests performed daily r=-0.12 p=0.0146
CHAN [119],	Prospective case-series. 5 year, this includes a 2-week cross-sectional and a 9-month longitudinal survey.	No details	n=1898	Regular (no detail)	SMBG versus not was associated with two to three fold increased odds of reaching the A1C goal of <7%.
BRINCHMANN-HANSEN 1992 [97]	Prospective case-series 7 years	Unclear	n=45	Regular (no detail)	Intensified insulin treatment and home blood glucose monitoring improved concentrations of HbA1c from 11.2% to 9.5%
Studies showing no relationship between SMBG and glucose control					
GORDON [276]	Cross-over study 3 times for 12 weeks	Average 3.3 (0.03 to 11.8) dose changes per week	n=25	4 versus 1 times a day	No relationship between frequency of altering insulin dosage and HbA1c
MCCLEAN 2005[493]	Cross-sectional	NA	n=290	Daily SMBG (no detail) versus no daily testing	SMBG was not associated with risk of developing retinopathy/neuropathy
BRUTTOMESSO 1992 [103]	Retrospective case-series, mean 23.6 months (3-83months)	Unclear	n=17	0.5 to 5 times a day	A weak correlation was found between number of blood glucose readings/day and daily blood glucose level, r=0.44, and serum HbA1c r=0.45, both p<0.05

Study	Study design	Insulin regimen	Number of patients	Frequency of SMBG	Outcome
MERIMEE1994[503]	Prospective case-series 6 months	Minimum of 2 times a day injections of insulin with supplementary insulin given on the basis of monitoring blood glucose 4 times a day	n=15	4 times 7 days a week then 2 days a week	HbA1cdecreased despite lower frequency of SMBG
WOO 2011[783] Abstract	Cross-sectional	NA	n=618	<2 to >3 times a day	No relationship between frequency and HbA1c
BELL 1994 [67]	Prospective case-series. Questionnaire	History of SH 2.72 injections/ day. No history of SH 3.06 injections/ day	n=211	2.3 to 2.5 times a day	Patients with severe hypoglycaemia more likely to perform SMBG at home more frequently
BELL 1984 [69]	Prospective case-series, 3-4 months	Insulin 1-2 times a day	n=36	<1 to 4 times a day	Frequent testing was not more prevalent in those whose haemoglobin A1 improved.
TILDESELEV 2004 [728]	Prospective case-series. 10 years	The majority used 2 injections/day, with a treatment goal of ACI <8% (normal 4-6%)	n=934	<1 to 1 times a day	No relationship between frequency and HbA1c
BRAGD 2003 [92]	Prospective case-series. 2 different time points	Multiple injection therapy	n=178	Multiple	SMBG not a predictor of severe hypoglycaemia

Table 36: Frequency of self-monitoring of blood glucose and HbA1c(%)

Study	0	0-1	0-2	1	1-2	2-3	2	>2	3	3-4	≥3	<4	>4	4	5-6	5	6	7	7-9	8	≥10	SBMG Non-specific
ABDELGADIR2006 [11] Cross-sectional	9.4±2.1																					5.6±1.5
Bott 1994 [86] Case-series	10.4±2.2	9.5±1.8			9.3±1.6			8.9±1.5														
Gordon 1991[276] Cross-over 3x12 weeks							9.7±1.8 9.7±2.0							9.5±2.0 9.6±2.0 9.4±1.9 9.6±2.1								
Karter2001[388] Case-series, registry database	9.1	8.9		8.5							7.7											
Klein 1992 [404] Case-series, 4 years	-0.6	-0.6			-1.0			-1.3			-1.1											
MILLLER 2013 [506] Cross-sectional			9.6 8.6 8.4							8.6 8.0 8.0 7.6					8.0 7.6 7.7 7.5				7.7 7.4 7.3 7.2		7.5 7.1 7.2 6.9	
Schiffrin1982 [655] Cross-over trial							10.3±0.5 10.2±0.5							7.9±0.4 8.0±0.1								

Study	0	0-1	0-2	1	1-2	2-3	2	>2	3	3-4	≥3	<4	>4	4	5-6	5	6	7	7-9	8	≥10	SBMG Non-specific
							10.0 ±0.9 10							8.2± 0.4 8.1± 0.2 8.1± 0.4 8.0± 0.6 8.6 8.7									
SCHUTT 2006[663]Case-series ≥4 times a day insulin	10.5			9.9			10.1		9.6					8.8		8.2	7.9	8.1		8.1		
1-3day insulin	9			8.7			8.3		8.5					8.1		7.8	7.9	7.7				
Weitgasser 1994 [769] Case-series												7.2± 1.6	6.2± 1.4									
WOO 2011[783] Cross-sectional			8.65			8.58					8.22											
ZIEGLER 1993 [803] Cross-sectional														6.7± 1.1								

Table 37: Results of studies reporting on the timing of measuring blood glucose levels and effect on HbA1c

Paper	Number of patients	SBMG regime	Result
HILLMAN2004 [327]	n=146	6 times a day Before and after breakfast, lunch and dinner	Best predictors of HbA1c were post-breakfast glycaemia, pre-breakfast glycaemia and pre-dinner glycaemia
SERVICE2007[672]	n=565	7 times a day before and after each meal and before bedtime	The strongest correlation between HbA1c and blood glucose measurements was detected from the mean of 7 measurements over a 24 hour period. The next best correlation was with mean of after breakfast+ before and after lunch+ before and after supper Subsequently, it was best correlated with mean postprandial.
SHIMIZU 2008[679]	n=15 type 1 diabetes	6 times a day Fasting glucose before breakfast, lunch and dinner.Post-prandial glucose.	No significant correlation between HbA1c and fasting glucose levels A correlation was found between HbA1c and all post-prandial levels.
WILLEY 1993 [779]	n=12	1 times a day versus 4 times a day Once-daily home blood monitoring at a variable time of day versus four times daily: pre-breakfast; pre-lunch, pre-dinner; pre-bed.	Measuring blood glucose four times a day (pre-breakfast, pre-lunch, pre-dinner and pre-bed) was no better than at a variable time of the day for mean blood glucose levels.

Table 38: Results of studies reporting on target of blood glucose levels and clinical outcomes

Author	Number of patients	SMBG regime	Result
COX 1994 [148]1994	n=78	50 SMBG over 2-3 weeks at baseline and 6 months	Blood glucose index • <2.75 BG index = 5.2 hypoglycaemic episodes • ≥2.75 BG index = 13.6 hypoglycaemic episodes • <4.6 SMBG SD = 6.5 • ≥4.6 SBBG SD = 12.3 • <9.85 HbA1c = 9.3 • ≥9.85 HbA1c= 6.3
MUHLHAUSER 1998 [518]	n=669	<2 times a day 15% ≥2 times a day 85%	Trend to show the higher the number of BG values under 3.3 the higher the number of episodes of severe hypoglycaemia. Blood glucose levels at which first symptoms are felt • ≥2.8 mmol/litre 66%;2.2-2.7 mmol/litre 20%;<2.2 mmol/litre 13% never feeling symptoms 1%
KOVATCHEV 2000 [418]2000	n=608	SBMB 2-4 times a day	A lower blood glucose value was associated with a lower HbA1c level. • <8.6 mM = 8.29 HbA1c • 8.6- 9.8 mM = 8.7 HbA1c • 9.7-10.6 mM = 9.14 HbA1c • 10.6-12 mM = 9.5 HbA1c • >12 mM = 10.52 HbA1c
SERVICE 2001 [671]2001	n=565	SMBG same for all patients 7 times a day (90 minutes post breakfast, lunch and supper values, and pre meal values and bedtime)	Association between MBG and retinopathy: • <8.3 mmol/litre = NS relationship • >8.3 mmol/litre = increased risk • Up to 16.6 mmol/litre versus 8.3 mmol/litre 15 times increased risk
VERVOORT 1996 [755]	n=31	Continuous, measuring in hospital via catheter.	Fasting blood glucose of: • ≥5.5mmol/litre was never preceded by 'early morning' hypoglycaemia. • <5.5 mmol/litre at 07.30 h was associated with 'early morning' hypoglycaemia in 6 of 12 patient-nights;

Author	Number of patients	SMBG regime	Result
WEI 2014 [767]	n=237	12 weeks: • 8-point SMBG (average SMBG of 11 days per person over the 12 weeks) • Monthly HbA1c	**Fasting blood glucose values for:** • HbA1c of 5.5-6.49 = 122 mg/dL (113-132) • HbA1c of 6.5-6.99 = 144 mg/dL (134-154) • HbA1c of 7.0-7.49 = 155 mg/dL (143-168) • HbA1c of 7.5-7.99 = 170 mg/dL (159-181) • HbA1c of 8.0-8.49 = 178 mg/dL (161-194) **Preprandial blood glucose values for:** • HbA1c of 5.5-6.49 = 119 mg/dL (115-124) • HbA1c of 6.5-6.99 = 140 mg/dL (134-147) • HbA1c of 7.0-7.49 = 156 mg/dL (150-163) • HbA1c of 7.5-7.99 = 159 mg/dL (151-166) • HbA1c of 8.0-8.49 = 175 mg/dL (162-188) **Postprandial blood glucose values for:** • HbA1c of 5.5-6.49 = 139 mg/dL (133-145) • HbA1c of 6.5-6.99 = 161 mg/dL (155-168 • HbA1c of 7.0-7.49 = 175 mg/dL (167-183) • HbA1c of 7.5-7.99 = 190 mg/dL (180-199) • HbA1c of 8.0-8.49 = 197 mg/dL (188-205) **Bedtime blood glucose values for:** • HbA1c of 5.5-6.49 = 140 mg/dL (132-148) • HbA1c of 6.5-6.99 = 154 mg/dL (144-164) • HbA1c of 7.0-7.49 = 180 mg/dL (164-195) • HbA1c of 7.5-7.99 = 179 mg/dL (166-193) • HbA1c of 8.0-8.49 = 214 mg/dL (189-240)

Author	Number of patients	SMBG regime	Result
WHITE 1982 [773]	n=36	Intensive treatment group: home blood glucose Conventional therapy: unclear frequency of SMBG	• All participants in the intensively treated group achieved excellent glycaemic control with preprandial blood glucose values mostly under 200 mg/dl and complete absence of glycosuria.

Table 39: Summary table showing association between blood glucose levels and diabetic control

Fasting <5.5 mmol/litre	Fasting ≥5.5 mmol/litre	<8.3 mmol/litre	>8.3 mmol/litre	<200 mg/dl
Associated with early morning hypoglycaemia in 6/12 patients	Never associated withearly morning hypoglycaemia	Not associated with retinopathy	Increased risk of retinopathy	"Excellent" glycaemic control with pre-prandial BG <200 mg/d
<.2.2 mmol/litre	2.2-2.7 mmol/litre	≥2.8 mmol/litre	<2.75 low BG index	≥2.75 low BG index
13% felt onset of symptoms of hypoglycaemia	20% felt onset of symptoms of hypoglycaemia	66% felt onset of symptoms of hypoglycaemia	5.2 hypoglycaemic episodes	13.6 hypoglycaemic episodes
<8.6 mM	8.6 - 9.7 mM	9.7 – 10.6 mM	10.6 – 12 mM	>12 mM
8.29% HbA1c	8.7% HbA_{1C}	9.14% HbA1c	9.50% HbA1c	10.52% HbA1c

8.2.5 Economic evidence

SMBG timing and frequency

Published literature

No relevant economic evaluations were identified.

New cost-effectiveness analysis

Original cost-effectiveness modelling was undertaken for this question. A summary is included here while the full analysis can be found in Appendix P.

The analysis was undertaken using a validated, internet-based model (IMS CORE Diabetes Model (CDM). IMS CDM is an interactive computer model developed to determine the long-term health outcomes and economic consequences of interventions for type 1 or type 2 diabetes mellitus. Separate transition probabilities and management strategies are used for each type where data exist, facilitating running diabetes type-specific analysis. IMS CDM has been widely used and validated against real-life clinical and epidemiological data.

Strategies compared in the model included different frequencies of SMBG and also included continuous glucose monitoring (CGM, see section8.4.6), specifically:

- SMBG twice a day
- SMBG 4 times a day
- SMBG 6 times a day
- SMBG 8 times a day
- SMBG 10 times a day
- CGM

A cohort of type 1 diabetes patients with defined demographic and racial characteristics reflecting the adult type 1 diabetes population in the UK was used in the base case analysis. Lifetime horizon was used in the analysis. Health outcomes and costs are discounted at an annual rate of 3.5%. These are used to calculate the net monetary benefit (NMB) associated with the different monitoring strategies. The analysis was undertaken from the perspective of the UK NHS and PSS. A willingness to pay threshold of £20,000 per QALY gained was adopted.

The main clinical outcome used in the model is the change in HbA1clevel which then influences the downstream events as defined in the CORE model. Strategy-specific HbA1creductions were obtained from the clinical literature (see 8.2.4): the study by Miller et al.[506] was used for the SMBG frequencies as this cross-sectional study was the only one to report frequencies that were selected for comparison in the model; for the effectiveness of CGM at reducing HbA1cthe meta-analysis conducted for our clinical review and reported insection 8.4.5, using the real-time CGM data only. The frequency of SMBG against which CGM was compared in the clinical studies was uncertain and therefore an assumption had been made that this was 4 times per day; this was varied in a sensitivity analysis where the reduction in HbA1cwas assumed to be estimated versus a higher frequency of 10 per day (best case scenario for CGM).

The overall effectiveness estimates are reported in the table below together with the annual cost of the interventions.

Table 40: Effectiveness and cost data associated with the strategies in the model

Intervention	Average HbA1c	Average HbA1c change from baseline[a]	Average HbA1cchange versus SMBG	Annual cost(b)
SMBG 2	9.11	-0.19		£212
SMBG 4	8.24	-1.06		£423
SMBG 6	7.74	-1.56		£635
SMBG 8	7.43	-1.87		£847
SMBG 10	7.21	-2.09		£1,059
CGM	NR		-0.30	£3,511

(a) HbA1c baseline was obtained by the National Diabetes Audit and was 8.8%
(b) Based on the average cost of lancets and strips obtained from the Drug Tariff, November 2014[541]

Hypoglycaemic event rates were not reported in the main study used to inform the effectiveness data of SMBG frequencies. We have kept the event rates constant for every strategy but we have changed this in a sensitivity analysis where lower rates were assumed for the more costly and effectve strategy.

Results

The average cost and QALYs gained with each strategy is reported in Table 41. In this table interventions are ranked according to their mean net monetary benefit (NMB), which depends on the costs, QALYs and willingness to pay (set at £20,000/QALY in our analysis).

Table 41: Base case probabilistic results in the model

Strategy	Mean discounted cost per patient (£)	Mean discounted QALYs per patient	Net monetary benefit (at £20,000/QALY threshold)	Rank by NMB
SMBG 2	41,805	10.808	174,355	5
SMBG 4	41,989	11.397	185,951	4
SMBG 6	43,685	11.715	190,615	3
SMBG 8	46,288	11.908	191,872	1
SMBG 10	49,146	12.03	191,454	2
CGM	93,980	11.615	138,320	6

Overall, SMBG 8 times was ranked the most cost effective strategy in the base case analysis, however the ICER of SMBG 10 times compared with SMBG 8 times was just above the £20,000 per QALY gained threshold (£23,426/QALY). CGM is less effective and more costly than SMBG 8 and SMBG 10 when its effectiveness in terms of HbA1c reduction was assumed to be estimated via the common comparator of SMBG 4 times. The deterministic base case analysis (Table 42) showed that overall QALYs are higher than in the probabilistic sensitivity analysis and the more effective strategies are also more cost effective in the deterministic than in the probabilistic analysis. This explains why SMBG 10 times daily is the first ranking in terms of NMB in the deterministic analysis (the ICER is £17,196 per QALY, below the cost effectiveness threshold).

Table 42: Deterministic results (mean per patient)

Strategy	Costs[a]	QALYs[b]	NMB[c]	Rank[d]
SMBG 2	44,075	12.1	197,925	5
SMBG 4	41,856	12.752	213,184	4
SMBG 6	42,692	13.103	219,368	3

Strategy	Costs[a]	QALYs[b]	NMB[c]	Rank[d]
SMBG 8	44,517	13.344	222,363	2
SMBG 10	47,062	13.492	222,778	1
CGM	98,992	12.996	160,928	6

(a) Discounted life-time costs per patient
(b) Discounted life-time quality-adjusted life years (QALYs) per patient
(c) Net monetary benefit calculated at a threshold of £20,000 per QALY gained
(d) Ranked in descending order according to NMB

One way sensitivity analyses were also conducted in order to test the robustness of model results to changes in key parameters. The following changes were tested:

- decrease in HbA1c achieved with CGM in the meta-analysis assumed to be estimated compared with SMBG 10 times (best case scenario for CGM)
- utility approach used in the CORE model (from a minimum value approach to a multiplicative one)
- no progression of HbA1c throughout the years
- alternative discounting factor (1.5%) for both costs and outcomes
- cohort of patients with a more recent diagnosis of type 1 diabetes

Throughout these sensitivity analyses, either SMBG 10 or 8 times remained always the most cost effective strategies, while CGM was always more effective but more costly and the ICER was always above the £20,000 per QALY threshold.

Another analysis was conducted in a hypothetical cohort of patients with hypoglycaemia unawareness problems to test if CGM could be cost effective in this group; in this analysis the number of hypoglycaemic events was increased six-fold (from 110 events per 100 patient-years to 660 events per 100 patient-years) in the comparator (SMBG 10 and 8) while it was kept 0 in the intervention (CGM). In addition the cost of CGM was assumed to be 70% of the figure used in the base case analysis and its HbA1creduction was assumed to be estimated compared with SMBG 10 times. In this scenario, CGM was still not cost effective and the ICER was £38,745 per QALY. However when it was compared with SMBG 4 times daily (which is considered the current practice), the ICER was £17,374per QALY in the scenario where CGM decreased hypo events to 0.

This analysis was limited for a number of reasons: the clinical effectiveness data on different frequencies of SMBG was obtained from a cross-sectional study; a higher frequency of testing could lead to a decrease in hypoglycaemic events but these data could not be obtained from the available study. Also the population in this analysis may not be representative of people with type 1 diabetes who have problems at controlling their HbA1clevel with SMBG and self-injection only. The cost effectiveness of CGM in combination with insulin pumps was not assessed and it may be that this combination is cost effective in people with glycaemic control issues.

SMBG targets

Published literature

No relevant economic evaluations were identified.

8.2.6 Evidence statements

Clinical

Frequency of self-monitoring of blood glucose

Low quality evidence from 35 studies (two RCTs, two cross-over studies, and 31 observational studies) showed the following:

- Evidence mostly from large studies showed that self-monitoring of blood glucose was associated with lower HbA1c levels than those who do not self-monitor blood glucose.
- Evidence mostly from large studies showed that more frequent self-monitoring of blood glucose levels up to 3 or 4 times a day is associated with lower HbA1c levels and with fewer complications such as hypoglycaemia, DKA, retinopathy, low-level (micro) albuminuria, physical complaints, psychological distress, leisure restrictions, conscious experience and management of hypoglycaemia, diet, and difficulties at work. Evidence from large studies also showed it was associated with lower mortality rates.
- Evidence mostly from large studies showed that self-monitoring of blood glucose at least 4 times a day and up to ten times a day is associated with lower HbA1c levels.
- Evidence mostly from small studies showed generally thatincreased frequency of self-monitoring of blood glucose is not associated with lower HbA1c levels, incidence of severe hypoglycaemia or other adverse events.

Timing of measuring blood glucose

Low quality evidence from 4 observational studies showed the following:

- In terms of HbA1c, evidence from large studies showed that the strongest correlation with HbA1c is the mean blood glucose reading taken after breakfast, before and after lunch and before and after dinner. And the best predictor of HbA1c level is blood glucose measured before and after breakfast, and before dinner. However, evidence from a single small showed that HbA1c did not correlate with post-prandial levels
- In terms of taking measurements at variable times of day, evidence from a single small study showed that measuring blood glucose four times a day was no better than at a variable time.

Optimal target of blood glucose

Low quality evidence from 7 observational studies showed the following:

- In terms of HbA1c, evidence from two large studies showed that higher blood glucose readings are associated with higher HbA1c values, and every 1% rise in HbA1c results in an increase in night-time as well as pre-and post-prandial blood glucose levels. At an HbA1c between 6.5 and 6.99, mean blood glucose values were 144 mg/dl (fasting), 140 mg/dl (preprandial), 161 mg/dl (postprandial) and 154 mg/dl (bedtime). At an HbA1c between 5.5 and 6.49, mean blood glucose values were: 122 mg/dl (fasting), 119 mg/dl (preprandial), 139 mg/dl (postprandial) and 140 mg/dl (bedtime). Evidence from a small study showed that intensively measured blood glucose levels at home achieved ‘excellent’ glycaemic control with preprandial blood glucose values mostly under 200 mg/dl and complete absence of glycosuria.
- In terms of hypoglycaemia, evidence from a small study showed that fewer hypoglycaemic events were associated with blood glucose readings of less than 2.75 mmol/litre. However, evidence from a large study showed that more severe hypoglycaemic events were associated with blood glucose readings of less than 3.3 mmol/litre, and hypoglycaemia symptoms were first felt by most people at more than or equal to 2.8 mmol/litre. Evidence from a small study also showed that fasting blood glucose of more than or equal to 5.5 mmol/litre is never preceded by early morning

hypoglycaemia. However, less than 5.5 mmol/litre are associated with early morning hypoglycaemia in 6/12 patient-nights.

- In terms of retinopathy, evidence from a large study showed an increased risk of retinopathy with blood glucose readings ofmore than 8.3mmol/litre.

Economic

One original cost–utility analysis found that either SMBG 10 times a day or SMBG 8 times a day was cost effective compared with other lower frequencies of SMBG orCGM. This analysis was assessed as directly applicable with potentially serious limitations.

8.2.7 Recommendations and link to evidence

The current guideline recommendations can be found at

https://www.nice.org.uk/guidance/ng17

Relative values of different outcomes	To determine whether self-monitoring of blood glucose levels (SMBG) was beneficial to individuals with type 1 diabetes, the GDG reviewed whether the following parameters of SMBG had any influence on clinical outcomes: • The frequency of SMBG • Blood glucose targets when using SMBG • The timing of SMBG (fasting, pre- versus post-prandial) The impact of these parameters of SMBG was assessed for the following clinical outcomes: • Improvement in glycaemic control, assessed by reduction in HbA1c. Extensive previous research has shown that an improvement in glycaemic control is associated with a reduction in microvascular complications. • Reduction in hypoglycaemia and severe hypoglycaemia (requiring help from 3rd party for correction). Hypoglycaemia is a regular occurrence in many people on insulin-based therapies and has been associated with a reduction in quality of life for people with diabetes. Hypoglycaemia occurrence can limit individuals achieving improvements in glycaemic control, and any adjunct therapy that achieves an improvement in glycaemic control without producing hypoglycaemia would be considered beneficial to patients with diabetes.
Trade-off between clinical benefits and harms	The GDG reviewed the available evidence for SMBG from randomised controlled trials (RCTs). Much of the available evidence from RCTs focused on the impact of SMBG parameters on glycaemic control, with little RCT evidence available to assess its impact on the frequency of hypoglycaemia. **Frequency of SMBG and impact on glycaemic control** RCT evidence showed that patients who monitored blood glucose had improved glycaemic control compared with those who did not monitor blood glucose levels at all.[11] Clinical outcomes from a large cross-sectional studyand a large case-series showed that increased blood glucose monitoring up to four times a day was associated with substantial improvements in blood glucose control.[506,663]Testing five times a day was associated with improved glycaemic control in comparison to testing three times a day.[149]In a small cross-over clinical trial, testing four times a day was associated with improved blood glucose control outcomes when compared with testing twice a

day.[655]

Increased frequency of blood glucose monitoring more than four times a day was associated with further improvements in blood glucose control in two studies, with testing up to ten times day associated with an improvement in HbA1c.[506,507]However, the increments in the clinical benefits gained were smaller with higher frequencies of blood glucose testing. From the evidence for routine testing, the GDG did not consider a test frequency of more than 8 times a day to be associated with clinically significant further improvement in glucose control. The indications for patients wanting to test at greater frequency should be discussed with the patient, and supported where the extra tests are needed to accommodate lifestyle issues.

Other large trials suggested a plateau effect with testing more than four times a day. [663] . The available evidence suggested that patients on insulin pump therapy might have a greater improvement in glycaemic control with increased frequency of testing than patients on multiple daily insulin regimens.[663]

In contrast, the DCCT showed no evidence that an increased frequency of monitoring (more than four times a day versus one to two times a day) had any impact on quality of life. Frequency of hypoglycaemia was higher in individuals testing more frequently (62 versus 19 hypoglycaemia episodes per 100 patient years) but the glycaemic control achieved in the intensively treated group was 7.2% compared with 8.9% in the non-intensively treated group. The GDG noted that the insulin regimens in the two groups differed substantially, and that frequency of SMBG monitoring was not the only variable likely to influence clinical outcome. An observational study[299], showed that people with HbA1c<7.5% versus those with HbA1c>8.5% were doing more frequent blood tests and had lessfrequent hypoglycaemia associated with this increased plasma glucose testing while another study[149] showed the converse, in that 5 tests per day better predicted hypoglycaemia than 3.

There was other observational study evidence[67,69,92,103,276,493,503,728]indicating that increased frequency of blood glucose testing might not improve glycaemic control, but the majority of these studies were small and less recent in comparison to those showing benefit.

Overall, no adverse outcomes were reported from an increased frequency of blood glucose monitoring.

Optimal blood glucose targets

Evidence was available from six RCTS regarding the impact of blood glucose targets on clinical outcomes.

Pre-prandial targets: One study reported that nocturnal hypoglycaemia was unlikely to occur if individuals with type 1 diabetes achieved a plasma glucose level above 5.5 mmol/litre on waking.[755]A second study reported that the risk of overnight hypoglycaemia was reduced if individuals achieved a waking plasma glucose above 5 mmol/litre.[125]

The GDG recognised that these recommendations were in line with recommendations from intensive education courses for type 1 diabetes. Targets for morning blood glucose levels on waking should be higher than other fasting values through the day in order to reduce the risk of nocturnal hypoglycaemia. The GDG therefore considered that fasting plasma glucose targets should be 5 to 7 mmol/litre on waking in the morning and 4 to 7 mmol/litre at other times of day).

Post-prandial glucose targets: One study(The Diabetes Control and Complications Trial)[281,721,3,4,5,24] reported that the risk of complications from retinopathy were greatly reduced if a plasma glucose level of less than 8.1 mmol/litre could be achieved post-prandially. The GDG therefore considered that individuals with type 1 diabetes should aim for a blood glucose level that was not above 9 mmol/litre post-prandially, whilst also avoiding hypoglycaemia, best avoided by keeping plasma

	glucose targets always above 4.5 mmol/litre). **Timing of SMBG testing:** Much of the available evidence looked at the relationship between timing of blood glucose testing and its ability to predict glycaemic control measures (as measured by HbA1c). Although the available RCT evidence did show that increased frequency of testing was associated with improved glycaemic control, it did not suggest an advantage in testing at specified times of day. The GDG noted that current clinical practice is to test blood glucose levels on waking, pre-prandially and before bed. There was concern that post-prandial blood glucose testing might lead to over-correction of blood glucose levels if they were found to be high, although there was no clinical evidence from an RCT to support this concern. The GDG concluded that further research was required to ascertain the importance of post-prandial testing in comparison to pre-prandial testing. The GDG recommended that for four times a day testing, patients should check blood glucose levels before meals and before bed. Post-prandial blood glucose testing was considered to be useful for educational purposes (for example, when learning to carbohydrate count), and may help patients to ensure they were taking adequate amounts of insulin at mealtimes. It was emphasised by the GDG that structured education in interpreting blood glucose values (for example, in relation to food, illness, recent exercise) was essential to allow patients to make informed decisions about insulin dose adjustment for improved blood glucose control.
Economic considerations	One original economic model was developed which compared different frequencies of SMBG and CGM. The change in HbA1c from baseline was the main clinical outcome used in the model, which determined other events such as complications and death over a lifetime horizon. Based on the effectiveness data used in the model, glycaemic control was better with higher frequencies of monitoring and therefore the maximum overall QALY gain was achieved with a strategy of SMBG 10 times a day. The cost of undertaking one additional SMBG test in one individual each day was calculated to be £106 per year, based on the cost of one lancet and one test strip per blood glucose check. Other costs accrued over the lifetime horizon were determined by the complications and their management and therefore decreased with more effective strategies. The model showed that testing 8 times a day was the optimal strategy in the probabilistic analysis as it improved outcomes (reducing HbA1c level) at an acceptable cost compared with testing less frequently. Testing 10 times a day was the most cost effective strategy in the deterministic analysis, while in the probabilistic analysis the ICER of this strategy compared with SMBG 8 times a day was £23,426 per QALY, just above the cost effectiveness threshold. For these reasons the GDG decided that supporting people who want to test more than 4 times a day would be cost effective, although they did not believe the recommendation had to be prescriptive on a specific frequency as either 8 times or 6 times daily could be cost effective. This analysis had some important limitations in terms of uncertainty in key parameters (quality of life associated with hypo events) and missing links between model outcomes (achieved HbA1c level and hypo events). Also the clinical effectiveness data on different frequencies of SMBG was obtained from a cross-sectional study; a higher frequency of testing could lead to a decrease in hypoglycaemic events but these data could not be obtained from the available study. The population in this analysis may not be representative of people with type 1 diabetes who have problems at controlling their HbA1c level with SMBG and self-injection only.
Quality of evidence	Only randomised controlled trials were included for assessment of SMBG on clinical outcomes. The GDG recognised that no trial evidence focusing solely on the impact of SMBG

	frequency/timing/targets was available for review. Most of the reviewed evidence was taken from RCTs that included the use of SMBG as part of the assessment, but there were none with identical insulin treatment regimens in which SMBG variations were the only variable tested. The economic evidence was assessed as directly applicable with potentially serious limitations.
Other considerations	Outside routine testing frequency recommendations, the GDG also recognised that individuals with type 1 diabetes were required to test blood glucose levels as a necessity for driving recommendations by the DVLA. It was recognised that there would be times where individuals with type 1 diabetes might want to test blood glucose levels more frequently (for example, before exercise, during periods of illness, when considering pregnancy, breastfeeding) and that during such periods, patients should be encouraged to increase their frequency of monitoring to avoid adverse outcomes. There is some RCT evidence to suggest that post-prandial blood glucose monitoring may be predictive of glycaemic control, and that availability of these test results might allow individuals to achieve further improvements in glycaemic control. However, analysis of the DCCT data base found only weak correlation between post-prandial glucose tests predicted HbA1c and there is anecdotal evidence [524]that post-prandial testing encourages excessive insulin administration and hypoglycaemia. Findings are not universal and the GDG recommends that research is undertaken to assess the importance of post-prandial blood glucose testing on glycaemic control and clinical outcomes. The GDG considered whether a nocturnal blood glucose target for test results undertaken before going to bed should be provided by the NICE Guidance. However, it was recognised that a pre-bedtime glucose value would be very dependent on when an individual with type 1 diabetes went to bed and at what time they ate their evening meal before testing. The GDG therefore decided not to provide additional guidance regarding pre-bedtime blood glucose targets. pre-bedtime fasting, pre-meal and post-prandial targets as appropriate to the time of last eating before bedtime If an adult with diabetes experienced overnight hypoglycaemia whilst trying to achieve these targets, this suggests that their basal and/or prandial insulin doses should be reviewed rather than adjustment of target blood glucose levels.

8.2.8 Research recommendations

10. In adults with type 1 diabetes, what is the clinical and cost effectiveness of post-prandial blood glucose monitoring?

8.3 Technologies for self-monitoring of blood glucose

This section was updated in 2015.

8.3.1 Introduction

In recent years blood glucose monitoring systems have been enhanced by software which can have a number of functions. In its simplest form this software allows blood glucose data to be downloaded and displayed in a variety of formats, such as daily profiles and average days, and provides simple statistical information such as mean glucose and measures of glucose variability. Apps are available to allow information to be transferred directly or indirectly onto a Smart phone platform so that graphical and statistical analysis of blood glucose data can be viewed in a mobile setting. All these developments still rely on the user to interpret and respond to the blood glucose data.

Building on the bolus advisor software integrated into some insulin pumps, blood glucose meters are now available which will suggest a bolus insulin dose to the user on the basis of their blood glucose measurement if they input their intended carbohydrate intake. This bolus advice is based on pre-programmed information about the individual's insulin sensitivity (correction factor) and mealtime bolus ratio (units of insulin per 10 g carbohydrate).

New technologies that allow the user to see not just a current value for blood glucose but also a trend for readings over the previous few hours, and which also do not require regular finger-pricking, were only just being introduced at the time of writing this guideline and no evidence existed to allow for their assessment in self-management by adults with type 1 diabetes. It should be noted that these devices have therefore not been included in either this analysis, or in the following analysis of continuous glucose monitoring. Use of such technologies locally should be based on assessment of emerging evidence.

The GDG considered this question:

- In adults with type 1 diabetes, what are the benefits of technologies (bolus calculators and downloads) for self-monitoring of blood glucose?

8.3.2 Review question: In adults with type 1 diabetes, what are the benefits of technologies (bolus calculators and downloads) for self-monitoring of blood glucose?

For full details see review protocol in Appendix C.

Table 43: PICO characteristics of review question

Population	Adults ≥18 years with type 1 diabetes
Intervention/s	• SMBG (finger pricks)- bolus calculators • SMBG (finger pricks)- downloads
Comparison/s	• SMBG (finger pricks) – standard SMBG methods
Outcomes	• Hypoglycaemia • Severe hypoglycaemia • Nocturnal hypoglycaemia • HbA1c • Quality of life • Adverse events • Adherence
Study design	RCTs

8.3.3 Clinical evidence

Two studies have been included in this review.[283,656] Evidence from these are summarised in the clinical evidence summary below (Table 44Table 44: Summary of studies included in the review).See also the study selection flow chart in Appendix D, forest plots in Appendix J, study evidence tables in Appendix G and exclusion list in Appendix K.

We searched for randomised trials assessing the benefits of the following technologies for self-monitoring of blood glucose:

- Bolus calculators
- Downloads

One parallel RCT [656,805] and one cross-over trial [283] were identified. Both studies looked at bolus calculators compared with standard care (that is, no technology for SMBG). We did not look for

technologies versus carbohydrate counting; these have been included as part of the carbohydrate counting review. However, the 3-arm Schmidt RCT did include a carbohydrate counting arm; the results of this arm/comparison are not included here but have been reported as part of the carbohydrate counting review.

Studies included participants that were assessed in both inpatient and outpatient hospital settings.

Outcomes reported include:

- Adverse events
- HbA1c
- Hypoglycaemia
- Hypoglycaemia Fear Survey (HFS)
- Problem Areas in Diabetes (PAID)
- Quality of life (QoL)

Included studies did not report on the following outcomes:

- Adherence
- Nocturnal hypoglycaemia
- Severe hypoglycaemia

Table 44: Summary of studies included in the review

Study	Intervention/comparison	Population	Follow-up	Outcomes	Comments
GROSS 2003	Bolus calculator software implemented on a PDA platform versus standard bolus period	n=49 Type 1 diabetes Continuous Subcutaneous Insulin Infusion (CSII)	7 days	Hypoglycaemic events/week Adverse events	Cross-over RCT (7 days each arm)
SCHMIDT 2012	3 arm trial. Used 2 relevant arms: CarbCount Automated Bolus Calculator (CarbCountABC) versus non-carb count control (no calculator)	Type 1 diabetes n= 51 (n=8, control; n=22, CarbCount Automated Bolus Calculator)	16 weeks	HbA1c Hypoglycaemia Fear Survey (HFS) Problem Areas In Diabetes (PAID) Audit of Diabetes-Dependent Quality of Life (ADDQoL)	-

Table 45: Evidence summary tables: bolus calculator versus no technology (less than 6 months)

Outcomes	Number of studies	Imprecision	GRADE rating	Absolute Difference Bolus	Control event rate (per 1000 patients) No technology
HbA1c(%)	1 study (n=30)	Serious	MODERATE	MD 0.60 lower (1.40 lower to 0.20 higher	-0.1 final value in control group
HFS: (0-100 scale) - higher scores indicate more fear	1 study (n=30)	Very serious	LOW	MD 1.48 lower (9.07 lower to 6.11 higher)	-1.92 final value in control group
PAID: (0-100 scale) - higher scores indicate more problems	1 study (n=30)	Serious	MODERATE	MD 3.6 lower (19.54 lower to 12.34 higher)	-3.3 final value in control group
ADDQoL: Total (-9 to 9) - higher scores indicate positive impact	1 study (n=30)	Serious	MODERATE	MD 0.20 lower (1.39 lower to 0.99 higher)	0.6 final value in control group
Severe hypoglycaemia	1 study (n=30)	Very serious	LOW	34 fewer per 1000 (from 115 fewer to 746 more)	10
Hypoglycaemic event/week	1 study (n=49)	No serious impression	MODERATE	MD 0.30 lower (1.49 lower to 0.89 higher)	3.4 final value in control group
Adverse events	1 study (n=49)	No serious imprecision	MODERATE	0 events in each arm	

8.3.4 Economic evidence

Published literature

No relevant economic evaluations were identified.

8.3.5 Evidence statements

Clinical

Bolus calculator versus no technology for SMBG

Moderate and low quality evidence from single studies showed that there was a clinically significant benefit of SMBG with bolus calculators versus no technology at less than or equal to 6 months for HbA1cand the number of people experiencing episodes of severe hypoglycaemia.

Moderate and low quality evidence from single studies showed that there was no clinically significant difference between SMBG with bolus calculators versus. no technology at less than or equal to 6 months for the QoL scores of HFS, PAID, and ADDQOL; and for both the number of hypoglycaemic events/week and number of adverse events.

Economic

No relevant economic evaluations were found.

8.3.6 Recommendations and link to the evidence

The current guideline recommendations can be found at

https://www.nice.org.uk/guidance/ng17

Relative values of different outcomes	The key issue for this question is whether the use of simple technological aids is clinically useful in allowing people with type 1 diabetes to better interpret and react to their blood glucose measurements. This should be manifest as better (lower) HbA1c levels indicating better overall control of diabetes. As discussed previously, there is a risk that lower HbA1c levels may be achieved at the expense of an increase in episodes of hypoglycaemia, and this was also regarded as an important outcome measure. The balance between HbA1c and hypoglycaemia might also be reflected in Quality of Life data, and the GDG also included this among the important outcomes.
Trade-off between clinical benefits and harms	There was evidence in a single study of a benefit of bolus calculators on both HbA1c and severe hypoglycaemia in the short term (<6 months). There was no statistically significant difference in the relatively small study, but the effect size, if genuine, would be of clear clinical benefit. There was no clinical benefit for any of the QOL outcomes that were reported in the studies. The GDG did not regard the use of bolus calculators as having the potential to do any harm, providing people are educated in their use and interpretation of the output.

Economic considerations	No economic evidence was found on this question. Bolus calculators can be standalone devices, come with blood glucose monitoring devices, online or on smartphone apps. The cost is likely to be small – free to £15. Patients are likely to require training to understand and use bolus calculators. This may be provided as an additional part of structured education programmes but the additional cost of GP/nurse/clinic time should be considered. There may be a cost element if people wish to switch from a simple glucometer to one which allows SMBG downloads and/or which incorporate bolus calculators. Again patients will require training, which may be available through structured education programmes, and there is an additional cost to the GP/nurse/clinics if they need to download the information, read and understand the data. Smartphone apps come in all shapes and sizes (and correspondingly costs). They range from glucometer add-ons (iBGstar - £24) to bolus calculators and blood glucose diaries (no cost). Again patients will require training, which may be available through structured education programmes, and this does have a cost impact in terms of healthcare professionals' time and resource.
Quality of evidence	The evidence of improvement in HbA1c and severe hypoglycaemia was from a single study which had a very small sample size (n=30). [656]
Other considerations	The GDG noted the absence of studies examining the impact of apps and bolus calculators on diabetes outcomes. The GDG members discussed their experience: some people with type 1 diabetes find apps that record their SMBG helpful, and bolus calculators or apps that calculate meal insulin doses based on carbohydrate counting may reduce the need for mental arithmetic skills, although GDG members also discussed concerns that automated downloads if SMBG data may dis-empower users from self-reflection. There is anecdotal evidence that use of bolus calculators that incorporate an estimate of insulin action from recent insulin administration may be helpful in reducing over-bolusing.

8.3.7 Research recommendations

11. In adults with type 1 diabetes who have chronically poorcontrol of blood glucose levels, what is the clinical and cost effectiveness of continuous glucose monitoring technologies?

Why this is important

Current continuous glucose monitoringsystems were found not to be cost-effective in the de novo analysis carried out for this guideline, even in people who had impaired awareness of hypoglycaemia. In adults with type 1 diabetes who havehigh HbA1c values, there still may be some value in using continuous glucose monitoringsystems, and further research is needed to determine whether newer technologies would prove to be cost-effective, particularly in this group.

8.4 Continuous glucose monitoring (CGM) compared with self-monitoring of blood glucose

This section was updated and replaced in 2022. The current recommendations and evidence review can be found at www.nice.org.uk/guidance/ng17

8.4.1 Introduction

This section was updated and replaced in 2022. The current recommendations and evidence review can be found at www.nice.org.uk/guidance/ng17

8.4.2 Review question:

This section was updated and replaced in 2022. The current recommendations and evidence review can be found at www.nice.org.uk/guidance/ng17

8.4.3 Review question:

8.4.4 This section was updated and replaced in 2022. The current recommendations and evidence review can be found at **www.nice.org.uk/guidance/ng17Review question:**

This section was updated and replaced in 2022. The current recommendations and evidence review can be found at www.nice.org.uk/guidance/ng17

8.4.5 Clinical evidence

This section was updated and replaced in 2022. The current recommendations and evidence review can be found at www.nice.org.uk/guidance/ng17

8.4.6 Economic evidence

This section was updated and replaced in 2022. The current recommendations and evidence review can be found at www.nice.org.uk/guidance/ng17

8.4.7 Evidence statements

This section was updated and replaced in 2022. The current recommendations and evidence review can be found at www.nice.org.uk/guidance/ng17

8.4.8 Recommendations and link to the evidence

The current guideline recommendations can be found at

https://www.nice.org.uk/guidance/ng17

9 Insulin therapy

This section was partially updated and replaced in 2021. See https://www.nice.org.uk/guidance/ng17/evidence for the 2021 evidence reviews.

The 2015 GDG updated the evidence and recommendations from the original guideline (CG15) for insulin regimens. New insulin formulations that have become available since 2004 (including insulin degludec, insulin degludec-aspart combinations and insulin detemir) have been considered as part of the evidence review.

In reviewing the evidence for these new insulins, the GDG considered that how insulins are used is more important than which specific insulin within class is used, but examined evidence forinsulin differences in studies where the insulins were compared in RCTs using the same regimens for each comparator.

Insulin therapy content from CG15 that has been superseded by the update can be found in Appendix S.

9.1 Introduction

Type 1 diabetes mellitus is treated by the administration of exogenous insulin. Currently, insulin can only be given effectively by injection and it needs to reach its effector sites via the circulation. Insulin can be administered intravenously, when its onset of action is fast, and its duration of action short, but for routine use, insulin is administered by the person with diabetes via the subcutaneous route.

The healthy pancreas secretes insulin directly into the liver via the hepatic portal vein in response to a variety of signals, keeping plasma glucose concentrations in a narrow range. A low dose of insulin is required at all times to control endogenous glucose production, primarily by the liver. When food is consumed, and absorbed into the circulation a much higher amount of insulin is required for a relatively short time, both to suppress endogenous glucose production and to dispose of glucose entering the circulation from the meal, storing excess glucose in muscle, fat and liver against future need. It is the aim of therapeutic insulin regimens to replicate, as far as possible, this physiological circulating insulin profile of continuous provision of basal insulin, with rapid-acting insulin provided at times of need.

Insulins for subcutaneous injection are manufactured to have different rates of absorption into the circulation. Absorption of active insulin needs to be fast and complete (rapid-acting) for use before eating and for treating high plasma glucose concentrations; the absorption is retarded and prolonged in intermediate and long-acting insulins intended to provide basal insulin replacement.

Insulin preparations have evolved since crystalline insulin was introduced in the early 1920s. Originally extracted and increasingly purified directly from animal pancreas, modern insulins are more commonly synthesized using genetic engineering. The insulin gene, either replicating the human insulin gene, or with the gene modified to confer some perceived benefit in terms of timing and site of insulin action, is used to generate large quantities of insulin by microorganisms. Current targets of insulin manufacture include the making of a faster onset, shorter acting insulin for meal use; and a longer, smoother acting insulin for basal replacement. It is hoped that combinations of such insulins will improve blood glucose control with reduced risk of hypoglycaemia. It is also desirable that the action profile of each insulin will be reproducible, so that the insulin has a predictable effect day after day.

It is important to recognise that the most important factor in optimising glucose control is helping the user manage combinations of different insulin classes (fast and delayed onset) in the most physiological manner possible: for this, structured education (recommendations 88, 89 and 92) is key. In this section, the GDG considered evidence for risk and benefit of one regimen over another and one insulin over another, assuming that in the studies the degree of patient education was similar in each comparator.

The updated review questions in this chapter are:

For insulin regimens:

- In adults with type 1 diabetes, what are the most effective long-acting insulins (detemir versus degludec versus glargine versus NPH) for optimal diabetic control?
- In adults with type 1 diabetes, is once-daily basal insulin more effective than twice-daily basal insulin for optimal diabetic control?
- In adults with type 1 diabetes, which are the most effective rapid-acting insulins for meal times: analogues versus human (intermediate NPH), for optimal diabetic control?
- In adults with type 1 diabetes, what are the most effective mixed insulins for optimal diabetic control?
- In adults with type 1 diabetes, are metformin (with or without insulin), or GLP1-agonists (with or without insulin) as effective as insulin alone for optimal diabetic control?

For insulin delivery:

- In adults with type 1 diabetes, what is the optimum needle length for insulin delivery?
- In adults with type 1 diabetes, what is the optimum injection site and rotation for insulin delivery?

9.2 Insulin regimens

9.2.1 Long-acting insulin

This section was updated and replaced in 2021. See https://www.nice.org.uk/guidance/ng17/evidence for the 2021 evidence reviews.

9.2.1.1 Recommendations and link to evidence

The current guideline recommendations can be found at

https://www.nice.org.uk/guidance/ng17

9.2.1.2 Research recommendations

12. **As background insulins with different (usually longer) action profiles are developed, research will be required to determine how they are best used in structured education programmes, particularly into the need for dose adjustment for flexible lifestyles, for example intermittent exercise or alcohol consumption; their ability to improve clinical outcomes and their long term safety data and cost effectiveness compared with currently recommended regimens.**

13. **Research is required to look at the impact of different intensities of glycaemic control soon after diagnosis (for example inpatient intravenous insulin management versus outpatient multiple daily dose insulin injection therapies) on long-term outcomes in adults with type 1 diabetes and whether selection of basal–bolus insulin regimens at diagnosis might produce long-term benefits through improved glucose control soon after diagnosis.**

9.2.2 Rapid-acting insulin

An insulin with a fast onset, high peak and rapid offset of action would be expected to provide better post-meal glucose control with less risk of hypoglycaemia later, especially at night, and be effective if given at the time of eating, rather than slightly before eating, as recommended for current rapid-acting insulins. Newer insulin analogues are therefore being designed to achieve faster onset, higher peak and shorter action of the insulin, as this would be expected to minimise both the rise in plasma glucose after eating and achieve the other targets.[338] The rapid-acting insulin analogues, insulins aspart, lispro and glulisine, are popular but remain more expensive than older insulins. Meanwhile, some insulin users detect subtle differences between different insulins.

9.2.2.1 Review question: In adults with type 1 diabetes, which are the most effective rapid-acting insulins for meal times: analogues versus human (intermediate NPH), for optimal diabetic control?

For full details see review protocol in Appendix C.

Table 46: PICO characteristics of review question

Population	Adults with type 1 diabetes
Intervention/s	Rapid-acting insulins
Comparison/s	Each other
Outcomes	Outcomes • HbA1c • Hypoglycaemia • Severe hypoglycaemia • Nocturnal hypoglycaemia • Quality of life – measured by DQoL or any measure used in the studies retrieved • Adverse events – Cancer • Injection site issues • Weight gain/loss • DKA
Study design	RCTs

9.2.2.2 Clinical evidence

We searched for randomised trials comparing the effectiveness of any of the short-acting insulins versus each other in adults with type 1 diabetes.

Twenty six studies in 28 papers[34,39,99,101,120,133,194,199-202,224,247,310,311,336,341,389,432,547,580,605,712,75785,257,340,342] were included in the review (one study was published as 3 papers[85,340,342]); seeTable 47. Evidence from the included studies are summarised in the clinical evidence summary below (Table 47). Some study data was not in a suitable format for including in the meta-analyses, and so has been included separately in GRADE. See also the study selection flow chart in Appendix D, forest plots in Appendix J, study evidence tables in Appendix G and exclusion list in Appendix K.

A Cochrane review[681] was also found which compared short-acting insulin analogues versus regular human insulins in both type 1 diabetes and type 2 diabetes. However this was used as a source of references rather than directly incorporated into this review since it was published in 2009 and new studies have been published since then, and the review also included studies that did not match our review protocol (because they included type 2 diabetes, or young people and children).

Data for the outcomes of HbA1c and severe hypoglycaemia were further analysed by performing subgroup analyses to see if there was an effect of using different basal regimens of NPH. Data for the SA insulin comparisons that used basal NPH (Lispro versus human, and Aspart versus human), were therefore divided into the following subgroups:

- NPH once/day
- NPH twice/day
- NPH mixed once or twice/day, more than twice/day, or regimen not stated.

Outcomes

There was no data reported in any of the studies for the following outcomes:

- Cancer
- DKA

Subgroup analyses for heterogeneity

For most of the drug comparisons, there was no heterogeneity between studies in the meta-analyses for the critical outcomes of HbA1c and major or severe hypoglycaemia. Where there was heterogeneity, it was not significant and it could be explained by differences in follow-up time (less than or equal to 6 months and more than 6 months).

Table 47: Summary of studies included in the review

Study	Intervention[a]	Comparison[a]	Long-acting insulin used during study	Population size	Follow-up	Comments[b]
Lispro versus human insulin						
PFUTZNER 1996[580]	Lispro Regimen not mentioned	Regular Human Regimen not mentioned	NPH Regimen not mentioned	n=107 Cross-over RCT Type 1 diabetes	3 months treatment (each period of the cross-over)	
ANNUZZI 2001[39]	Lispro Before meals	Regular human Before meals	NPH Once/day	n=85 Cross-over RCT Type 1 diabetes	3 months treatment (each period of the cross-over)	In both arms, patients were also taking an isocaloric diet
VIGNATI 1997[757]	Lispro Before meals	Regular human Before meals	NPH Twice/day	n=379 Cross-over RCT Mixed population: Type 1 diabetes/type 2 diabetes, but includes a type 1 diabetes subgroup analysis.	2 months treatment (each period of the cross-over)	
GALE 2000[247]	Lispro Before meals	Regular human Before meals	NPH Once/day	n=93 Cross-over RCT Type 1 diabetes	12 weeks treatment (each period of the cross-over)	
FERGUSON 2001[224]	Lispro Before meals or mixed with NPH as a twice/day regimen	Regular human Before meals or mixed with NPH as a twice/day regimen	NPH Once/day or mixed with SA insulin as a twice/day regimen (% on each are not given)	n=40 Cross-over RCT Type 1 diabetes	12 weeks treatment (each period of the cross-over)	Insulin regimen was either a standard basal–bolus MDI regimen, or a twice/day mixed basal plus bolus regimen. Percentages not given of patients who were on each of these.

Study	Intervention[a]	Comparison[a]	Long-acting insulin used during study	Population size	Follow-up	Comments[b]
HOLLEMAN 1997[336]	Lispro Before meals	Regular human Before meals	NPH Once/day	n=199 Cross-over RCT Type 1 diabetes	12 weeks treatment (each period of the cross-over)	
CHAN 2004[120]	Lispro Before meals	Regular human Before meals	NPH Twice/day	n=199 (n=12, type 1 diabetes) Cross-over RCT Mixed population: type 1 diabetes/type 2 diabetes, but has done a type 1 diabetes subgroup analysis.	12 weeks treatment (each period of the cross-over)	
HELLER 1999[310]	Lispro Before meals	Regular human Before meals	NPH Once/day	n=165 Cross-over RCT Type 1 diabetes	12 weeks treatment (each period of the cross-over)	
ANDERSON 1997[34]	Lispro Before meals	Regular human Before meals	NPH or ultralente (% on each not given) Once or twice/day (50% on each)	n=11,008 Cross-over RCT Type 1 diabetes	3 months treatment (each period of the cross-over)	NPH taken once/day by 50% of participants, and the other 50% took it twice/day.
LALLI 1999[432]	Lispro Before meals	Regular human Before meals	NPH Three or four times/day (Lispro group); twice/day for most patients in RH group.	n=56 RCT Type 1 diabetes	1 year	Participants were near-normoglycaemia (HbA1c of 6.0-7.5%)
CIOFETTA 1999[133]	Lispro	Regular human	NPH	n=16 RCT	3 months treatment	

Study	Intervention[a]	Comparison[a]	Long-acting insulin used during study	Population size	Follow-up	Comments[b]
	Before meals	Before meals	Once/day	Type 1 diabetes		
LILLY 1994[199]	Lispro Before meals	Regular human Before meals	NPH Once or twice/day (% on each are not given)	n=167 RCT Type 1 diabetes	1 year	Percentages not given of patients who were on once/day NPH or twice/day NPH.
LILLY 1995A[200]	Lispro Before meals	Regular human Before meals	NPH Regimen not mentioned	n=169 RCT Type 1 diabetes	1 year	
LILLY 1995B[201]	Lispro Before meals	Regular human Before meals	NPH Once/day	n=98 RCT Type 1 diabetes	1 year	
LILLY 1995C[202]	Lispro Before meals	Regular human Before meals	NPH Once or twice/day (% on each are not given)	n=1008 Cross-over RCT Type 1 diabetes	3 months treatment (each period of the cross-over)	Percentages not given of patients who were on once/day NPH or twice/day NPH.
BRUNETTI 2010[101]	Lispro Before meals	Regular human Before meals	Glargine Once/day	n=395 RCT Type 1 diabetes	16 weeks treatment	
Lispro versus glulisine						
DREYER 2005A[194]	Lispro Before meals	Glulisine Before meals	Glargine Once/day	n=683 Type 1 diabetes	26 weeks treatment	
KAWAMORI 2009[389]	Lispro Before meals	Glulisine Before meals	Glargine Once/day	n=267 Type 1 diabetes	28 weeks treatment	In both arms, patients were also following an intensive diet and exercise regime

Study	Intervention[a]	Comparison[a]	Long-acting insulin used during study	Population size	Follow-up	Comments[b]
Aspart versus human insulin						
HOME 1998[341]	Aspart Before meals	Regular human Before meals	NPH Once or twice/day (% on each are not given)	n=104 Cross-over RCT Type 1 diabetes	4 weeks treatment (each period of the cross-over)	
TAMAS 2001[712]	Aspart Before meals	Regular human Before meals	NPH Twice or three times/day (% on each are not given)	n=423 RCT Type 1 diabetes	12 weeks treatment	Percentages not given of patients who were on twice/day NPH or three times/day NPH.
NIELSEN 1995[547]	Aspart Before meals	Regular human Before meals	NPH Once/day	n=21 Cross-over RCT Type 1 diabetes	8 weeks treatment (each period of the cross-over)	
BROCK 2011[99]	Aspart Before meals	Regular human Before meals	NPH Twice/day	n=16 Cross-over RCT Type 1 diabetes	8 weeks treatment (each period of the cross-over)	
RASKIN 2000A[605]	Aspart Before meals	Regular human Before meals	NPH Once/day	n=882 Type 1 diabetes	6 months treatment	
HELLER 2004[311]	Aspart Before meals	Regular human Before meals	NPH Once or twice/day (mostly once/day)	n=155 Cross-over RCT Type 1 diabetes	16 weeks treatment (each period of the cross-over)	23% (mean of two groups) of patients were taking NPH twice/day by end of the study.
HOME 2000/BOTT 2003/HOME 2006[85,340,342]	Aspart Before meals	Regular human Before meals	NPH Once or twice/day	n=1070 (n=753 in extension) RCT	6 months treatment; plus 30 month extension	Percentages not given of patients who were on once/day NPH or twice/day NPH.

Study	Intervention[a]	Comparison[a]	Long-acting insulin used during study	Population size	Follow-up	Comments[b]
			(% on each are not given)	Type 1 diabetes		
Glulisine versus human insulin						
GARG 2005[257]	Glulisine Before meals Glulisine After meals	Regular human Before meals	Glargine Once/day	n=860 RCT – 3 arms Type 1 diabetes	12 weeks treatment	

(a) In all studies (unless specified), the dose of the intervention and comparison long-acting insulins were titrated
(b) In all studies that reported it, the mean baseline HbA1c varied between 6.2% and 9.0%

Table 48: Evidence summary table: Lispro versus human insulin

Outcomes	Number of studies	Imprecision	GRADE rating	Absolute difference Lispro	Control value: event rate (per 1000 patients) or median value Human
HbA1c % (final value) - ≤6 months basal once a day	5	No serious imprecision	LOW	MD 0.03 lower (0.16 lower to 0.10 higher)	7.4
HbA1c % (final value) - ≤6 months basal twice a day	1	Serious	LOW	MD 0.1 lower (0.31 lower to 0.11 higher)	7.9
HbA1c % (final value) - ≤6 months basal mixed or not stated	4	Serious	VERY LOW	MD 0.05 lower (0.08 to 0.02 lower)	8.2
HbA1c % (final value) - ≤6 months glulisine basal insulin	3	No serious imprecision	LOW	MD 0.15 lower (0.31 lower to 0.01 higher)	7.1
HbA1c % (final value) - >6 months basal once a day	1	Very serious[b]	VERY LOW	MD 0.07 lower (0.98 lower to 0.84 higher)	7.8
HbA1c % (final value) - >6 months basal mixed or not stated	3	No serious imprecision	LOW	MD 0.33 lower (0.47 to 0.2 lower)	8.2

Outcomes	Number of studies	Imprecision	GRADE rating	Absolute difference Lispro	Control value: event rate (per 1000 patients) or median value Human
Severe/major hypoglycaemia (no. of patients)	6	No serious imprecision	LOW	2 fewer per 1000 (from 0 fewer to 3 fewer)	6.6
Severe/major hypoglycaemia (no. of patients) - ≤6 months basal once a day	3	Serious	VERY LOW	86 fewer per 1000 (from 1 to 114 fewer)	128
Severe/major hypoglycaemia (no. of patients) - ≤6 months basal mixed or not stated	2	Serious	VERY LOW	1 fewer per 1000 (from 2 fewer to 1 more)	4.9
Severe/major hypoglycaemia (no. of patients) - >6 months basal mixed or not stated	1	No serious imprecision	MODERATE	0	0
Severe hypoglycaemia (episodes) - ≤6 months basal once a day	2	No serious imprecision	LOW	MD 9.46 lower (17.81 to 1.11 lower)	34
Severe hypoglycaemia (episodes) - ≤6 months basal mixed or not stated	1	Serious	VERY LOW	MD 29 lower (61.73 lower to 3.73 higher)	84
Hypoglycaemia/minor hypo (no. of patients) ALL TRIALS (≤6 months and >6 months)	4	No serious imprecision	LOW	27 more per 1000 (from 33 fewer to 93 more)	668
Hypoglycaemia/minor hypo (no. of patients) - ≤6 months	1	Serious	LOW	46 more per 1000 (from 46 fewer to 162 more)	508
Hypoglycaemia/minor hypo (no. of patients) - >6 months	3	No serious imprecision	LOW	8 more per 1000 (from 65 fewer to 82 more)	816
Hypoglycaemia (episodes) - ≤6 months	1	No serious imprecision	LOW	MD 381 lower (741.05 to 20.95 lower)	1156
Hypoglycaemia (episodes) - >6 months	1	No serious imprecision	MODERATE	MD 4.1 lower (5.75 to 2.45 lower)	11.5
Hypoglycaemia (episodes/month) - ≤6 months	4	No serious imprecision	VERY LOW	MD 0.41 lower (1.04 to 0.21 higher)	5.8

Outcomes	Number of studies	Imprecision	GRADE rating	Absolute difference Lispro	Control value: event rate (per 1000 patients) or median value Human
Hypoglycaemia/mild hypo (episodes/patient/month) - ≤6 months	3	Serious	VERY LOW	MD 1.41 lower (3.87 lower to 1.05 higher)	7.2
Hypoglycaemia/mild hypo (episodes/patient/month) - >6 months	3	No serious imprecision	LOW	MD 0.19 lower (1.11 lower to 0.724 higher)	3.7
Nocturnal hypoglycaemia (episodes) - ≤6 months	2	No serious imprecision	LOW	MD 132.26 lower (187.13 to 77.39 lower)	247
Nocturnal hypoglycaemia (episodes/month) - ≤6 months	1	No serious imprecision	LOW	MD 1.1 lower (1.79 to 0.41 lower)	1.8
Weight, kg (final value) - ≤6 months	4	Very serious	VERY LOW	MD 0.36 lower (2.1 lower to 1.38 higher)	3.7
Weight, kg (final value) - >6 months	3	No serious imprecision	VERY LOW	MD 0.09 higher (2.37 lower to 2.55 higher)	71.6
QoL - WED score - ≤6 months	1	Serious	VERY LOW	MD 0.0	2.1

Table 49: Evidence summary table: Lispro versus glulisine

Outcomes	Number of studies	Imprecision	GRADE rating	Absolute difference Lispro	Control value: event rate (per 1000 patients) or median value Glulisine
HbA1c % (final value) - >6 months	2	No serious imprecision	MODERATE	MD 0.01 lower (0.15 lower to 0.13 higher)	7.5
Hypoglycaemia (episodes/patient-month) - >6 months	1	No serious imprecision	MODERATE	MD 0.07 higher (0.03 lower to 0.17 higher)	3.9
Hypoglycaemia (episodes/patient -months) -	1	Very serious	VERY LOW	MD 0.16 lower (0.83 lower to	3.6

Outcomes	Number of studies	Imprecision	GRADE rating	Absolute difference Lispro	Control value: event rate (per 1000 patients) or median value Glulisine
>6 months				0.51 higher)	
Severe hypoglycaemia (episodes/patient - month) - >6 months	1	Serious	LOW	Mean difference 0.0	0.02
Severe hypoglycaemia (episodes/patient - months) - >6 months	1	No serious imprecision	MODERATE	MD 0.01 lower (0.03 lower to 0.01 higher)	0.03
Nocturnal hypoglycaemia (episodes/patient -months) - >6 months	1	No serious imprecision	MODERATE	MD 0.02 lower (0.15 lower to 0.11 higher)	0.55
Injection site reactions (no. of patients) - >6 months	1	Very serious	VERY LOW	9 more per 1000 (from 13 fewer to 57 more)	32

Table 50: Evidence summary table:Aspart versus human insulin

Outcomes	Number of studies	Imprecision	GRADE rating	Absolute Difference Aspart	Control value: event rate (per 1000 patients) or median value Human
HbA1c % (final value) - ≤6 months basal once a day	3	No serious imprecision	LOW	MD 0.15 lower (0.26 to 0.04 lower)	7.8
HbA1c % (final value) - ≤6 months basal twice a day	1	Serious	VERY LOW	MD 0,0	7.0
HbA1c % (final value) - ≤6 months basal mixed or not stated	2	No serious imprecision	LOW	MD 0.14 lower (0.21 to 0.07 lower)	8.1
HbA1c % (final value) - >6 months basal mixed or not stated	1	No serious imprecision	LOW	MD 0.16 lower (0.32 lower to 0 higher)	8.3

Outcomes	Number of studies	Imprecision	GRADE rating	Absolute Difference Aspart	Control value: event rate (per 1000 patients) or median value Human
Severe/major hypoglycaemia (no. of patients) ALL STUDIES (≤6 months and >6 months)	3	Serious	VERY LOW	20 fewer per 1000 (from 48 fewer to 13 more)	185
Severe/major hypoglycaemia (no. of patients) - ≤6 months basal mixed or not stated	2	Serious	LOW	19 fewer per 1000 (from 47 fewer to 17 more)	144
Severe/major hypoglycaemia (no. of patients) - >6 months basal mixed or not stated	1	No serious imprecision	LOW	25 fewer per 1000 (from 90 fewer to 56 more)	312
Hypoglycaemia/minor hypo (no. of patients) - ≤6 months basal mixed or not stated	2	No serious imprecision	VERY LOW	57 less per 1000 (from 261 fewer to 261 more)	636
Hypoglycaemia/minor hypo (no. of patients) - >6 months	1	No serious imprecision	LOW	41 more per 1000 (from 25 fewer to 107 more)	823
Hypoglycaemia (episodes/patient/week) - ≤6 months	1	No serious imprecision	LOW	MD 0.2 lower (0.3 to 0.1 lower)	1.1
QoL - DTSQ (score 0-6) - ≤6 months	1	No serious imprecision	MODERATE	MD 0.33 lower (0.56 to 0.1 lower)	Not reported
QoL - DTSQ (score 0-36) - ≤6 months basal mixed or not stated	1	no serious imprecision	MODERATE	MD 2.3 higher (1.29 to 3.31 higher)	29.7

Table 51: Evidence summary table: Glulisine versus human insulin

Outcomes	Number of studies	Imprecision	GRADE rating	Absolute Difference Glulisine	Control value: event rate (per 1000 patients) or median value Human
HbA1c (change from baseline) - <6 months	2	No serious imprecision	Moderate	MD 0.03 lower (0.13 lower to 0.08 higher)	-0.13
Severe/major hypoglycaemia (no. of patients) - <6 months	2	Serious	Low	16 fewer per 1000 (from 42 fewer to 20 more)	101
Severe hypoglycaemia (episodes/patient/month) - <6 months	1	No serious imprecision	Moderate	MD 0.08 lower (0.2 lower to 0.04 higher)	0.13
Hypoglycaemia/minor hypo (no. of patients) - <6 months basal once a day	2	No serious imprecision	Moderate	16 more per 1000 (from 25 fewer to 57 more)	820
Hypoglycaemia (episodes/patient/month) - <6 months	1	Very serious	Very low	MD 0.08 higher (0.41 lower to 0.58 higher)	3.49
Nocturnal hypoglycaemia (no. of patients) - <6 months	1	No serious imprecision	Moderate	0 fewer per 1000 (from 54 fewer to 65 more)	543
Nocturnal hypoglycaemia (episodes/patient/month) - <6 months	1	No serious imprecision	Moderate	MD 0.07 lower (0.24 lower to 0.1 higher)	0.71

9.2.2.3 Economic evidence

Published literature

Two studies were included with the relevant comparisons.[113594] These are summarised in the economic evidence profiles below (Table 52 and Table 53). See also the study selection flow chart in Appendix E and study evidence tables in Appendix H.

CG15 included one study with the relevant comparison.[165] This study along with one further study[616]that met the inclusion criteria were selectively excluded in the guideline update due to the availability of more applicable evidence– these are summarised in Appendix L, with reasons for exclusion given.

See also the economic article selection flow chart in Appendix E.

Table 52: Economic evidence profile: Insulin aspart versus regular human insulin

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Cameron 2009 [113] [CAN]	Partially[a]	Minor[b]	Used IMS-CDM. This is an abridged version of a report by CADTH[114]	Saves £351	0.055 QALYs	Insulin aspart is dominant compared with regular human insulin	Probabilistic sensitivity analysis demonstrated a 52.3% probability that insulin aspart will be cost effective over regular human insulin at a £26K threshold. One-way sensitivity analysis maintained the insulin aspart as the dominant in all analyses except where there was no difference in HbA1c, where the ICER increased to £55,704.

(a) Study performed from a Canadian healthcare payer perspective

(b) There are discrepancies between the effectiveness data in the clinical review and economic review. However the authors explained this is due to the meta-analysis being updated over time; a 5% discount rate is used for both costs and outcomes which does not conform to the NICE reference case discount rate of 3.5%; treatment effectiveness was assumed to be maintained over the lifetime of the patient, although the trials included had short follow-up times; the report is not completely incremental as it provides the results of four pairwise simulations; the analysis is conducted on the IMS-CDM which, although highly validated, has its own limitations.

Table 53: Economic evidence profile: Insulin lispro versus regular human insulin

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Pratoomsoot 2009 [594][UK]	Directly applicable[a]	Potentially serious limitations[b]	Used IMS-CDM. Treatment effect taken from a Cochrane Review.	Saves £1,953	0.105 QALYs	Insulin lispro is dominant compared with regular human insulin	Probabilistic sensitivity analysis demonstrated a 83.9% probability that insulin lispro will be cost-effective over regular human insulin at a 30K threshold. Insulin lispro was dominant over regular human insulin for all sensitivity analyses. In addition, in the base-case analysis, the probability that insulin lispro was more cost-effective than regular human

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
							insulin was higher at a £20K threshold than at £30K.
Cameron 2009 [113] [CAN]	Partially applicable[c]	Minor limitations[d]	Used IMS-CDM. This is an abridged version of a report by CADTH[114]	£97	0.006 QALYs	£15,442[e]	Probabilistic sensitivity analysis demonstrated a 46.1% probability that insulin lispro will be cost effective over regular human insulin at a £26K threshold. One-way sensitivity analysis maintained the insulin lispro was either cost-effective or dominant compared with regular human insulin except where there was no difference in HbA1c, where the ICER increased to £358,432.

(a) Study performed from a UK NHS perspective

(a) Cohort mean age is higher than may be anticipated; a constant treatment effect of insulin over the long-term is assumed; certain sources of data come from a type 2 diabetes specific population; analysis conducted on the IMS-CDM which has its own limitations

(b) Study performed from a Canadian healthcare payer perspective

(c) There are discrepancies between the effectiveness data in the clinical review and economic review. However the authors explained this is due to the meta-analysis being updated over time; a 5% discount rate is used for both costs and outcomes which does not conform to the NICE reference case discount rate of 3.5%; treatment effectiveness was assumed to be maintained over the lifetime of the patient, although the trials included had short follow-up times; the report is not completely incremental as it provides the results of four pairwise simulations; the analysis is conducted on the IMS-CDM which, although highly validated, has its own limitations.

(d) Due to rounding of QALYs, ICERs were not recalculated from the study, only converted into GBP.

Unit costs

In the absence of recent UK cost-effectiveness analysis for some insulin regimens, relevant unit costs are provided in Appendix Q to aid consideration of cost effectiveness.

9.2.2.4 Evidence statements

Clinical

Lispro versus human insulin

Low and Very low quality evidence showed a clinical benefit of insulin lispro compared with human insulin on HbA1c at more than 6 months, in studies where the basal insulin regimen was a mixture of once or twice/day, or not stated. There was no clinical effect on HbA1c at 6 months or more than 6 months in studies in which the basal insulin was taken once a day.

Evidence that was mainly Low and Very low quality, showed a clinical benefit of insulin lispro compared with human insulin on severe hypoglycaemia when measured in terms of 'number of patients', and 'number of episodes', when the basal insulin regimen used by the studies were once/day, and at time-points less than or equal to 6 months. When the basal insulin regimen was mixed or not stated by the studies, there was clinical benefit on severe hypoglycaemia in terms of 'number of episodes' at time-points less than or equal to 6 months, but no clinical difference in terms of 'number of patients' at any time-point.

Evidence that was mainly Low and Very low quality showed that at both less than or equal to 6 months and more than 6 months there was a clinical benefit of insulin lispro compared with human insulin for the outcome of hypoglycaemia when measured in terms of 'total number of episodes'. However there was no clinical difference between the two insulins when hypoglycaemia was measured in terms of 'number of patients experiencing hypoglycaemia', 'episodes/month', 'episodes/patient/month'.

Low quality evidence showed a clinical benefit of lispro compared with human insulin for nocturnal hypoglycaemia when measured in terms of 'number of episodes' and 'episodes/month' at less than or equal to 6 months.

Low quality evidence showed no clinical difference between lispro and human insulin for final body weight at less than or equal to 6 months and more than 6 months, nor for QoL (WED score) at less than or equal to 6 months.

Lispro versus glulisine

Evidence that was mostly moderate and very low quality, and mostly from a single study, showed that there was no clinical difference between lispro and glulisine for any of the outcomes measured (HbA1c, severe hypoglycaemia, hypoglycaemia, nocturnal hypoglycaemia, and injection site reactions).

Aspart versus human insulin

Moderate quality evidence from a single study showed a clinical benefit of aspart compared with human insulin for QoL – DTSQ score at less than or equal to 6 months.

Evidence that was mostly low and very low quality evidence showed that there was no clinically significant difference between aspart and human insulin for the following outcomes: HbA1c, severe hypoglycaemia, and hypoglycaemia at both less than or equal to 6 months and more than 6 months;

and for QoL – DTSQ score 0-6 at less than or equal to 6 months, regardless of the basal insulin regimen used by the studies.

Glulisine versus human insulin

Moderate, low and very low quality evidence mostly from single studies, showed that there was no clinical difference between glulisine and human insulin for any of the outcomes measured at less than or equal to 6 months (HbA1c, severe hypoglycaemia, hypoglycaemia, and nocturnal hypoglycaemia).

Economic

- One cost-utility analysis found that insulin aspart was dominant (less costly and more effective) compared with regular human insulin. This analysis was assessed as partially applicable with minor limitations.
- One cost-utility analysis found that insulin lispro was dominant (less costly and more effective) compared with regular human insulin. This analysis was assessed as directly applicable with potentially serious limitations.
- Another cost-utility analysis found that insulin lispro was cost-effective compared with regular human insulin (ICER; £15,442 per QALY gained). This analysis was assessed as partially applicable with minor limitations.

9.2.2.5 Recommendations and link to evidence

The current guideline recommendations can be found at

https://www.nice.org.uk/guidance/ng17

Relative values of different outcomes	Choice of rapid-acting insulin therapy was influenced by the impact of individual insulin therapies on clinical outcomes at <6 months and >6 months, specifically improvement in glycaemic control, assessed by: • reduction in HbA1c. Extensive previous research has shown that an improvement in glycaemic control is associated with a reduction in microvascular complications, and • reduction in the incidence of hypoglycaemia. Hypoglycaemia is a regular occurrence in many people on insulin-based therapies and has been associated with a reduction in quality of life for people with diabetes, and an obstacle to improved control. Any therapy that achieves an improvement in glycaemic control without producing hypoglycaemia would be beneficial to patients with diabetes. When contemplating the impact of rapid-acting insulin therapies on clinical outcomes, particular focus was given to: • Reduction in incidence of severe hypoglycaemia (requiring help from 3rd party for correction), which has been recognised as having a significant impact on quality of life in patients with type 1 diabetes. • Reduction in the incidence of nocturnal hypoglycaemia. • Adverse events; the literature was reviewed for any incidence of neoplastic disease associated with the use of rapid-acting insulins. • Incidence of diabetic ketoacidosis (DKA); the literature was reviewed to see if any particular choice of insulin regimen was associated with an increased incidence of DKA. • The impact of particular rapid-acting insulins on quality of life when used in individuals with type 1 diabetes.

	• Injection site issues associated with choice of insulin therapy. • Impact on weight: initiation and intensification of insulin-based therapies are associated with increases in weight.The literature was reviewed to see if weight gain was differently associated with any particular choice of rapid-acting insulin.
Trade-off between clinical benefits and harms	The GDG reviewed the available evidence from randomised controlled trials that compared clinical outcomes with the use of different rapid-acting insulins. **Lispro versus rapid-acting human insulin** Lispro produced a clinically significant improvement in glycaemic control (0.3% improvement in HbA1c) compared with human insulin. This benefit was sustained in studies of >6 months duration, and achieved alongside clinically significant improvements in the incidence of severe/major hypoglycaemia and nocturnal hypoglycaemia. These improvements were achieved irrespective of the choice of basal insulin used. No clinically significant differences in outcomes for weight or quality of life measures were found in the comparison. **Aspart versus rapid-acting human insulin** A reduction in HbA1c, and a reduction in the incidence of both major and minor hypoglycaemia, was achieved with use of aspart compared with human insulin but the magnitude of each was not considered to be clinically significant at <6 months or at >6 months. Evidence from a single study[311] showed a clinically significantbenefit of aspart therapy versus human insulin therapy on the incidence of nocturnal hypoglycaemia. The GDG noted that this outcome was assessed using GRADE criteria, because it did not report SDs alongside the number of events. Evidence assessing impact of treatment on quality of life favoured the use of aspart over rapid-acting human insulin. **Glulisine versus rapid-acting human insulin** No data on improvement in glycaemic control were available for the comparison of glulisine therapy to rapid-acting human insulin therapy, and there was no clinically significant difference in hypoglycaemia outcomes (severe/major hypoglycaemia, minor hypoglycaemia, nocturnal hypoglycaemia). **Lispro versus glulisine** The available evidence comparing lispro use to glulisine did not demonstrate a clinically significant difference in outcomes assessing glycaemic control (improvement in HbA1c), incidence of hypoglycaemia (severe/major hypoglycaemia, minor hypoglycaemia or nocturnal hypoglycaemia) or injection site difficulties at <6 months and >6 months. No data were reported for impact on incidence of neoplastic disease or diabetic ketoacidosis in any of the randomised controlled trials on rapid-acting insulin use.
Economicconsiderations	Two cost-utility analyses, one directly and one partially applicable, with minor limitations were considered. Both analyses used the IMS-CDM model which uses HbA1c levels as a proxy to project the risk of long-term micro and macrovascular complications, amongst others, including the incidence of hypoglycaemia (mild and severe) in assessing cost-effectiveness. One study, Pratoomsoot et al 2009[594], a UK cost-utility analysis with minor limitations, compared insulin lispro against regular human insulin. • A Cochrane meta-analysis provided the difference in HbA1c between the two interventions; a reduction of 0.1% for insulin lispro over regular human insulin.

	Severe hypoglycaemia was recalculated from the Cochrane meta-analysis to provide rates of 21.8 per 100 patient years for insulin lispro, and 46.1 per 100 patient years for regular human insulin. • Insulin lispro dominated regular human insulin, with a cost-saving of £1,953 and a 0.105 QALY increase over a lifetime time horizon. At a £20K per QALY threshold, there is a greater than 83.9% probability that insulin lispro is cost-effective. • The clinical values used for HbA1c reduction and incidence of hypoglycaemia (mild and severe) in this analysis lie at, or slightly below, the lower 95% CI limit as established by the clinical evidence. As such, this analysis is representative of the best treatment effects that can be expected. The second study, Cameron 2009, a Canadian cost-utility analysis with minor limitations, compared insulin lispro and insulin aspart against regular human insulin in two pairwise analyses. • Their meta-analysis provided the difference in HbA1c between insulin lispro and aspart compared with regular human insulin; a reduction of 0.01% and 0.12% respectively. The relative risk of severe hypoglycaemia was 0.83 for insulin lispro and aspart compared with regular human insulin. • Insulin lispro was cost-effective compared with regular human insulin, with an ICER of £15,442 per QALY gained. At a 26K per QALY threshold, there is a 46.1% probability that insulin lispro is cost-effective compared with regular human insulin. • Insulin aspart was dominant compared with regular human insulin, with a cost-saving of £351 and a 0.055 QALY increase over a lifetime time horizon. At a 26K per QALY threshold, there is a 52.3% probability that insulin aspart is cost-effective compared with regular human insulin. The clinical values used for HbA1c reduction and incidence of hypoglycaemia (mild and severe) used in this analysis are more consistent with those established from previous clinical studies than those used in Pratoomsoot et al. 2009. However, both insulin lispro and insulin aspart have a less favourable reduction in HbA1c, whilst insulin lispro has a less favourable reduction in severe hypoglycaemia risk compared with regular human insulin, than those in the results of our meta-analysis. As such, the result of this analysis is likely to be conservative and potentially underestimate the true treatment benefit. In summary, taking these studies in the context of the differences in HbA1cand hypoglycaemia seen in our meta-analysis, it is highly likely that rapid-acting insulin analogues are cost-effective.
Quality of evidence	Only UK licensed rapid-acting insulin preparations were considered in the evidence review. Clinical outcomes were assessed from randomised controlled trials (RCT) using rapid-acting insulin as part of a multiple daily injection insulin regimen; trials assessing outcomes from insulin pump studies were not included for this guideline. **Lispro versus rapid-acting human insulin studies** • 16 RCT studies compared clinical outcomes with lispro to rapid-acting human insulin[36,39,101,120,133,224,247,310,336,432,580,757](Lilly 1994, Lilly 1995A, Lilly 1995B, Lilly 1995C). • The quality of the available evidence was Very low to Moderate, and considered to be at serious to very serious risk of bias. • 12 of the studies were <6 months duration, 4 of the studies were >6 months duration. • 15 of the studies used NPH as the basal insulin in the regimen (between once and four times a day; twice a day in most study participants).Only 1 study used glargine

	and there was no evidence about use of Lispro with other basal insulins. **Aspart versus rapid-acting human insulin** • 7 RCT studies compared clinical outcomes with aspart to rapid-acting human insulin[85,99,311,340-342,547,605,712]. • The quality of the available evidence was Very low to Moderate, and considered to be at serious to very serious risk of bias. • 6 of the studies were <6 months duration, 1 study was >6 months duration. • All 7 RCTs used NPH (once or twice a day) as the basal insulin. **Glulisine versus rapid-acting human insulin** • 1 RCT study compared clinical outcomes with glulisine to rapid-acting human insulin[257]. • The quality of the available evidence was Low to Moderate, and considered to be at serious risk of bias. • The study was of <6 months duration. • The study used glargine as the basal insulin. • No comparison of impact on glycaemic control was made in the trials. **Lispro versus glulisine** • 2 RCT studies compared clinical outcomes with lispro to glulisine[194,389]. • The quality of the available evidence was Very low to Moderate, and considered to be at serious risk of bias. • Both studies were of 6 months duration. • Both studies used glargine as the basal insulin for selected regimens. The GDG noted that a comparison of lispro use versus aspart was difficult to make, as no RCT data directly comparing the two insulins was available, and the aspart studies included in the evidence review tended to be of shorter duration than the lispro studies. The GDG considered that the available evidence was sufficient to recommend the use of rapid-acting insulin analogues over rapid-acting human insulins, and that this choice was cost-effective. The economic evidence was assessed as partially applicable with minor or potentially serious limitations.
Other considerations	The GDG discussed the timing of administration of rapid-acting insulin for meal coverage. There is evidence that injection given 15 minutes after starting to eat a meal gives similar post prandial control to conventional human insulin given immediately before meals[654] but agreed that in adults with type 1 diabetes, the advice that rapid-acting analogues could routinely be given after was inappropriate. The GDG agreed that adults with type 1 diabetes should be advised to take their rapid-acting insulin before meals, as it is widely accepted that this will provide improved glucose control in comparison to insulin taken during or after meals in adults with type 1 diabetes. This was based on clinical experience that adults with type 1 diabetes may take much longer than 15 minutes to eat a meal; the suboptimal post-meal glucose profile of human soluble insulin being given immediately before meals (the prescribing advice has been to take these insulins 20-40 minutes before eating) and clinical experience that optimal post prandial glucose control (minimal post prandial rise and reduced risk of later hypoglycaemia) is achieved with analogue injections given about 15 minutes before eating. In making this recommendation, the GDG recognised that in some exceptional cases this guidance might not be

	followed (for example, individuals with gastroparesis, where carbohydrate absorption might be delayed). Although permitted in the British National Formulary and summary of product characteristics for analogue insulins, in adults with type 1 diabetes, routine use of post-meal injection should therefore be avoided, even with rapid-acting analogues, as it is associated with high post-prandial glucose and increased risk of later hypoglycaemia. The GDG recognised that some adults with type 1 diabetes may have a personal preference for a particular type or class of rapid-acting insulin over the recommended choice. Historically, some adults with type 1 diabetes reported that they preferred the use of animal insulin over human or analogue insulin. The GDG therefore advise that that an individual's preference for a specific rapid-acting insulin should be respected, even if this choice was against the weight of published evidence, as there is no evidence for major harm with other available fast acting insulins. However, when people are not achieving glycaemic targets with insulins other than those recommended as first line, they should be advised about the potential benefits of these.

9.2.2.6 Research recommendation

14. Research is required into the optimal timing and use of rapid-acting insulin around specific meal compositions and modalities of exercise

9.2.3 Mixed insulin

Although modern flexible insulin therapy mandates independent replacement of basal and meal-related insulin in order to achieve optimal glucose control and support a flexible lifestyle, regimens using a mixture of fast and intermediate acting insulin given twice a day have the attraction of fewer daily injections. The regimen uses a pre-breakfast meal injection to cover breakfast (the fast acting component) and lunch (the delayed acting, isophane insulin) and a second injection before the evening meal from which the fast acting component covers the meal and the delayed acting insulin the overnight requirement. The disadvantage of such regimens include the need for lunch to occur as predicted; frequently, for optimal control, a need for routine between meal and bedtime snacking and a high risk of inadequate overnight control but the idea of less intensive self-management of the insulin regimen remains attractive. Pre-mixed insulins are now available using analogues, as well as human insulin.Given that some people may opt for a pre-mixed insulin regimen, the GDG reviewed the evidence for mixed insulins.

9.2.3.1 Review question: In adults with type 1 diabetes, what are the most effective mixed insulins (degludec-aspart versus glargine versus NPH) for optimal diabetic control?

For full details see review protocol in Appendix C.

Table 54: PICO characteristics of review question

Population	Adults with type 1 diabetes
Intervention/s	• Mixed insulins Only UK licensed interventions and doses will be considered
Comparison/s	• Each other • Long plus short-acting insulin (basal–bolus) regimen

	Only UK licensed interventions and doses will be considered
Outcomes	Outcomes • HbA1c • Hypoglycaemia • Severe hypoglycaemia • Nocturnal hypoglycaemia • Quality of life – measured by DQoL or any measure used in the studies retrieved • Adverse events – Cancer • Injection site issues • Weight gain/loss • DKA
Study design	RCTs

9.2.3.2 Clinical evidence

We searched for randomised trials comparing the effectiveness of any of mixed insulins versus each other or versus a basal–bolus regimen, in adults with type 1 diabetes.

Fourteen studies[81,122,133,155,196,220,324,330,367,393,619-621,719] were included in the review; see Table 55: Summary of studies included in the review. Evidence from the included studies are summarised in the clinical evidence summary below (Table 55). Some study data was not in a suitable format for including in the meta-analyses, and so has been included separately in GRADE. See also the study selection flow chart in Appendix D, forest plots in Appendix J, study evidence tables in Appendix G, GRADE tables in Appendix Iand exclusion list in Appendix K.

One Cochrane review[681] was found and was used as a source of references for our review, because it contained some studies that were younger age groups and were type 2 diabetes.

Outcomes

There was no data reported in any of the studies for the following outcomes:

- Cancer

Subgroup analyses for heterogeneity

Where there was heterogeneity between studies in the meta-analyses for the critical outcomes (HbA1c and major/severe hypoglycaemia), it was agreed that this would be explored using pre-specified subgroups in the protocol. These were:

- Baseline HbA1c (differences between studies in baseline HbA1c levels)
- Different doses/regimens (clinically relevant regimens)
- Elderly/older people/frailty (if there were significant differences between studies in subject ages)
- Baseline weight (if possible, bearing in mind that some studies give BMI and some give weight in kg)
- Baseline hypoglycaemia (if this is known and there are significant differences).

Nocturnal hypoglycaemia

For nocturnal hypoglycaemia, a subgroup analysis of the insulins used in each study was performed. This analysis showed that the use of different types of insulins explained the heterogeneity between the studies (see Appendix J).

HbA1c

For HbA1c, a subgroup analysis of the insulins used in each study was performed. This analysis showed that the use of different types of insulin did not explain the heterogeneity between the studies (see Appendix J). Other pre-specified sources of heterogeneity were therefore explored, and the results are as follows:

- **Baseline** HbA1c– this was much higher for the Herz study (approximately 11%), but when the Herz study was removed from the meta-analysis, significant heterogeneity remained (that is, baseline HbA1c did not explain the differences in effects between the trials).
- **Dose/regimen** – the studies all used different basal–bolus drugs, and additionally the Fanelli and Janssen studies used different mixed insulin regimens to the other studies in the meta-analysis. The different drugs and regimens used could be one possible explanation for the heterogeneity between the trials.
- **Age of participants** – the mean age of participants in the trials included in the meta-analysis was very similar (late twenties to mid-thirties) and so this would not explain any heterogeneity between the trials.
- **Baseline weight** – baseline weight was not given for most of the studies and so it was not possible to explore this as a source of heterogeneity.
- **Baseline hypoglycaemia** - the Herz study and the Fanelli studies both excluded patients who had a history of severe hypoglycaemia, whereas the other studies in the meta-analysis did not. However, when these studies were removed from the meta-analysis, the heterogeneity still remained statistically significant.

1 **Table 55: Summary of studies included in the review**

Study	Intervention[a]	Comparison[a]	Study type and population	Follow-up	Comments
Mixed versus basal–bolus					
Human mix					
FANELLI 2002[220]	Basal–bolus using mixed evening treatment Mixed insulin (Regular plus NPH) at dinner Regular insulin at breakfast and lunch	Basal–bolus NPH at bedtime Regular insulin before all 3 meals.	n=22 Cross-over RCT Type 1 diabetes	4 months treatment	Patients with hypoglycaemia unawareness or history of severe hypoglycaemia were excluded. Mix arm: mixed insulin given part of the insulin basal–bolus treatment
KHACHADURIAN 1989[393]	Patient mix: 30% human/70% NPH Twice/day Patients mixed in syringe, as no pre-mix available at the time.	Basal–bolus: NPH plus Human RA NPH (Novolin N) – timing not given in paper RA human (Novolin R) could be added if necessary.	n=78 RCT Mixed population: 70% type 1 diabetes/30% type 2 diabetes	12 weeks treatment	Mix arm: True mixed insulin regimen – mix given twice/day versus basal–bolus treatment
Lispro mix					
CIOFETTA 1999[133]	Patient mix plus NPH NPH at bedtime Pre-mixes Lispro plus NPH at meals	Basal–bolus: NPH plus Human regular NPH at bedtime Human regular at meals Basal–bolus: NPH plus Lispro NPH at bedtime Lispro at meals	n=24 RCT – 3 arms Type 1 diabetes	3 months treatment	>1 episode of severe hypoglycaemia within 6 months of study Mix arm: mixed insulin given part of the basal–bolus treatment
HERZ 2002[324]	Humalog Mix 50 plus NPH Humalog 50 = 50% Lispro/50% Lispro- protamine NPH at bedtime	Basal–bolus: NPH plus Human soluble NPH at bedtime Human insulin pre-meals	n=109 Cross-over RCT Type 1 diabetes	12 weeks treatment (each period	Severe hypo patients (≥2 episodes in past 3 months) were excluded. High baseline HbA1c values (Mean 11.1%)

Study	Intervention[a]	Comparison[a]	Study type and population	Follow-up	Comments
	Mix50 pre-meals			of cross-over)	Mix arm: mixed insulin given part of the basal–bolus treatment
JANSSEN 2000[367]	PT MIX: 75%Lispro/25%NPL Twice/day (before meals) Patients mixed in syringe, as no pre-mix available at the time.	Basal–bolus: NPH plus Human regular SA NPH (Novolin N) Human insulin at all meals.	n=35 RCT Type 1 diabetes	12-14 weeks treatment	Mix arm: true mixed insulin regimen – mix given twice/day versus basal–bolus treatment
Aspart mix					
CHEN 2006[122]	BIAsp30 plus NPH NPH at bedtime (in some patients) BIAsp30 pre-meals	Basal–bolus: NPH plus Human soluble (ActRapid) NPH at bedtime ActRapid pre-meals	n=27 Cross-over RCT Type 1 diabetes	12 weeks treatment (each period of cross-over)	Patients with diabetic complications requiring acute treatment were excluded. Mix arm: mixed insulin given part of the basal–bolus treatment
HIRSCH 2012B[330]	IDegAsp plus Aspart Once/day (with main meal) Aspart given at other meals.	Basal–bolus: IDet plus IAsp Detemir once/day with evening meal or at bedtime Aspart at all meals.	n=548 RCT Type 1 diabetes	26 weeks treatment	Patients with recurrent severe hypoglycaemia or hypoglycaemia unawareness were excluded. Patients with proliferative retinopathy or maculopathy requiring treatment were excluded. Mix arm: mixed insulin given part of the basal–bolus treatment
TESTA 2012A [719]	LISPRO MIX or ASPART MIX Humalog25 or Novolog30 Humalog25 = 25% Lispro/75% Lispro- protamine Novolog 30 = 30% aspart/70% aspart-protamine. Twice/day	Basal–bolus: Glargine plus Glulisine Glargine once/day Glulisine at all meals.	n=82 type 1 diabetes Cross-over RCT Mixed population: type 1 diabetes/type 2 diabetes, but paper includes a type 1 diabetes subgroup analysis.	12 weeks treatment	HbA1c between 7.0 and 9.0% Mix arm: true mixed insulin regimen – mix given twice/day versus Basal–bolus treatment

Study	Intervention[a]	Comparison[a]	Study type and population	Follow-up	Comments
Mixed versus mixed					
BOEHM 2002[81]	BIAsp 30 Biphasic Aspart: 30% Aspart/70% Aspart-protamine Twice/day (breakfast and dinner)	BHI 30 Biphasic human insulin: 30/70% equivalent of BIAsp Twice/day (breakfast and dinner)	n=104 type 1 diabetes RCT Mixed population: type 1 diabetes/type 2 diabetes, but paper includes a type 1 diabetes subgroup analysis.	12 weeks treatment	-
CUCINOTTA 1991[155]	Actraphane 3/7 Actraphane = NPH plus human) Timing not mentioned	Regular mix: 2/8 to 4/6 Human regular plus NPH mix Twice/day at breakfast and dinner	n=20 Cross-over RCT Type 1 diabetes	4 months treatment	-
DUNBAR 1999[196]	PREMIX (pen) Twice/day (morning and evening) Patients may use different mixtures in morn and eve Penmix (Novo Nordisk)10/90%, 20/80%, 30/70%, 40/60% and 50/50%	PT MIX (ActRapid plus Human Monotard) Patients continuing their usual/previous treatment	n=100 type 1 diabetes RCT Mixed population: type 1 diabetes/type 2 diabetes, but paper includes a type 1 diabetes subgroup analysis.	2 months treatment	-
ROACH 1999[621]	Lispro Mix25 and Mix50 AM before breakfast: Lispro mix50 (50% Lispro/50% NPL) PM before dinner: Lispro mix25 (25% Lispro/75% NPL) Twice/day	Human insulin Mix 50 and 30 Twice/day AM before breakfast: Human mix50 (50% regular/50% NPH) PM before dinner: Human mix30 (30% regular/70% NPH)	n=37 type 1 diabetes Cross-over RCT Mixed population: type 1 diabetes/type 2 diabetes, but paper includes a type 1 diabetes subgroup analysis.	3 months treatment (each period of cross-over)	HbA1c between 7.0 and 9.0%
ROACH 2001[620]	PT MIX: Lispro plus NPL Twice/day (morning and	PT MIX: Human plus NPH NPH = Humulin N	n=100 type 1 diabetes RCT	12 months treatment	Recurrent severe hypoglycaemia patients were excluded.

Study	Intervention[a]	Comparison[a]	Study type and population	Follow-up	Comments
	evening)	Human = Humulin R Twice/day (morning and evening)	Mixed population: type 1 diabetes/type 2 diabetes, but paper includes a type 1 diabetes subgroup analysis.		
ROACH 2004[619]	PREMIX (H or M) plus NPH NPH at bedtime Pre-mixes at meals High Mix = 25%Lispro/75% NPL Medium Mix = 50%Lispro/50% NPL	SELF-MIX (H or M) plus NPH NPH at bedtime Pre-mixed Lispro/NPH self-selected ratios	n=89 Cross-over RCT Type 1 diabetes	8 weeks treatment (each period of cross-over)	>1 episode of severe hypoglycaemia within 6 months of study

(a) In all studies the dose of the intervention and comparison long-acting insulins were titrated

Table 56: Evidence summary table: Mixed insulin (human mix) versus basal–bolus insulin (less than or equal to 6 months)

Outcomes	Number of studies	Imprecision	GRADE rating	Absolute difference	Final value for control group
				MIX	Basal–bolus
HbA1c - final value (≤6 months) - True mix (twice/day versus basal–bolus)	1	Serious	VERY LOW	MD 0.5 higher (0.17 to 0.83 higher)	7.0
Nocturnal hypoglycaemia, episodes/patient-day (≤6 months) - Mix part of basal–bolus	1	No serious imprecision	LOW	MD 0.02 higher (0.01 to 0.03 higher)	0.027
Severe/major Hypoglycaemia, number of patients- Mix part of basal–bolus (≤6 months)	1	No serious imprecision	LOW	0 events in each arm	0
Ketoacidosis, number of patients (≤6 months)- True mix (twice/day versus basal–bolus)	1	Very serious	VERY LOW	RR 4.4 (0.19 to 104.42)	0%

Injection site reactions, number of patients (≤6 months) - True mix (twice/day versus basal–bolus)	1	Very serious	VERY LOW	1 fewer per 1000 (from 57 fewer to 317 more)	70

Table 57: Evidence summary table: Mixed insulin (Lispro mix) versus basal–bolus insulin (less than or equal to 6 months)

Outcomes	Number of studies	Imprecision	GRADE rating	Absolute difference	Final value for control group
				MIX	Basal–bolus
HbA1c - final value (≤6 months) - True mix (twice/day versus basal–bolus)	1	Serious	VERY LOW	MD 0.5 higher (0.25 to 0.75 higher)	6.7
HbA1c - final value (≤6 months) - Mix part of basal–bolus	3	Serious	VERY LOW	MD 0.32 lower (0.54 to 0.11 lower)	6.96
Hypoglycaemia, episodes/patient (≤6 months) - Mix part of basal–bolus	1	No serious imprecision	LOW	MD 0.3 lower (1.67 lower to 1.07 higher)	5.1
Hypoglycaemia, episodes/patient/month (≤6 months) - Mix part of basal–bolus	2	Very serious	VERY LOW	MD 0.80 lower (4.82 lower to 3.21 higher)	6.1
Nocturnal Hypoglycaemia, number of patients (≤6 months) - Mix part of basal–bolus	1	No serious imprecision	LOW	20 fewer per 1000 (from 130 fewer to 117 more)	651
Severe/major Hypoglycaemia, number of patients (≤6 months) - True mix (twice/day versus basal–bolus)	1	Very serious	VERY LOW	3 more per 1000 (from 52 fewer to 812 more)	56
Severe/major Hypoglycaemia, number of patients (≤6 months) - Mix part of basal–bolus	3	Very serious	VERY LOW	51 fewer per 1000 (from 104 fewer to 86 more)	139
Weight change, kg (≤6 months) - Mix part of basal–bolus	1	No serious imprecision	LOW	MD 0.7 lower (1.28 to 0.12 lower)	1.0

Table 58: Evidence summary table: Mixed insulin (aspart mix) versus basal–bolus insulin (less than or equal to 6 months)

Outcomes	Number of studies	Imprecision	GRADE rating	Absolute difference MIX	Final value for control group Basal–bolus
Hypoglycaemia, number of patients - Mix part of basal–bolus (≤6 months)	1	No serious imprecision	LOW	9 more per 1000 (from 37 fewer to 56 more)	933
Nocturnal hypoglycaemia, number of patients - Mix part of basal–bolus (≤6 months)	1	Serious	VERY LOW	167 fewer per 1000 (from 83 fewer to 229 fewer)	694
Severe/major hypoglycaemia, number of patients - Mix part of basal–bolus (≤6 months)	2	Very serious	VERY LOW	19 fewer per 1000 (from 54 fewer to 39 more)	111
SF-36 Physical (≤6 months) - True mix (twice/day versus basal–bolus)	1	No serious imprecision	LOW	MD 0.3 higher (0.65 lower to 1.25 higher)	Not reported
SF-36 Mental (≤6 months) - True mix (twice/day versus basal–bolus)	1	No serious imprecision	LOW	MD 0.1 lower (1.55 lower to 1.35 higher)	Not reported
Treatment satisfaction, % (≤6 months - Lispro or Aspart) - True mix (twice/day versus basal–bolus)	1	No serious imprecision	LOW	MD 27.7 lower (39.22 to 16.18 lower)	56.2%
Regimen acceptance, % (≤6 months) - Lispro or Aspart - True mix (twice/day versus basal–bolus)	1	Serious	VERY LOW	MD 4 lower (7.55 to 0.45 lower)	64.6%

Table 59: Evidence summary table: Mixed insulin versus mixed insulin (less than or equal to 6 months)

Outcomes	Number of studies	Imprecision	GRADE rating	Absolute difference MIX	Final value for control group Basal–bolus
HbA1c, final value (≤6 months)	2	no serious imprecision	LOW	MD 0.09 lower (0.33 lower to 0.15 higher)	9.55
Nocturnal hypoglycaemia, episodes/patient (≤6 months)	1	serious	VERY LOW	MD 1.40 lower (3.16 lower to 0.36 higher)	7.40
Severe/major hypoglycaemia, number of patients (≤6 months)	1	Very serious	VERY LOW	7 more per 1000 (from 32 fewer to 103 more)	59

9.2.3.3 Economic evidence

Published literature

No relevant economic evaluations comparing pre-mix insulin were identified.

One paper was identified in CG15 that compared pre-mix insulin [193]. Due to severe methodological limitations, it has been excluded. This study is summarised in Appendix L, with reasons for exclusion given.

Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided in Appendix Q to aid consideration of cost effectiveness.

9.2.3.4 Evidence statements

Clinical

Mixed insulin (human mix) versus basal–bolus insulin

Low and very low quality evidence from single studies showed a clinically significant harm of human mixed insulin at less than or equal to 6 months compared with basal–bolus insulin in terms of reduction in HbA1c (the mix used was part of a basal–bolus regimen). However there was no clinical difference for either nocturnal hypoglycaemia or severe/major hypoglycaemia (the mix was part of a basal–bolus regimen), nor for the number of patients experiencing ketoacidosis, nor for injection site reactions (the mix used was a clinically relevant regimen, that is, twice/day).

Mixed insulin (lispro mix) versus basal–bolus insulin

Low and very low quality evidence showed a clinically significant harm of lispro mixed insulin at less than or equal to 6 months compared with basal–bolus insulin in terms of reduction in HbA1c (if the mix used was a clinically relevant regimen, that is, twice/day), whereas if the mix used was part of a basal–bolus regimen, there was a clinically significant benefit of lispro mix compared with basal–bolus. However there was no clinical difference for hypoglycaemia episodes (mix was part of a basal–bolus regimen), nocturnal hypoglycaemia episodes (mix was part of a basal–bolus regimen), severe/major hypoglycaemia (regardless of whether the mix used was a clinically relevant regimen, that is, twice/day, or if the mix used was part of the basal–bolus regimen), nor for weight change (mix was part of a basal–bolus regimen).

Mixed insulin (aspart mix) versus basal–bolus insulin

Low and very low quality evidence showed a clinically significant harm of aspart mixed insulin at less than or equal to 6 months compared with basal–bolus insulin in terms of the percentage of patients with treatment satisfaction (the mix used was either lispro or aspart and given as a clinically relevant regimen, that is, twice/day). However, there was no clinical difference for number of patients experiencing measures of hypoglycaemia: hypoglycaemia, nocturnal hypoglycaemia, and severe/major hypoglycaemia (in all measures the mix was part of a basal–bolus regimen), nor for SF-36 Physical or mental, treatment satisfaction, or regimen acceptance (in all measures the mix was given as a clinically relevant regimen, that is, twice/day).

Mixed insulin versus mixed insulin

Low and very low quality evidence showed no clinical benefit of mixed insulin at less than or equal to 6 months compared with another mixed insulin in terms of HbA1c, episodes of nocturnal hypoglycaemia, and episodes of severe/major hypoglycaemia.

Economic

No relevant economic evaluations were identified.

9.2.3.5 Recommendations and link to evidence

The current guideline recommendations can be found at

https://www.nice.org.uk/guidance/ng17

Relative values of different outcomes	When considering the use of different insulin regimens in type 1 diabetes, impact on clinical outcomes at <6 months and >6 months were considered in the following order of importance: • Improvement in glycaemic control, assessed by reduction in HbA1c. Extensive previous research has shown that an improvement in glycaemic control is associated with a reduction in microvascular complications. • Reduction in the incidence of hypoglycaemia. Hypoglycaemia is a regular occurrence in many people on insulin-based therapies and has been associated with a reduction in quality of life for people with diabetes, and an obstacle to improved control. Any therapy that achieves an improvement in glycaemic control without producing hypoglycaemia would be beneficial to patients with diabetes. • Reduction in incidence of severe hypoglycaemia (requiring help from 3rd party for correction), which has been recognised as having a significant impact on quality of life in patients with type 1 diabetes. • Reduction in the incidence of nocturnal hypoglycaemia. • Adverse events: the literature was reviewed for any incidence of neoplastic disease associated with the use of mixed insulins. • Incidence of diabetic ketoacidosis (DKA): the literature was reviewed to see if any particular choice of insulin regimen was associated with an increased incidence of DKA. • Quality of life: the impact of particular insulin regimens with varying numbers of insulin injections when used in individuals with type 1 diabetes • Injection site issues associated with choice of insulin therapy • Impact on weight: initiation and intensification of insulin-based therapies are associated with increases in weight. The literature was reviewed to see if weight gain was associated with any particular choice of insulin therapy.
Trade-off between clinical benefits and harms	It was recognised by the GDG that insulin regimens requiring a greater number of insulin injections might be considered to be detrimental to quality of life. However, this was not demonstrated in the Diabetes Control and Complications Trial, nor is it found in studies of structured education in flexible insulin therapy. The increased number of injections for many people may be counterbalanced by any improvement in blood glucose control, other aspects of lifestyle such as flexibility of meal timing, and by confidence in managing the regimens. **Multiple daily injection basal–bolus insulin regimens versus twice-daily mixed insulin** Glycaemic control outcomes were better in subjects using basal–bolus regimens in comparison to twice-daily mixed insulin regimens.

	No clinically beneficial advantage in the overall incidence of hypoglycaemia or severe hypoglycaemia was seen with use of either insulin regimen. Trials suggested that basal–bolus regimens might produce less nocturnal hypoglycaemia, whilst mixed insulin regimens might have a lower incidence of severe hypoglycaemia. However, the GDG considered the differences were not sufficient to be clinically important. Incidence of ketoacidosis was markedly less in individuals on basal–bolus regimens. Although no significant difference was obtained between regimens in mental and physical quality of life studies, treatment satisfaction was described as greater in individuals on twice-daily mixed regimens, as was regimen acceptance. No difference in injection site outcomes was described between groups. Individuals on mixed insulin regimens gained less weight than those on basal–bolus regimens. **Human mixed insulin versus analogue mixed insulin** No difference in glycaemic control outcomes was noted between groups and there was no difference in incidence of severe hypoglycaemia. One trial suggested that nocturnal hypoglycaemia incidence might be reduced in individuals using analogue insulins. No data were available regarding quality of life outcomes, adverse outcomes (including neoplastic disease outcomes), injection site outcomes, weight change or incidence of diabetic ketoacidosis in human mixed insulin versus analogue mixed insulin studies.
Economic considerations	No relevant economic evaluations comparing mixed insulin therapies to each other or multiple daily injection insulin regimens were found. The GDG concluded that the clinical benefits produced by multiple daily injection basal–bolus insulin regimens were sufficient to justify any increase in cost that they might have over twice-daily mixed insulin regimens. No difference in clinical outcomes was noted when comparing twice-daily human mixed insulins with twice-daily analogue mixed insulin regimens. Twice-daily human mixed insulins are substantially cheaper than analogue twice-daily mixed insulins. Therefore, where a twice-daily mixed insulin regimen is selected for use in an individual with type 1 diabetes, human mixed insulin should be selected in preference to analogue mixed insulin initially. If the individual later experiences an unacceptable frequency of hypoglycaemia whilst using human mixed insulin, this could be substituted with a trial of analogue mixed insulin to see if the frequency of hypoglycaemia episode might be reduced.
Quality of evidence	Only UK licensed mixed insulin preparations were considered in the analysis. Only randomised controlled trials were included for assessment of clinical outcome with mixed insulin therapies. It was noted that many of the studies available for analysis using mixed insulin were undertaken in heterogeneous populations containing individuals with type 1 diabetes and individuals with type 2 diabetes. In addition, some studies combined adult and paediatric populations with type 1 diabetes. Quality of the studies available for analysis ranged from 'Very low' to 'Low' according to GRADE criteria. Caution was given to conclusions reached by studies as the GDG noted that many of the studies had low numbers of participants. Four studies compared multiple daily injection (MDI) regimens using mixed insulins to basal–bolus regimens using only short-acting insulins and once-daily insulatard in the evening (Ciofetta et al 1999, Fanelli et al 2002, Herz et al 2002, Chen et al 2006).

	The GDG noted that such MDI mixed insulin regimens have not been commonly used in practice, and have been largely superseded by MDI regimens with twice-daily and/or once-daily longer acting analogue insulins to provide background insulin replacement (see section on MDI). No trial compared MDI with pre-mixed insulin using more modern regimens. One study compared degludec-aspart mixed insulin therapy with additional aspart insulin injections versus a detemir-aspart basal–bolus regimen (Hirsch et al 2012). Although the study suggested that the incidence of nocturnal hypoglycaemia might be reduced by this regimen, it was noted that patients with recurrent hypoglycaemia were excluded from the study. Three studies undertook a direct comparison of twice-daily mixed insulin regimens versus basal–bolus regimens (Khachadurian et al 1989, Janssen et al 2000, Testa et al 2012). It was noted that the study reporting greater satisfaction and regimen acceptance with mixed insulin regimens did not include measures of glycaemic control in its outcomes assessment (Testa et al 2012). Seven studies compared mixed insulin regimens with each other, with three studies comparing analogue mixed insulins with human mixed insulins (Roach et al 1999, Roach et al 2001, Boehm et al 2002). It was noted that in the one study that suggested that analogue insulins may have a beneficial impact on nocturnal hypoglycaemia, glycaemic control was better in the human insulin treated group (Roach et al, 1999).
Other considerations	The GDG recognised that evidence regarding choice of insulin regimen (basal–bolus versus twice-daily mixed insulin versus basal insulin regimens alone) at the time of diagnosis of type 1 diabetes is insufficient at present to allow a recommendation of a particular regimen. There is evidence that establishing tight glycaemic control soon after diagnosis produces long-term benefits by preserving endogenous insulin production, and that this may have beneficial effects in reducing the risk of vascular complications during the lifetime of an individual with type 1 diabetes. As the current evidence indicates that basal–bolus regimens produce better glycaemic control than twice-daily mixed insulin regimens, this might suggest that basal–bolus regimens should be commenced immediately at the time of diagnosis. However, evidence for this hypothesis is currently lacking. It also does not take into account that some individuals may prefer to use an insulin regimen with fewer injections whilst they come to terms with their diagnosis, at a time when ongoing endogenous insulin production allows good glycaemic control to be achieved with fewer insulin injections. After weighing up these issues the GDG agreed that the balance of evidence was in favour of using a basal–bolus regimen as first choice, but acknowledging that there are factors such as limiting the number of injections required which might lead to a different choice in some individuals. Further research is needed to answer whether a particular insulin regimen commenced at the time of diagnosis of type 1 diabetes has any clear advantage over other available regimens.

9.2.3.6 Research recommendation

No research recommendations for mixed insulin.

9.2.4 Adjunctive non-insulin therapies [2015]

9.2.4.1 Introduction

Tight glucose control in type 1 diabetes has been proven to reduce development of microvascular complications (DCCT, 1993). Whilst management is predominantly controlled through insulin treatment there has been recent interest in adjunctive therapies, particularly where insulin resistance has been identified. Insulin resistance in type 1 diabetes is associated with a higher risk of both micro- and macrovascular complications. Improved glycaemic control was shown to reduce these risks. The aim of treatment therefore, is to reduce blood glucose levels and thereby reduce insulin resistance and potential future complications (DCCT, 1993).

Metformin and GLP-1 receptor agonists have both been identified as agents able to reduce insulin resistance (Hamilton, 2003, Parlevliet, 2010). There is limited evidence of use within the type 1 population, although pramlintide, metformin and GLP-1 receptor agonists have all been studied and hold licenses for use in combination with insulin. Pramlintide is the only agent that holds a licence for use in type 1 diabetes. These agents have all been considered for potential use alongside insulin treatment with the aim of improving glycaemic control and reducing insulin resistance.

The evidence review excluded data on other antidiabetic medications as their pharmacology excludes use in type 1 diabetes and therefore falls outside the agreed standard operating procedures for NICE guidelines.

9.2.4.2 Review question: In adults with type 1 diabetes, are metformin (with or without insulin), or GLP1-agonists (with or without insulin) as effective as insulin alone for optimal diabetic control?

For full details see review protocol in Appendix C.

Table 60: PICO characteristics of review question

Population	Adults with type 1 diabetes • Adult is defined as aged ≥18 years • Type 1 diabetes is defined as (if details of diabetes is specified)

Intervention/s	• Metformin
	• Metformin plus insulin
	• GLP-1 agonists
	  ○ exenatide
	  ○ pramlintide
	  ○ liraglutide
	• GLP1 plus insulin
	Note: only UK licensed interventions and doses will be considered

Comparison/s	Insulin Only UK licensed interventions and doses were considered
Outcomes	Outcomes • HbA1c • Hypoglycaemia • Severe hypoglycaemia • Nocturnal hypoglycameia • Quality of life • Adverse events • Weight loss/change • Dose of insulin

Study design	RCTs

9.2.4.3 Clinical Evidence

Sixteen studies were included in the review[197,364,396,410,411,468,552,607,726,727,771505775452105,394,587,647]. Evidence from these are summarised in the clinical evidence summary below (Table 61). See also the study selection flow chart in Appendix D, forest plots in Appendix J, study evidence tables in Appendix G, GRADE tables in Appendix I and exclusion list in Appendix K.

We searched for randomised trials comparing the effectiveness of GLP-1 agonists, Metformin, or amylin analogues (with or without mention of insulin) versus placebo or usual care with insulin in improving diabetic control in adults with type 1 diabetes.

Sixteen randomised trials were identified, reported in 19 published papers. All trials compared the addition of a pharmacological agent to insulin versus insulin alone. Eight trials compared the addition of pramlintide (an amylin analogue), six trials compared the addition of Metformin, one trial compared the addition of liraglutide, and one trial the addition of exenatide.

Studies included participants that were assessed in both inpatient and outpatient hospital settings.

Outcomes reported include:

- Change in glycosylated haemoglobin (HbA1c)
- Hypoglycaemia
- Severe hypoglycaemia
- Insulin dose
- Weight change
- Adverse events
- Quality of life (QoL)

For the purpose of this review, the follow-up periods for the outcomes reported have been grouped into less than or into 6 months and more than 6 months.

Subgroup analyses for heterogeneity

Where there was heterogeneity between studies in the meta-analyses for the critical outcomes (HbA1c and major or severe hypoglycaemia), it was agreed that this would be explored using pre-specified subgroups in the protocol. These were:

- difference in doses used between studies
- different frequency of administration

There was considerable heterogeneity between the trials for the outcome of HbA1c at more than 6 months follow-up. The pre-specified subgroup analysis of different dose, did not explain the heterogeneity (Ratner study was 60-90 micrograms versus the other two trials were 30-60 micrograms). Different frequency of administration however, did explain the heterogeneity, as all 3 studies used a different frequency. The data were therefore split into these subgroups, and considered separately.

Table 61: Summary of included studies

Study	Intervention/ comparison	Population	Follow-up	Outcomes	Comments
Pramlintide studies					
Edelman 2006[197] Marrero 2007[482], Kovatchev 2008[419]	Pramlintide 30-60 micrograms/meal versus placebo (TDS or QDS depending on meal pattern)	Adult type 1 diabetes of >1 year using MDI or CSII n= 296 n=148 Pramlintide (30 micrograms=41; 60 micrograms=101; 15-45 micrograms=5) n=147, Placebo	29 weeks	HbA1c Hypoglycaemia Quality of Life Gastrointestinal Adverse Events Weight change	Pramlintide initiated at 15 micrograms/meal and increased weekly to 60 micrograms/meal. Those unable to tolerate 60 µg were treated with 30 micrograms/meal for the duration; others were treated with 15 microgramsand 45 microgramsdoses. Treatment was accompanied by insulin optimization.
Ratner 2004 [607]	Pramlintide 60-90 micrograms/meal TDS versus placebo	Age 16-76 type 1 diabetes of >1 year n=304 Safety population, n= 631	1 year	HbA1c Insulin dose Gastrointestinal Adverse events	Patients randomized to receive different dosing regimens. Placebo based run-in period (4 weeks). Number entering run-in not reported
Whitehouse2002 [775]	Pramlintide 30-60 micrograms/day QDS versus placebo	Aged 16-60 years with type 1 diabetes of >1 year n=480	1 year	HbA1c Insulin dose Gastrointestinal Adverse events	At 20 weeks, pramlintide patients with <1% change in HbA1cwere re-randomised to 30 or 60 microgramsQDS
Levetan 2003 [452]	Pramlintide 30 micrograms/meal TDS versus placebo	All people type 1 diabetes of >1 year using CSII n=24 n=18, Pramlintide	6 weeks	Insulin dose	Treatment was accompanied by insulin optimization.

Study	Intervention/ comparison	Population	Follow-up	Outcomes	Comments
		n=6, Placebo			
Kolterman 1996[410]	Pramlintide 30-300 micrograms/meal versus placebo	Adult type 1 diabetes of >2 years C-peptide-negative n= 84 n= 62, Pramlintide (30 micrograms=18; 100 micrograms=23; 300 micrograms=21) n=22, Placebo	2 weeks	Gastrointestinal Adverse Events	Patients randomized to receive different doses. Dose groups analysed separately. Pre-treatment insulin infusion test prior to randomization. Number of patients entering prerandomization not reported.
Nyholm 1999[552] Cross-over RCT	Pramlintide 30 microgramsQDS versus placebo	Adult men with type 1 diabetes n=14	4 weeks with 3-5 week washout	HbA1c Hypoglycaemia Weight change	Treatment was accompanied by insulin optimization.
Thompson 1997[726]	Pramlintide 30-60 micrograms(in four different dosing regimens) versus placebo	Adults with type 1 diabetes n=215 n=173, Pramlintide (30 microgramsQDS, n=45; 30 microgramsTDS (lunch), n=41; 30 µg TDS (snack), n=44; 60 micrograms BD, n=43) n=42 Placebo	4 weeks	Hypoglycaemia Gastrointestinal Adverse Events	Placebo based run-in period. Number entering run-in not reported. Four dosing regimens: 30 micrograms(breakfast, lunch, snack, dinner); 60 micrograms(breakfast, dinner); 30 micrograms(breakfast, lunch, dinner) 30 micrograms(breakfast, snack, dinner)
Thompson 1997[727]	Pramlintide 10-100 microgramsQDS versus placebo	Adults with type 1 diabetes of >1 year n=168 n=146, Pramlintide (10 micrograms, n=43; 30 micrograms, n=41;	2 weeks	Hypoglycaemia Gastrointestinal Adverse Events	Placebo based run-in period. Number entering run-in not reported.

Study	Intervention/ comparison	Population	Follow-up	Outcomes	Comments
		100 micrograms, n=42) n=42, Placebo			
Metformin studies					
Burchardt 2013[105]	Metformin (doses up to 2550 mg/day for the most obese) versus insulin alone	Obese adults with type 1 diabetes of >5 years n=68 n=34, Metformin n=34, Placebo	6 months	HbA1c	1 week insulin dose optimisation period before randomisation. Dose of metformin adjusted based on level of obesity.
Jacobsen 2009[364]	Metformin 1 g BD versus placebo	Adults with type 1 diabetes of >1 year using MDI n=24 n=12, Metformin n=12, Placebo	24 weeks	HbA1c Gastrointestinal Adverse Events Weight change Dose of insulin	Run-in period of 4 weeks in which glycaemic control was optimised. Number entering run-in period not reported.
Khan 2006 [394] Cross-over RCT	Metformin 850 mg TDS versus placebo	All people with type 1 diabetes of >1 year; BMI >27; C-peptide-negative n=15	16 weeks	HbA1c Insulin dose Weight change Gastrointestinal Adverse events	Metformin initiated once daily, titrated up.
Lund 2008[468]	Metformin 1 g BD versus placebo	Adults with type 1 diabetes of≥5 years n=100 n=49, Metformin n=51, Placebo	1 year	HbA1c Hypoglycaemia Dose of insulin Weight change	Placebo based run-in period. Number entering run-in not reported. Metformin dose increased by forced titration weekly as tolerated.
Meyer 2002 [505]	Metformin 850 mg BD versus placebo	All people with type 1 diabetes of >1 year using CSII n=62	6 months	HbA1c Insulin dose Hypoglycaemia Gastrointestinal Adverse	Placebo based run-in period (8 weeks). Number entering run-in not reported.

Study	Intervention/ comparison	Population	Follow-up	Outcomes	Comments
				events	
Pitocco 2013[587]	Metformin 850 mg TDS versus placebo	Adults with type 1 diabetes of ≥5 years n=42 n=21, Metformin n=21, Placebo	6 months	HbA1c Insulin dose Hypoglycaemia Weight change	Metformin titrated up.
Liraglutide studies					
Kielgast 2011[396]	Liraglutide 0.6-1.2 mg/day versus usual Care	Adults with type 1 diabetes ; C-peptide-negative n=19 n=9, Liraglutide n=10, Usual Care	4 weeks	HbA1c Dose of insulin Weight change	C-peptide-positive patients were also included in this study but not randomised, and were subsequently analysed separately
Exenatide studies					
Sarkar 2014[647]	Exenatide plus/minus daclizumab versus insulin alone	Adults with type 1 diabetes for long duration (mean 21 years)	6 months (each cross-over treatment period)	HbA1c Dose of insulin Weight change	Analysis in the study showed no effect of daclizumab and so results for all exenatide patients were pooled together; % patients on daclizumab not given. 2-4 months insulin optimisation period, followed by a run-in period, before randomisation.

Table 62: Clinical evidence summary: Pramlintide plus insulin versus insulin alone (less than or equal to 6 months follow-up)

Outcome	Number of studies	Imprecision	GRADE rating	Absolute difference	Control event rate (per 1000)
HbA1c%	1	Serious imprecision	LOW	MD 0.3 lower (0.87 lower to 0.27 higher)	8.2%
Severe Hypoglycaemia, no. of patients	1	Very serious imprecision	VERY LOW	6 fewer per 1000 (from 22 fewer to 139 more)	24
Hypoglycaemia, no. of patients	2	Serious imprecision	VERY LOW	110 more per 1000 (from 176 fewer to 542 more)	732
Weight Change, kg	1	No serious imprecision	MODERATE	MD 1 lower (2.18 lower to 1.18 higher)	-1.3
Adverse events – Nausea, no. of patients	1	No serious imprecision	MODERATE	190 more per 1000 (from 6 more to 1000 more)	24
Adverse events – Anorexia, no. of patients	1	Serious imprecision	LOW	40 more per 1000	0

Table 63: Clinical evidence summary: Pramlintide plus insulin versus insulin alone (more than 6 months follow-up)

Outcome	Number of studies	Imprecision	GRADE rating	Absolute difference	Control event rate (per 1000)
HbA1c% SUBGROUP pramlintide 3 times/day	1	No serious imprecision	MODERATE	MD 0.28 lower (0.55 to 0.00 lower)	-0.12
HbA1c% SUBGROUP pramlintide 4 times/day	1	No serious imprecision	MODERATE	MD 0.00 lower (0.20 lower to 0.20 higher)	-0.04
HbA1c% SUBGROUP pramlintide 3 or 4 times/day	1	No serious imprecision	MODERATE	MD 0.17 lower (0.29 to 0.04 lower)	-0.05
Hypoglycaemia, no. of	1	No serious imprecision	MODERATE	9 more per 1000 (from 55 fewer to 73 more)	912

Outcome	Number of studies	Imprecision	GRADE rating	Absolute difference	Control event rate (per 1000)
patients					
Weight Change, kg	1	Serious imprecision	MODERATE	MD 2.5 lower (3.25 to 1.75 lower)	+1.2 kg
Adverse events – Nausea, no. of patients	1	No serious imprecision	LOW	267 more per 1000 (from 130 more to 443 more)	361
Adverse events – Vomiting, no. of patients	1	Serious imprecision	LOW	74 more per 1000 (from 2 more to 226 more)	61
Adverse events – Anorexia, no. of patients	1	No serious imprecision	MODERATE	71 more per 1000 (from 6 more to 294 more)	20

Table 64: Clinical evidence summary: Metformin plus insulin versus insulin alone (less than or equal to 6 months follow-up)

Outcome	Number of studies	Imprecision	GRADE rating	Absolute Difference	Control event rate (per 1000)
HbA1c %	4	Serious imprecision	LOW	MD 0.17 lower (0.44 lower to 0.10 higher)	7.8%
HbA1c %	1	Serious imprecision	LOW	MD 0.17 higher (0.36 lower to 0.72 higher)	Not reported
Severe hypoglycaemia, no. of patients	1	Serious imprecision	LOW	65 fewer per 1000 (from 135 fewer to 210 more)	161
Severe hypoglycaemia – episodes	1	No serious imprecision	MODERATE	Zero events in each arm	Not reported
Dose of insulin	3	Serious imprecision	LOW	MD 4.99 lower (8.35 lower to 1.65 higher)	1.7
Dose of insulin	1	Serious imprecision	LOW	MD 0.027 lower (0.10 lower to 0.51 higher)	Not reported
Weight Change, kg	2	No serious imprecision	LOW	MD 3.7 lower (5.76 to 1.36 lower)	45
Weight Change, kg	1	No serious imprecision	MODERATE	MD 2.27 lower (3.99 to 0.54 lower)	Not reported
Gastrointestinal discomfort, no. of patients	3	Serious imprecision	LOW	148 more per 1000 (from 13 more to 561 more)	53
Adverse events –	1	Very serious imprecision	VERY LOW	RR 2.77 (0.12 to 61.65)	0

Outcome	Number of studies	Imprecision	GRADE rating	Absolute Difference	Control event rate (per 1000)
Vomiting, no. of patients					

Table 65: Clinical evidence summary: Metformin plus insulin versus insulin alone (more than 6 months follow-up)

Outcome	Number of studies	Imprecision	GRADE rating	Absolute Difference	Control event rate (per 1000)
HbA1c %	1	Serious imprecision	MODERATE	MD 0.13 higher (0.18 lower to 0.44 higher)	-0.23
Hypoglycaemia, no. of patients	1	No serious imprecision	HIGH	0 fewer per 1000 (from 59 fewer to 59 more)	980
Dose of insulin	1	No serious imprecision	HIGH	MD 5.7 lower (8.49 to 2.91 lower)	2.5
Weight Change, kg	1	Serious imprecision	MODERATE	MD 1.74 lower (3.31 to 0.17 lower)	0.53
Gastrointestinal discomfort, no. of patients	1	Serious imprecision	MODERATE	101 more per 1000 (from 47 fewer to 273 more)	780

Table 66: Clinical evidence summary: Liraglutide plus insulin versus insulin alone (less than or equal to 6 months follow-up)

Outcome	Number of studies	Imprecision	GRADE rating	Absolute Difference	Control event rate (per 1000)
HbA1c%	1	Serious imprecision	MODERATE	MD 0.27 lower (0.62 lower to 0.08 higher	-0.2
Dose of insulin	1	No serious imprecision	HIGH	MD 0.15 lower (0.23 to 0.06 lower)	0.017
Weight change, kg	1	Serious imprecision	MODERATE	MD 2 lower (3.32 to 0.68 lower)	0.2

Table 67: Clinical evidence summary: Exenatide plus insulin versus insulin alone (less than or equal to 6 months follow-up)

Outcome	Number of studies	Imprecision	GRADE rating	Absolute Difference	Control event rate (per 1000)
HbA1c	1	Very serious imprecision	VERY LOW	MD 0.10 lower (0.52 to 0.32 higher)	6.37
Dose of insulin	1	Serious imprecision	VERY LOW	MD 0.07 lower (0.16 to 0.12 higher)	0.54

Outcome	Number of studies	Imprecision	GRADE rating	Absolute Difference	Control event rate (per 1000)
Weight change, kg	1	Serious imprecision	VERY LOW	MD 4.20 lower (13.08 to 4.68 higher)	76.9

9.2.4.4 Economic evidence

Published literature

No relevant economic evaluations comparing adjunctive insulin treatments were identified.

Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided below to aid consideration of cost effectiveness.

Table 68: Unit cost of adjunctive insulin treatments

Drug	Supplied as	Unit cost	Cost per day
Metformin	28 x 500 mg tab	£1.32[a]	£0.19[b]
Liraglutide	3 x 3 ml (6 mg/ml) pre-filled pens	£117.72	£2.62

(a) Source: Drug Tariff 2014
(b) Assuming dose of 4 times 500 mg per day
(c) Source: BNF 2014[379]

9.2.4.5 Evidence statements

Clinical evidence statements

Pramlintide with insulin versus insulin alone

Less than or equal to 6 months follow-up -Moderate, low and very Low quality evidence, mainly from single studies, showed a clinical benefit of pramlintide as an adjunct to insulin for reducing the number of people experiencing episodes of severe hypoglycaemia. However, the evidence also suggested clinical harm in terms of the adverse events of nausea and anorexia. There was no clinical difference between adjunctive pramlintide versus insulin alone for HbA1c, hypoglycaemia, and weight change.

More than 6 months follow-up-Moderate and low quality evidence, mainly from single studies showed a clinical benefit of pramlintide as an adjunct to insulin for reduction in weight, but the evidence also suggested clinical harmin terms of the adverse events of nausea, vomiting, and anorexia.There was no clinical difference between adjunctive pramlintide versus insulin alone for HbA1c, nor for hypoglycaemia.

Metformin with insulin versus insulin alone

Less than or equal to 6 months follow-up -Low and very low quality evidence, mainly from several studies pooled together, showed a clinical benefit of metformin as an adjunct to insulin for reducing the number of people experiencing episodes of severe hypoglycaemia, reduction in insulin dose, as well as weight reduction. However, the evidence also suggested clinical harm in terms of the adverse events of GI discomfort and vomiting. There was no clinical difference between adjunctive metformin versus insulin alone for HbA1c.

In a single study of moderate quality evidence, no clinical difference between metformin as an adjunct versus insulin alone was shown for HbA1c, episodes of severe hypoglycaemia, and insulin dose. However there was a clinical benefit of adjunctive metformin for weight reduction.

More than 6 months follow-up-Moderate and high quality evidence from a single study showed a clinical benefit of metformin as an adjunct to insulin for reduction in dose of insulin. However, there

was no clinical difference between adjunctive metformin versus insulin alone for HbA1c, hypoglycaemia, weight change, and the adverse event of GI discomfort.

Liraglutide with insulin versus insulin alone

Less than or equal to 6 months follow-up -Moderate and high quality evidence from a single study showed no clinical difference between adjunctive liraglutide versus insulin alone for HbA1c, dose of insulin, and weight change.

Exenatide with insulin versus insulin alone

Less than or equal to 6 months follow-up -Very low quality evidence from a single study showed a clinical benefit of exenatide as an adjunct to insulin for reduction in weight. However, there was no clinical difference between adjunctive exenatide versus insulin alone for HbA1c, nor for insulin requirement.

Economic evidence statements

No relevant economic evaluations were identified.

9.2.4.6 Recommendations and link to evidence

The current guideline recommendations can be found at

https://www.nice.org.uk/guidance/ng17

Relative values of different outcomes	It is critically important that none of these adjunct therapies are considered appropriate treatment for type 1 diabetes in the absence of insulin as none of them will substitute for insulin deficiency. When considering the use of adjunct non-insulin therapies in type 1 diabetes, impact on clinical outcomes at <6 months and >6 months was considered in the following order of importance: • Improvement in glycaemic control, assessed by reduction in HbA1c. Extensive previous research has shown that an improvement in glycaemic control is associated with a reduction in microvascular complications. • Reduction in hypoglycaemia and severe hypoglycaemia (requiring help from a third party for correction). Hypoglycaemia is a regular occurrence in many people on insulin-based therapies and has been associated with a reduction in quality of life for people with diabetes. Hypoglycaemia occurrence can limit individuals achieving improvements in glycaemic control, and any adjunct therapy that achieves an improvement in glycaemic control without producing hypoglycaemia would be considered beneficial to patients with diabetes. • Impact on weight – many insulin-based therapies have been associated with increases in weight; any adjunct therapy that can improve glycaemic control with minimal weight gain and/or weight loss might be considered beneficial in patients with type 1 diabetes and an increased body mass index (>25 kg/m^2). • Impact on insulin dose – a reduction in insulin dose may be considered beneficial at least for theoretical reasons and may have a cost benefit by reducing insulin use. • Side-effects associated with adjunct therapy administration, with particular focus given to gastrointestinal side-effects, nausea, vomiting and anorexia for the agents under review.

	Weight gain is a common side effect of improving glycaemic control with insulin alone and is undesirable to many people. There was concern that some adjunct therapies might be used for weight loss alone and the GDG considered thisinappropriate, where the adjunct therapy is not licensed for weight reduction, nor of proven efficacy in type 1 diabetes, and would beparticularly undesirable where BMI was <25 kg/m^2. It was also noted that in studies where a reduction in insulin dose was achieved, greater clinical benefit might have been obtained by on-going titration of the insulin dose while on metformin, in order to bring about an improvement in glycaemic control, but the very small numbers recruited in these studies inflects caution and the need for further research and larger studies in this area. Reduction in insulin dose was felt to be of reduced importance in comparison to other clinical outcomes.
Trade-off between clinical benefits and harms	Impact of adjunct therapies on assessed outcomes: **Metformin** • Produced no clinically beneficial reduction in HbA1c after <6 months and >6 months therapy. • Was associated with a clinically beneficial reduction in severe hypoglycaemia in trials of <6 months duration, although not in trials >6 months duration. • Was associated with a clinically beneficial reduction in weight in trials of <6 months duration, although not in trials >6 months duration. • Reduced insulin dose requirements in trials after <6 months therapy, and also in trials of >6 months therapy. • Metformin was associated with a clinically significant increase in the incidence of vomiting and gastro-intestinal side-effects in trials of <6 months duration. **Amylin analogues (pramlintide)** • Produced a reduction in HbA1c that could be considered clinically beneficial (0.3%) in trials of <6 months duration and >6 months duration. • Was associated with a clinically beneficial reduction in severe hypoglycaemia in trials of <6 months duration, although not in trials >6 months duration. • Had no clinically beneficial reduction in weight after <6 months and >6 months therapy. • Pramlintide was associated with clinically significant increases in nausea, anorexia and gastro-intestinal side-effects in trials of <6 months duration, and with a clinically significant increase in nausea, vomiting and anorexia in trials of >6 months duration. **GLP-1 receptor agonists (liraglutide)** Only one study was available for the GLP-1 analogue Liraglutide. This showed: • A reduction in HbA1c that could be considered clinically beneficial (0.3%) No clinically beneficial reduction in weight or insulin dose was achieved. • No data on side-effects were reported in this study. **GLP-1 receptor agonists (exenatide)** Only one study was available for the GLP-1 analogue Exenatide. This showed: • A reduction in HbA1c and dose of insulin, both of which were not considered to be clinically beneficial. • A clinical benefit for weight reduction. • No data on side-effects were reported in this study. The GDG recognised that when treating individuals with type 1 diabetes, an improvement in glycaemic control (HbA1c) is generally considered to be the main

	goal of therapeutic interventions. However, it was also recognised that achieving this goal might lead to an increase in the incidence of hypoglycaemia, and that improvement in HbA1c might be considered to particularly detrimental if it led to an increased incidence of severe hypoglycaemia.
Economic considerations	No studies using adjunct non-insulin therapies assessed the cost-effectiveness of the clinical outcomes obtained. Metformin is an inexpensive treatment (anticipated cost £18.30 per year for a daily dose of 1.5 g), and only a small improvement in clinical benefit might be required to achieve cost-effectiveness. Metformin might also be cost-effective if a reduction in patient insulin dose was achieved. It was recognised that some prescribers may choose to use the metformin glucophage SR preparation, given its propensity to cause less gastro-intestinal side-effects. Glucophage SR is a more expensive preparation (approximately five times the cost of metformin), although this was not felt to be so great that metformin might not still be considered cost-effective if any improvement in clinical outcome was achieved. The GDG therefore considered that the conventional formulation of metformin should be tried first and replaced with Glucophage SR if use of conventional formulations is associated with unacceptable gastrointestinal side effects. Amylin analogues and GLP-1 analogues were noted to be considerably more expensive than metformin, and therefore greater clinical benefit would need to be achieved for their use to be considered cost-effective. In the view of the side-effects reported with pramlintide use, the GDG felt that amylin analogue use could be associated with increased co-morbidity with potential to incur additional healthcare costs, and their use was therefore considered less likely to be cost-effective.
Quality of evidence	Only randomised controlled trials were included for assessments of clinical outcome with adjunct therapies. It was noted that many of the studies available for analysis using the adjunct therapies identified for this guideline were undertaken in heterogeneous populations containing individuals with type 1 diabetes and individuals with type 2 diabetes. In addition, some studies combined adult and paediatric populations with type 1 diabetes. **Metformin studies** Four studies regarding the use of metformin in people with type 1 diabetes were available for analysis. All compared clinical outcomes of metformin versus placebo in people already established on insulin therapy. Only one of the trials was of >6 months duration[468]: this study was assessed as being of Moderate to High quality. The GDG considered that the available evidence collected in adults with a BMI of >25 kg/m^2 was insufficient to be able to recommend its use routinely in this subgroup. **Amylin analogues** Eight studies were available on the use of amylin analogues in adults with type 1 diabetes already established on insulin therapy. All the studies used the amylin analogue pramlintide and compared outcomes to the use of placebo. All 8 studies were judged to be at serious risk of bias, and the quality of the available evidence ranged from Very low to Moderate. **GLP-1 receptor agonists** Only one study on GLP-1 analogue use in adults with type 1 diabetes was available for analysis (Kielgast et al, 2011).[396] This study used liraglutide in just 9 patients compared with 10 controls. The study did not report side-effects from the medication and was of a duration of <6 months.
Other considerations	The evidence for metformin showed that some reduction in insulin dosage could be

	achieved together with weight loss, without deterioration in HbA1c. However, the benefits were modest and at the risk of side-effects, particularly gastro-intestinal. The GDG therefore did not recommend metformin should be considered for all patients, but noted that there are some who are particularly concerned about weight and who wish to limit their insulin dose if this is possible. A recommendation was designed to allow a trial of metformin in this group of people. The amylin analogue pramlintide was not licensed for clinical use in the UK when the evidence was considered. The GDG wished to include data on pramlintide because they understood that a licence for use in the UK might be obtained at a later date, and because they wished to see evidence beyond a single agent (metformin) for the principle of using adjunctive agents with insulin in type 1 diabetes. Evidence that GLP-1 analogues can improve clinical outcomes in adults with type 1 diabetes is currently insufficient to recommend its use as an adjunct therapy in type 1 diabetes, and further evidence is required prior to recommendations regarding their use in this patient group.

9.2.4.7 Research recommendations

15. Future studies on the use of metformin as an adjunct to insulin therapy in people with type 1 diabetes should focus on whether improvement in glycaemic control and weight loss (or less weight gain) can be achieved in individuals with a body mass index of more than 25 kg/m^2.

16. Further studies on the use of GLP-1 receptor agonists and other potential pharmacological adjuncts to insulin therapy, and their impact on clinical outcomes in people with type 1 diabetes are required prior to recommendations regarding their use in this patient group.

9.3 Insulin delivery

This chapter refers primarily to intermittent insulin injection therapy and readers are referred to TA151 for NICE guidance on the use of continuous subcutaneous insulin therapy (CSII, or insulin pump therapy).

9.3.1 Introduction

Because it is subject to digestion, exogenous insulin is injected subcutaneously, and for those not using continuous subcutaneous insulin infusion (CSII or insulin pump therapy), this is achieved by intermittent injection using with a needle that is attached to an insulin pen delivery device or an insulin syringe that usually comes with a needle already attached. Needles are disposable and designed for single use and the range of pen needle lengths and diameters (gauges) has increased significantly over recent years.

Injecting insulin into deeper intramuscular tissue can increase the variability of absorption and cause erratic blood glucose levels and hypoglycaemia[387] so choosing an appropriate needle length for the individual patient with regular review is vital.

The recommended injection technique is to insert the needle at a 90 degree angle into the skin, administer the insulin and wait for at least 10 seconds after the plunger is depressed before withdrawing the needle. This is to minimise insulin leakage, which may be detected as dampness around the injection site. With the original longer needle lengths it was advised to lift a skin fold and hold it during insulin administration to minimise the risk of intramuscular injection but this may not always be necessary with use of shorter needles.

Shorter needles are likely to be more attractive to the patient, but the influence of varying needle lengths on long and short term blood glucose control, hypoglycaemic events, bleeding and bruising, insulin leakage and pain perception is uncertain.

Recommended injection sites are the abdomen, buttock, upper outer thigh and upper posterior arm as they generally have ample amount of subcutaneous tissue. Absorption rates may vary according to injection site and type of insulin used and although this problem is reduced with modern analogue insulins, consistency with use of the same area of the body for each daily injection may help stabilise blood glucose levels.

Injection sites should be inspected prior to injection for signs of infection, swelling and lipohypertrophy, which is bulkiness underneath the skin caused by an accumulation of fat tissue caused by overuse of a single site. This can affect the rate of insulin absorption and lead to erratic blood glucose levels, but usually resolves if the site is avoided for several months. Teaching patients to rotate injection sites from the start of insulin therapy can help avoid overuse of sites.

Initial and ongoing provision of accurate advice regarding injection sites and site rotation will enable patients to make informed decisions. With the aim of providing clarity the GDG also asked: in adults with type 1 diabetes what is the optimum injection site and rotation for insulin delivery?

9.3.2 Review questions: In adults with type 1 diabetes, what is the optimum needle length for insulin delivery?

For full details see review protocol in Appendix C.

Table 69: PICO characteristics of review question

Population	Adults with type 1 diabetes (over 18 years)
Intervention	Insulin – delivered by needle
Comparison	As for intervention, but different length of needle
Outcomes	• Pain • Discomfort • Patient satisfaction • HbA1c • Hypoglycaemia - preferably severe hypoglycaemia if reported • Quality of life • Adverse events • Adherence
Study design	RCTs, observational (retrospective and prospective cohort studies)

9.3.3 Review question: In adults with type 1 diabetes, what is the optimum injection site and rotationfor insulin delivery?

For full details see review protocol in Appendix C.

Table 70: PICO characteristics of review question

Population	Adults with type 1 diabetes (over 18 years)
Intervention	Insulin – delivered by needle
Comparison	As for intervention, but different site of delivery
Outcomes	• HbA1c • Hypoglycaemia - preferably severe hypoglycaemia if reported • Quality of life

	• Adverse events • Adherence
Study design	RCTs, observational (retrospective and prospective cohort studies)

9.3.4 Clinical evidence

9.3.4.1 Needle length

We conducted an updated literature search and 12 new studies were found that met the inclusion criteria for this review. [45,49,75,262,305,331,360,421,500,508,509,511,520,683]. Five of the studies [331,360,421,500,508] were directly comparing different needle lengths. Evidence from these are summarised in the clinical evidence summary below (Table 71). See also the study selection flow chart in Appendix D, forest plots in Appendix J, study evidence tables in Appendix G, GRADE tables in Appendix Iand exclusion list in Appendix K. The remainder of the studies were either:

- Conference abstracts (these were included in the review for additional information only, and not pooled in the meta-analysis or GRADE with the fully published RCTs, due to the limited information they provide)
- Studies that assessed a slightly different aspect of needles (the effect of tapering, or needle wall thickness) were also included in the review to be considered as additional information only, and not put in meta-analysis or GRADE, because these were aspects of needles that the GDG were interested in *post-hoc*, and not part of the main review which was specifically looking at needle length.

Due to the paucity of evidence in type 1 diabetes for this review, we have included studies with a mixed population of both type 1 and type 2 diabetes, regardless of the percentages of type 1 or type 2 diabetes, as type of diabetes was not considered to affect several of the outcome measures for this question. No data was reported separately for the population with type 1 diabetes.

Several studies did not report data for some outcomes that was suitable for GRADE, therefore, we have included narrative summaries for these.

The included studies reported the following relevant outcomes:

- HbA1c
- Adverse events
- Hypoglycaemia
- Pain (injection site, during insertion, or VAS pain score)
- Overall satisfaction

The included studies did not report on any of the following outcomes:

- Discomfort
- Adherence
- Severe hypoglycaemia
- Quality of life (QoL)

9.3.4.2 Needle site or rotation sequence

No studies were included in this review which addressed the question of which is the best injection site and rotation. The original 2004 guideline included one RCT[57] which assessed the effects of needle rotation in n=22 people with type 1 diabetes, but this study did report any of our pre-specified outcomes. No new evidence was found to address this in the updated literature search.

Table 71: Summary of studies included in the review: insulin delivery – needle length

Study	Intervention/comparison	Population	Follow-up	Outcomes	Comments
HIRSCH 2010[331] and HIRSCH 2012A[332] RCT - cross over	4 mm x 32G pen needles (PN) versus 5 mm x 31G PN versus 8 mm x 31G PN	n=173 adults with diabetes (37% type 1 diabetes) (n= 85: 4mm versus 5mm; n= 83: 4mm versus 8mm)	3 weeks each needle	Pain (VAS) score Hypoglycaemia Injection site pain Insulin backflow	Mixed population: Type 1 diabetes (37%) and type 2 diabetes No sub-group analysis or data reported separately for type 1 diabetes group OBESE: BMI (kg/m^2), mean: 30.6 Post-hoc subgroup analysis – impact of obesity (BMI of ≥30): The 4 mm PN was statistically significantly less painful in all groups except for the non-obese in the 4 mm versus 5 mm group. Obese patients reported more leakage (regardless of needle size) Less leakage with the 4 mm (versus 5 mm and 8 mm), regardless of BMI.
IGNAUT 2012[360], RCT - cross over	5mm needles versus 8mm needles Both used HumanPen Memoir insulin pen to deliver 20U and 60 U equivalent volume	n=56 adults with diabetes (n=13, 23% type 1 diabetes)	Not reported	Pain (VAS) score Adverse events Insulin leakage	Mixed population: Type 1 diabetes (23%) and type 2 diabetes No sub-group analysis or data reported separately for type 1 diabetes group OBESE: BMI (kg/m^2), mean (SD): 35.63 (5.54)
KREUGEL 2011[421] RCT - cross over	5mm x 31G PN versus 8mm x 31G PN Both used BD microfine Mini and short insulin pen needles	n=119 adults with diabetes (n=5, 4% type 1 diabetes)	3 months each needle	HbA1c Hypoglycaemia Pain (VAS) Insulin backflow Adverse events	Mixed population: Type 1 diabetes (4%) and type 2 diabetes No sub-group analysis or data reported separately for type 1 diabetes group OBESE: BMI (kg/m^2), mean (range): 36.4(30 – 62.5)
MCKAY 2009[500] RCT - cross	6 mm x 32G PN versus 8mm x 30G PN Both used Novofine needles with FlexPen (NovoNordisk); patients	n=119 adults with diabetes (n=26, 22% type 1 diabetes)	1-2 weeks each needle	Pain (VAS) Patient preference Adverse events	Mixed population: Type 1 diabetes (22%) and type 2 diabetes No sub-group analysis or data reported separately for type 1 diabetes group

Study	Intervention/comparison	Population	Follow-up	Outcomes	Comments
over	injected their usual insulin.				Mainly obese: BMI (kg/m^2), mean (SD; range): 31 (5.7; 20 – 48.7)
MIWA 2012[508] RCT - cross over	4 mm X 32G needle versus 6 mm X 32G needle	n=41 adults with diabetes (n=5, 12% type 1 diabetes).	2 months each needle	Pain (VAS) score Adverse events Insulin leakage	Mixed population: Type 1 diabetes (12%) and type 2 diabetes No sub-group analysis or data reported separately for type 1 diabetes group BMI (kg/m^2), mean (SD): 23.2 (3.2)

Table 72: Summary of additional studies included in the review (not in GRADE or meta-analysis as these are conference abstracts and were used for additional information): insulin delivery – needle length

Study	Intervention/comparison	Population	Follow-up	Outcomes	Comments	Results
Needle length (but not fully published studies)						
BIRKEBAEK 2008 [75] Letter of a case-series	4 mm pen needles (PN) versus 6 mm PN IM Injections using simulated insulin; inserted into abdomen and thigh, perpendicular to the cutis without a skinfold. Volumes equivalent of 10 U and 40 U of insulin.	n=53 diabetic adults and children	Immediate	Risk of IM insulin injections Leakage (backflow) of insulin	Mixed population: diabetes types and %not specified adults and children (60% adults) No sub-group analysis or data reported separately for the type 1 diabetes or the adult group Lean patients (BMI Z score <0)	Statistically significantly more patients injected subcutaneously with the 4 mm versus 6 mm needle at both abdomen and thigh (p<0.032 and 0.001, respectively) Leakage of test medium to skin surface was negligible (regardless of needle length or site) OVERALL: 4 mm needles reduce risk of IM injections without increasing the amount of backflow to the skin surface.
HEINEMANN 2009[305] Conference abstract of an RCT (cross-over)	ID 1.5 mm x 35G needles versus SC 8mm x 31G needles 5 arm trial: intradermal versus sc injections of lispro versus regular human insulin, each using the 2 different needle types. And different injection	n=29 young people and adults with type 1 diabetes	Up to 4 hours	Prandial blood glucose	BMI (kg/m^2), mean: 25.7	ID administration resulted in reduction of post-prandial blood glucose with regular insulin and for lispro. However, there was NS difference between SC or ID (for post-prandial blood glucose).

Study	Intervention/comparison	Population	Follow-up	Outcomes	Comments	Results
	times (2 and 17 minutes before standard high-carb liquid meal)					
MOK 2012[511] Conference abstract of a before and after study	4mm PN versus 5 mm, 6 mm or 8 mm PN (needles that patients were using prior to study of 4 mm PN) Insulin regimen not reported.	n=34 adults with diabetes (47% type 1 diabetes).	2-4 weeks	Pain (Likert scale) Leakage	Mixed population: Type 1 diabetes 47% adults and young people (mean age, 18.6 years; range; 13-76 years) No sub-group analysis or data reported separately for the type 1 diabetes or the adult group BMI (kg/m^2), mean (SD, range): 24.0 (45.1, 17-45)	Pre- versus post-use of 4 mm insulin PN Leakage: NS difference regardless of site (abdomen or thigh) Pain level: NS difference

Abbreviations: IM, intramuscular; ID, intradermal; sc, subcutaneous; RA, rapid-acting; IA, intermediate-acting; LA, long-acting.

Table 73: Summary of additional studies included in the review (not in GRADE or meta-analysis as used for additional information post-hoc): thin wall and tapered needles

Study	Intervention/comparison	Population	Follow-up	Outcomes	Comments	Results
Tapered needles						
ASAKURA 2006[49] RCT (cross-over)	3.5 mm micro tapered needle (needle T, Terumo Corp.) versus 5 mm Standard needle (BD Microfine, 31G thin wall) Injected insulin (no further details given)	n=99 diabetic adults (n=13, 14% type 1 diabetes).	1 day (2 or more injections)	Pain (VAS) Leakage Bleeding Patient preference	Mixed population: Type 1 diabetes (14%) and type 2 diabetes No sub-group analysis or data reported separately for type 1 diabetes group Weight or BMI not reported.	44% of patients preferred needle T (19% needle B, 37% had no preference). Pain (VAS): SS less for needle T (P<0.001) Bleeding and leakage: NS difference between needles.
MIYAKOSHI 2007[509] RCT (cross-over)	5 mm x 33G tapered needle (Terumo NanoPass) versus 5 mm x 31G standard needle	n=40 adults with type 1 diabetes	1 week each needle	Pain (VAS) Leakage Bleeding Patient	All type 1 diabetes adults. Not obese: BMI (kg/m^2), mean: 23.0 (3.1).	Pain (VAS), bleeding, leakage and patient satisfaction, all statistically significantly less for NanoPass. All p<0.001

Study	Intervention/comparison	Population	Follow-up	Outcomes	Comments	Results
	(BD MicroFine Plus) Injected usual insulin (all 4 times a day – RA and IA or LA insulin).			satisfaction		
NAGAI 2012[520]	5 mm x 33Gbase and 28G tip tapered needle versus 4 mm x 32G standard needle	n=84 adults with type 1 diabetes or type 2 diabetes (11% type 1 diabetes)	4 weeks each needle	Pain (VAS) Leakage Bleeding	All adults (type 1 diabetes and type 2 diabetes). Not obese: BMI (kg/m^2), mean: 24.8 (3.7).	Pain (VAS): statistically significantly less for tapered. Bleeding: less for tapered. Leakage: less for tapered.
Thin wall needles						
ARONSON 2013[45]	Extra thin wall (ETW) needles versus patient's usual needle (most patients used 8 mm and 5 mm, and most 31G).	n=216 diabetic adults with type 1 diabetes or type 2 diabetes (10% type 1 diabetes).	1 week each needle	Pain (VAS) Bleeding Dose delivery Patient preference	All adults - mixed population type 1 diabetes and type 2 diabetes Weight and BMI not reported	Extra thin wall needles were better than regular needles for pain, bleeding, confidence in full dose delivery, and overall patient preference.
SIEGMUND 2009[683] Observational cross over trial (not randomised)	31G thin wall needle (BD microfine PN) versus 31G regular wall needle (Ypsomed optifine) Length of needle: not specified in paper.	n=97 diabetic adults (n=27, 28% type 1 diabetes).	2 weeks each needle	Recurring pain (questions) Skin irritation Bleeding Leakage of insulin Patient preference	Mixed population: Type 1 diabetes (28%) and type 2 diabetes No sub-group analysis or data reported separately for type 1 diabetes group Obese: BMI (kg/m^2), mean (SD): 29.9 (6.0)	Thin wall needles were statistically significantly better than regular needles for pain, bleeding, needle occlusion ($p<0.001$). Statistically significantly more patients preferred using thin walled needles (78%, $p<0.001$ versus regular needles).

Additional information: skin thickness

- One study (Gibney 2010)[262] looked at the differences in skin thickness (ST) and subcutaneous adipose layer thickness (SCT) with patient weight, in n=388 adults with diabetes (28% type 1 diabetes). The study showed that:
- Mean ST (95% CI) was: arm 2.2 mm (2.2, 2.3), thigh 1.9 mm (1.8, 1.9), abdomen 2.2 mm (2.1, 2.2) and buttocks 2.4 mm (2.4, 2.5).
- Multivariate analyses showed body site, gender, BMI, and race are statistically significant factors for ST but effects were small.

Differences of 10 kg/m^2 account for 0.2 mm ST variation. Mean SCT was: arm 10.8 mm (10.2, 11.3), thigh 10.4 mm (9.8, 10.9), abdomen 13.9 mm (13.2, 17.7) and buttocks 15.4 mm (14.7, 16.2). Females had 5.1 mm greater SCT. Differences of 10 kg/m^2 account for 4 mm SCT variation. These data suggest that needles of less than or equal to 8 mm deliver insulin to the subcutaneous site.

9.3.4.3 RCTs – additional data (narrative summary)

The following studies are summarised as narratives because the outcome(s) were not appropriate for GRADE due to incomplete outcome reporting:

Visual Analogue Scale (VAS) pain score

- One study (IGNAUT)[360] comparing insulin diluent leakage post injection using two different needle lengths and injection volumes reported "no significant difference between the 5 mm needle versus the 8 mm needle with respect to pain score with either the 20 U or 60 U equivalent volume. Mean ± SD differences in pain score for 20 U and 60 U equivalent volumes were 0.14 ± 2.56 and 0.74 ± 2.49, respectively".
- One study (KREUGEL)[421] reported no significant difference in Pain perception (VAS) between the 5 mm versus 8 mm needles (median value 7 and 9 respectively; p-value not reported).
- One study (McKAY)[500] reported statistically significantly less pain perception (VAS) with the 6 mm/32G versus 8 mm/30G needle needles (p<0.001).

Adverse events

- One study (IGNAUT)[360] comparing insulin diluent leakage post injection using two different needle lengths and injection volumes reported "no serious adverse events during the study".
- One study (MIWA)[508] comparing the effects of a new 32-guage X 4 mm pen needle and a 32-guage X 6 mm pen needle on glycaemic control and safety reported "no adverse events during the trials".
- One study (McKAY)[500] reported a similar number of adverse events (bleeding or bruising) for the 6 mm/32G versus 8 mm/30G needle (n=1 event versus n=3 events).

Hypoglycaemia

- One study (KREUGEL)[421] reported NS difference in hypoglycaemia between the 5 mm versus 8 mm needles (p=0.337).

Insulin leakage or backflow

- One study (HIRSCH 2010)[331] showed that slightly less patients reported leakage when using the 4 mm versus the 5 mm or 8 mm needle (44%, 47% and 56%), and the 5 mm needle was better than the 8 mm needle.
- One study (IGNAUT)[360] reported NS difference in leakage between the 5 mm needle and the 8 mm needle (regardless of injection volume – 20 U or 40 U.)
- One study (KREUGEL)[421] reported SS less insulin backflow for the 8 mm versus 5 mm needles (p=0.01).
- One study (MIWA)[508] reported NS difference in leakage between the 4 mm needle and the 6 mm needle.

Patient preference

- One study (McKAY)[500] reported statistically significantly patient preference for the 6 mm/32G versus 8 mm/30G needle (58% versus 27%; p<0.001).
- One study (KREUGEL)[421] reported NS in patient preference for the 5 mm versus 8 mm needles (46% versus. 41%; p-value not given).

Table 74: Clinical evidence summary tables – Insulin delivery (needle length) - 4 mm x 32G PN versus 5 mm x 31G PN for insulin delivery (less than or equal to 6 months follow-up)

Outcomes	Number of studies	Imprecision	GRADE rating	Absolute difference	Control event rate (per 1000 patients)
Hypoglycaemia, no. of patients	1 study (n=173)	Very serious imprecision	VERY LOW	29 fewer per 1000 (from 106 fewer to 99 more)	236
Injection site pain, no. of patients	1 study (n=173)	Very serious imprecision	VERY LOW	32 more per 1000 (from 42 fewer to 177 more)	124
Visual analogue pain score, 150 mm	1 study (n=173)	No serious imprecision	LOW	MD 11.91 lower (22.91 lower to 0.91 lower)	Not given

Table 75: Clinical evidence summary tables – Insulin delivery (needle length) - 4 mm x 32G PN versus 6 mm x 32G PN for insulin delivery (less than or equal to 6 months follow-up)

Outcomes	Number of studies	Imprecision	GRADE rating	Absolute difference	Control event rate (per 1000 patients)
Visual analogue pain score, 150 mm	1 study (n=41)	Serious imprecision	VERY LOW	MD 16.60 lower (25.95 lower to 7.25 lower)	Not reported

Table 76: Clinical evidence summary tables – Insulin delivery (needle length) - 4 mm x 32G PN versus 8 mm x 31G PN for insulin delivery (less than or equal to 6 months follow-up)

Outcomes	Number of studies	Imprecision	GRADE rating	Absolute difference	Control event rate (per 1000 patients)
Hypoglycaemia, no. of patients	1 study (n=173)	Very serious imprecision	VERY LOW	55 fewer per 1000 (from 131 fewer to 68 more)	262
Injection site pain	1 study (n=173)	Very serious imprecision	VERY LOW	25 more per 1000 (from 50 fewer to 168 more)	131
Visual analogue pain score, 150 mm	1 study (n=173)	No serious imprecision	LOW	MD 23.26 lower (13.57 lower to 14.95 lower)	Not given

Table 77: Clinical evidence summary tables – Insulin delivery (needle length) - 5 mm x 31G PN versus 8 mm x 31G PN for insulin delivery (less than or equal to 6 months follow-up)

Outcomes	Number of studies	Imprecision	GRADE rating	Absolute difference	Control event rate (per 1000 patients)
HbA1c (final value)	1 study (n=130)	No serious imprecision	VERY LOW	MD 0.12 lower (0.35 lower to 0.11 higher)	7.59

9.3.5 Economic evidence

Published literature

No relevant economic evaluations were identified.

Unit cost

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided below to aid consideration of cost effectiveness.

Table 78: Needle costs[a]

Needle Length	4 mm	4.5 mm	5 mm	6 mm	8 mm	10 mm	12 mm
Cost per needle[b]	£0.11	£0.12	£0.14	£0.10	£0.10	£0.07	£0.08
Cost per day	£0.54	£0.62	£0.69	£0.52	£0.50	£0.37	£0.40
Cost per week	£3.81	£4.31	£4.86	£3.61	£3.52	£2.61	£2.82
Cost per month	£15.23	£17.25	£19.45	£14.46	£14.09	£10.43	£11.28
Cost per year	£198.59	£224.84	£253.52	£188.46	£183.69	£136.02	£147.00

(a) Assuming five injections a day with single use needles
(b) Average of all needles that length (source: MIMS accessed on October 2013)

9.3.6 Evidence statements

9.3.6.1 Clinical [2015]

Needle length: 4 mm versus 5 mm PN for insulin delivery

Very low quality evidence, from a single study, showed a clinically important benefit at less than or equal to 6 months of 4 mm PN compared with the 5mm PN for reducing the number of people experiencing episodes ofhypoglycaemia, and reduction in the number of people experiencing injection site pain. However, Low quality evidence from the same study showed that there was no clinical difference between 4 mm and 5 mm PN for pain measured on a VAS.

Needle length: 4 mm versus 6 mm PN for insulin delivery

Very low quality evidence, from a small single study, showed a clinically important benefit at less than or equal to 6 months of 4 mm PN compared with the 6 mm PN for a reduction in pain measured on a VAS.

Needle length: 4 mm versus 8 mm PN for insulin delivery

Low and very low quality evidence, from a single study, showed a clinically important benefit at less than or equal to 6 months of 4 mm PN compared with the 8 mm PN for reducing the number of people experiencing episodes of hypoglycaemia, reduction in the number of people experiencing injection site pain, and reduction in pain measured on a VAS.

Needle length: 5 mm versus 8 mm PN for insulin delivery

Very low quality evidence, from a single study, showed no clinical difference at less than or equal to 6 months between the 5 mm PN and 8 mm PN for a reduction in HbA1c.

9.3.6.2 Economic [2015]

No relevant economic evaluations were identified.

9.3.7 Recommendations and links to the evidence

The current guideline recommendations can be found at

https://www.nice.org.uk/guidance/ng17

Relative values of different outcomes	To determine the optimum use of needles for insulin delivery in individuals with type 1 diabetes, the GDG reviewed whether the following parameters of needle use in insulin administration had any influence on clinical outcomes: • The length of the insulin needle • The site and frequency of site rotation for insulin delivery The impact of these parameters on needle use for insulin delivery was assessed for the following clinical outcomes: • Quality of life: Particular attention was paid to impact of needle length choice on pain, discomfort and patient satisfaction. • Improvement in glycaemic control: assessed by reduction in HbA1c. • Reduction in hypoglycaemia and severe hypoglycaemia (requiring help from 3rd party for correction). • Adverse events. • Adherence to treatment.
Trade-off between clinical benefits and harms	Studies assessing impact of needle length on clinical outcome reported outcomes using needles for use with pre-filled and reusable insulin pen injectors. Length of needle used in the studies ranged from 3.5 to 8 mm, with gauge 30 to 32 G. **Impact on quality of life** One study[329] investigated the impact of needle size on injection site pain, and found no significant difference in injection site pain with different needle lengths (4 mm versus 5 mm versus 8 mm). Five studies[329,360,421,500,508] investigated the impact of needle size on injection site pain scores, including visual analogue pain scores. Two studies[360,421] reported no significant difference in visual analogue scale (VAS) pain scores using needles of different lengths (5 mm versus 8 mm), whilst three studies[331,500,508] reported that pain perception was less using shorter needles (6 mm versus 8 mm; 4 mm versus 5 mm; 4 mm versus 6 mm, respectively). The Hirsch 2010[331] study also showed (in terms of VAS pain), no clinical benefit of the 4mm needle over the 5 mm needle, but a clinically significant benefit of the 5 mm over the 8 mm needle. In studies assessing patient preferences, one study reported that patients had a preference for using shorter needles (6 mm versus 8 mm)[500], whilst a second study reported no significant difference in preference for needle size (5 mm versus 8 mm)[421]. One study[49] reported that tapered needles produced less pain at the site of injection than thin-walled needles, and two studies[509,520] reported less pain with tapered needles compared with regular needles. Two studies[45,683]reported that thinner walled needles were better than regular

	needles for reducing pain. **Impact on glycaemic control** One RCT[331] investigated the impact of 4 mm 32 G needle use versus 5 mm 31 G needle use on glycaemic control – no significant impact on clinical outcome was reported with variation in needle size. **Impact on frequency of hypoglycaemia** Two studies[331,421,683] investigated the impact of needle length on frequency of hypoglycaemia, and no clinically important significant difference was found in frequency of hypoglycaemia with variation in needle size. **Adverse events** Three studies[360,500,508] reported adverse events; none of the three demonstrated any significant difference between the needle sizes used. **Impact on leakage of insulin from injection site** One study[331] reported that a slightly lower proportion of patients experienced insulin leakage post-injection when using shorter needles (5mm versus 8mm) but a similar mean number of leakage events. A second study[421] reported more leakage with the shorter needle (5 mm versus 8mm), whilst a third[508] (4 mm versus 6 mm) and a fourth study[360] (5 mm versus 8 mm) reported no significant difference in leakage between needles of different sizes. One study[262] reported that needles ≥8 mm inserted perpendicularly may frequently enter muscle in the limbs of males and individuals with a body mass index ≤25 kg/m^2. From a review of all of the available evidence, the GDG concluded that there was no evidence to suggest that needle length impacted on biomedical outcomes. The GDG noted that the studies were mostly non-inferiority or equivalence trials, and were therefore not designed to demonstrate statistically significant differences in glycaemic control or hypoglycaemia. There was some evidence to suggest that the use of shorter needles (4 to 5 mm) may have some benefits over longer needles (6 to 8 mm) in terms of quality of life and patient preference, but the evidence was weak and insufficient to make a firm recommendation regarding optimal needle length. **Insulin injection site rotation** No studies reporting the influence of injection site or site rotation on clinical outcomes were identified. All members of the GDG had clinical experience of reviewing patients with lipohypertrophy from repeated administration of insulin in the same skin area without variation of administration site. They had witnessed lipohypertrophy with the whole range of insulin. In the absence of any clinical trial evidence, the GDG recognised that there was sufficient clinical experience from its members to make a recommendation for insulin injection site rotation so that the incidence of lipohypertrophy might be reduced in adults using insulin for the treatment of type 1 diabetes. The GDG also recognised the need for a research recommendation to be made regarding choice of anatomical site for insulin administration and investigation of injection site rotation.
Economic considerations	No economic evaluations regarding needle length, choice of site and site rotation in the administration of insulin were identified by the GDG. The GDG noted that the prescription cost for needles used for the administration of insulin was £39 million in

	2012 (2012 prescription cost analysis)[302] Longer needles tended to be cheaper per unit cost (average cost for an 8 mm 31 gauge needle £0.09 versus £0.13 for a 5 mm 31 gauge needle), and the GDG recognised that a recommendation regarding the use of shorter needles could potentially increase the cost of care in type 1 diabetes management. Evidence supporting the use of shorter needles was felt to be insubstantial given their increased cost, although the GDG also recognised that potential savings regarding brand choice might still allow shorter needle sizes to be selected as the equipment of choice by healthcare professionals.
Quality of evidence	Randomised controlled trial evidence alone was insufficient for assessment of needle length choice, site of administration and frequency of rotation on clinical outcomes, and therefore evidence from observational retrospective and prospective cohort studies were also included in the review. Twelve studies were available for the assessment of needle length on clinical outcome. Five studies[329,360,421,500,508] were randomised cross-over trials, and subsequent GRADE assessment of these RCTs indicated that the quality of the evidence ranged from Moderate to Very low, with some of the evidence at serious risk of bias. Seven further studies[49,75,262,305,509,511,683] were not able to be GRADE assessed as they were not full study reports (conference abstracts, letters) but they provided useful information to the GDG. No studies were available for review of the impact of choice of needle site and site rotation on clinical outcomes.
Other considerations	Patient representatives on the GDG recognised that the majority of individuals with type 1 diabetes would have a preference for shorter needles in the administration of insulin. However, other members of the GDG recognised that there might be theoretical circumstances where a shorter needle option might be inappropriate, for example in individuals with obesity. On reflection, the GDG felt that if an individual with type 1 diabetes was experiencing problemswith insulin self-administration that might be related to apre-selected needle choice, healthcare professionals should support patients in trialling different needle sizes. Healthcare professionals should subsequently balance the cost of a needle against a patient's desired choice prior to a decision on long-term needle use. The GDG recognised that although choice of needle type may have some influence on clinical outcomes, this was likely to be of secondary importance to structured education regarding the administration of insulin injections: the teaching of good subcutaneous injection technique is likely to be the most important factor influencing clinical outcome for insulin injections, highlighting the need for structured education to be made available to all individuals with type 1 diabetes.

9.3.7.1 Recommendations [2004]

The current guideline recommendations can be found at

https://www.nice.org.uk/guidance/ng17

9.3.8 Research recommendations

17. In adults with type 1 diabetes, what is the clinical and cost effectiveness of basal insulins with longer action profiles compared to existing regimens, particularly in terms of dose adjustment for flexible lifestyles, such as intermittent exercise or alcohol consumption, and their long term safety data?

18. In adults with type 1 diabetes who have recently been diagnosed, what is the clinical and cost effectiveness (particularly in terms of preservation of residual insulin secretion and other long-term outcomes) of different intensities of glycaemic control (for example, inpatient intravenous insulin management versus outpatient multiple daily dose insulin injection therapies)?

19. In adults with type 1 diabetes who have recently been diagnosed, what is the clinical and cost effectiveness (particularly in terms of preservation of residual insulin secretion and other long-term outcomes) of using basal–bolus insulin regimens?

20. In adults with type 1 diabetes, what modifications of rapid-acting insulin use (including but not limited to timing of administration, and the nature of the insulin) could be employed to improve glycaemic control around different meal compositions?

21. In adults with type 1 diabetes, what modifications of rapid-acting insulin (including timing of administration and nature of the insulin) could be employed to improve glycaemic control around different modalities of exercise?

22. In adults with type 1 diabetes and a BMI of ≥25 kg/m^2, what is the clinical and cost effectiveness of metformin as an adjunct to insulin, particularly in terms of glycaemic control and weight loss (or reduction in weight gain)?

23. In adults with type 1 diabetes, what is the clinical and cost effectiveness of GLP-1 receptor agonistsand other potential pharmacological adjuncts to insulin therapy?

24. In adults with type 1 diabetes, what is the optimum needle length and type for administration of exogenous insulin in terms of clinical and cost effectiveness?

25. In adults with type 1 diabetes, what is the optimum injection site and injection site rotation regimen in terms of clinical and cost effectiveness?

10 Referral for islet or pancreas transplantation

This section was updated in 2015.

Islet and pancreas transplantation were not covered in 2004; this is an entirely new section.

10.1 Introduction

People with type 1 diabetes rely on insulin replacement therapies to regulate blood glucose. Insulin is usually given by subcutaneous injection, or continuous subcutaneous infusion via an insulin pump. Insulin doses and regimens must be carefully balanced on a continual basis by people with type 1 diabetes against their diet, physical activity, stress, hormonal responses, variations in temperature and a host of other factors in order to minimise blood glucose variation. Many studies [521]demonstrate the benefit of improved blood glucose control in preventing the development of micro- and macro-vascular complications and modern insulin regimens aim to optimise glucose control with this in mind. This requires a high degree of knowledge and engagement by the person with diabetes. Furthermore, a major and persistent risk of exogenous insulin therapy is hypoglycaemia, which for some people can be severe and frequent enough to be disabling.[258,347]

Whole pancreas and islet cell transplantation offer a surgical alternative for sub-cutaneous exogenous insulin replacement, in which insulin is provided by secretion from transplanted beta-cells, and is thus under more physiological control than in conventional exogenous insulin treatments. Whole pancreas transplantation is a more complex procedure which carries significant operative risk. It is most commonly undertaken alongside a kidney transplant but can be carried out in isolation. Islet cell transplantation is a relatively new procedure which involves infusing insulin-producing beta cells isolated from a donor organ into the recipient, currently by infusion into the hepatic portal system. Transplantation allows a person with type 1 diabetes to begin to generate their own insulin in response to carbohydrate and basal insulin requirements without the need to calculate or administer doses manually. Importantly, insulin secretion from transplanted organs or cells ceases in the presence of low blood glucose concentrations preventing hypoglycaemia.

The risks of transplantation include those of the surgeries themselves, and also the potential side-effects of the immunosuppressive medications that need to be taken after transplant. Additionally, long-term insulin independence is difficult to maintain. The transplanted organ or cells may stop working effectively and many people need to re-commence insulin injections or infusion within 5 years.[127,286] Indeed, some do not regain insulin independence at all. However, even partial function of transplanted cells can improve blood glucose control and very successfully protect against severe hypoglycaemia.[100,138,286] Ongoing research is exploring ways of improving transplantation outcomes including stem cell and nano-encapsulation technologies and novel immune-suppressive interactions to protect transplanted cells.

Because of the balance of risks and benefits, transplantation has usually been offered to people who are already taking or will need to be taking immunosuppressive medication, or who have profound problems with blood glucose management and/or a complete lack of hypoglycaemia awareness. However it is a potentially life-changing treatment intervention with proven effectiveness in tackling severe hypoglycaemia.[127,286]

The GDG asked this question:

- Which adults with type 1 diabetes are most suitable to be considered for a pancreas transplant, or pancreatic islet cell transplantation?

As already noted, whole pancreas transplantation currently takes place most frequently alongside kidney transplantation in people with end-stage renal failure as a complication of type 1 diabetes. In

this situation the major drive to transplant is the renal failure rather than the diabetes per se, and consideration of suitability for transplantation is therefore beyond the immediate scope of this guideline.

10.2 Review question: Which adults with type 1 diabetes are most suitable to be considered for a pancreas transplant, or pancreatic islet cell transplantation?

For full details see review protocol in Appendix C.

Table 79: PICO characteristics of review question

Population	Adults with type 1 diabetes
Intervention/s	• Whole pancreas transplant • Islet cell transplantation
Comparison/s	• Any comparison • No comparison
Outcomes	Outcomes • The referral criteria themselves • HbA1c • Severe hypoglycaemia • Longevity of the transplant/organ survival (C-peptide and insulin independence) • Insulin dependence at 1 year and 5 years • Mortality - in-hospital/procedural • Mortality – long-term • Quality of life – any measure used in the paper
Review strategy	Strategy for this review is: Use available clinical data for obtaining clinical outcomes. This will be sourced from: • publications of the UK consortia data (National transplant programmes); to see whether patients do well after a transplant which is based on the current UK referral criteria • NICE IPG 257 guidance on transplantation • Report what referral criteria are currently used in the UK. This will be sourced from: • NHS England service specifications document • NICE IPG 257 guidance for any information given on referral criteria. • International criteria: Collaborative Islet Transplant Registry ([CITR] data can be found on their website and any relevant publications)

10.3 Clinical evidence

We looked for UK-specific data on the referral criteria for whole pancreas transplant as well as islet cell transplantation. Our search consisted of looking specifically at data from the CITR as well as the UK National Islet transplant programme, and NHS England data. We also looked at the NICE guidance on allogeneic pancreatic islet cell transplantation (IPG 257).

Data and information from these sources are summarised below.

10.3.1 Islet cell transplantation

10.3.1.1 Current listing criteria [2015]

Islet transplant alone (ITA)

The standard listing criteria for an ITA are:

- all patients listed should have insulin-treated diabetes
- patients should have type 1 diabetes or diabetes secondary to pancreatectomy or pancreatitis and have confirmed C-peptide negativity in the presence of a glucose level of more than 4 mmol/litre
- at least 2 severe hypoglycaemic episodes in the last 24 months and be assessed by a diabetologist to have disabling hypoglycaemia

Islet after kidney (IAK) transplant

The standard listing criteria for an IAK transplant are:

- all patients listed should have insulin-treated diabetes
- should have type 1 diabetes or diabetes secondary to pancreatectomy or pancreatitis and have confirmed C-peptide negativity in the presence of a glucose level of more than 4 mmol/litre
- a history of severe hypoglycaemia within the last 2 years or HBA_{1c} of more than or equal to 53 mmol/mol (7%)

10.3.1.2 2013 NHS England contract A17/S(NHSS)c for islet cell transplantation service – service specifications[544]

Referral criteria (further described in the Service Standards)

Referrals are from specialist diabetes services. Referral criteria are described in the service standards. A summary is given below:

Established type 1 diabetes:

- children will not ordinarily be considered for transplant given the potential long-term complications of immunosuppression
- insulin dependence for at least 5 years
- negative C-peptide (less than 0.16 nmol/litre with no increment at 6 minutes after 1 mg glucagon IV)

Note: This is because the benefits of islet transplantation are associated with the replacement of C-peptide positivity.

Intensive diabetes management:

Evidence of compliance with expert medical advice (with glucose testing 3 or more times daily), formal diabetes self-management, re-education and intensified insulin therapy, including optimised insulin regimens, and where appropriate, continuous subcutaneous insulin infusion pump therapy.

Absence of insulin resistance

Current islet replacement techniques are not sufficiently efficient to overcome insulin resistance. This is defined as an insulin requirement of more than 0.7 U/kg body weight per day to achieve a

HbA1c of less than 75 mmol/mol (9%). BMI should not be greater than 28 kg/m^2. Chronic treatment with oral steroids is only permissible for those with renal grafts or Addison's disease, and current prednisolone dose should be less than 5 mg daily. Euglycaemic insulin clamps will be used in the early phases to assess insulin sensitivity.

Absence of contraindications to the use of the immunosuppressants:

- impaired renal function (creatinine of more than 135 micromoles/litre, or creatinine clearance of less than 80 ml per minute per 1.73 m^2)
- macroalbuminuria (albumin excretion rate of more than 300 mg per 24 hours) or overt proteinuria
- uncontrolled hypertension
- uncontrolled dyslipidaemia (fasting LDL of more than 3.4 mmol/litre; triglycerides of more than 2.4 mmol/litre)
- active infection, including hepatitis B virus, hepatitis C virus, HIV, tuberculosis or *Aspergillus* within the previous year
- any history of malignancy except completely resected squamous or basal cell carcinoma of skin
- high index of suspicion of non-compliance with conventional therapy
- pregnancy or plans for pregnancy (including fatherhood)

Absence of contraindications to surgery:

- untreated proliferative retinopathy
- recent myocardial infarction or uncorrected myocardial ischaemia
- portal hypertension, gall stones or liver haemangioma on baseline ultrasound
- anaemia/leucopenia/thrombocytopenia; coagulopathy
- on anticoagulants (excluding aspirin)
- active gastric or duodenal ulcer; pancreatitis
- abnormal liver function tests (persistently more than 1.5 times upper limit of normal)
- panel of reactive antibody (more than 20% by flow cytometry)

Other contraindications:

- Addison's disease (untreated) or untreated malabsorptive disease
- inability to reach hospital within 2 hours of notification
- evidence of alcohol excess or other drug abuse

Individuals with severe hypoglycaemia and normal renal function ('Edmonton profile')

As above but to include:

- experience of at least 2 episodes of severe hypoglycaemia requiring third party intervention within the last 2 years. Usually the rate of severe hypoglycaemia will be higher, but this criterion is used to allow inclusion of patients who begin to experience recurrence of severe hypoglycaemia having previously obtained benefit from optimisation of therapy and those who have relaxed control in an attempt to avoid hypoglycaemia
- evidence of altered hypoglycaemia awareness
- (Clarke score of more than or equal to 4; Ryan HYPO score of more than or equal to the 90th centile; and evidence of presymptomatic biochemical hypoglycaemia on monitoring)

- or marked glycaemic lability as defined by Ryan Lability Index; continuous subcutaneous glucose monitoring profiles

Individuals with suboptimal control despite a functional renal graft:

- islet transplantation may be considered in those at more than 3 months and less than 5 years post-renal transplant who are stable on tacrolimus-based immunosuppression (in combination with mycophenolate mofetil or sirolimus; with prednisolone dose of less than 5 mg daily)
- all with severe hypoglycaemia or altered hypoglycaemia awareness would be eligible
- in addition any person with HbA1c of more than 53 mmol/mol (7%) or marked glycaemic lability
- glomerular filtration rate (GFR) should not be less than 40 ml per minute per 1.73 m and serum creatinine not more than 175 micromoles/litre

This group of patients may also be considered for pancreas after kidney (PAK) transplantation, but only if without high cardiovascular risk precluding the more major whole organ transplant procedure, or previous prolonged peritoneal dialysis or other abdominal pathology adversely increasing operative risk. Children will not ordinarily be considered for transplant given the potential long-term complications of immunosuppression.

Exclusion criteria

See service standards for exclusions.

10.3.1.3 2008 NICE IPG 257 for islet cell transplantation [531]

Recommendation (section 10.3)

Patient selection for this procedure should involve a multidisciplinary team. Selection criteria should take into account that the procedure is particularly indicated for patients with hypoglycaemia unawareness and/or those already on immunosuppressive therapy because of renal transplantation.

Outcome data

Evidence was based on a report using CITR data of 1999-2004 (North American data – second report) – CLOSE 2007[137]. This registry study included n=112 patients. The IPG also focused on efficacy data from 3 case series of n=23, n=36 and n=65 patients[590,635,674] and a non-randomised study of n=99 patients.[732] The results are summarised inTable 80.

Table 80: Results of the main studies used in IPG257

Outcome	CLOSE 2007[137]. (n=112) CITR Registry data	SHAPIRO 2006[674] (n=36) Case-series	RYAN 2005[635] (n=65) Case-series	TOSO 2007[732] (n=99) Non-randomised CCT	POGGIOLI 2006[590] (n=23) Case-series
Mortality	None	-	-	-	-
Severe hypoglycaemia - episodes	82% over 1 year pre-transplant 5% over 1 year post-transplant	None at 1-12 years post-transplant (in patients with residual graft function)	Significantly improved severity, up to 4 years from baseline	-	-
Insulin independence	67% at 6 months 58% at 1 year (post-transplant)	58% during median 41 months 76% of these were insulin dependent again after 2 years 44% at 1 year (post-transplant)	68% for >1 month (median follow-up 36 months) Median duration of insulin independence was 15 months (post-transplant)	-	-
Insulin requirements in insulin dependent people	Reduction from baseline: 57% at 6 months 69% at 1 year (post-transplant)	-	Most patients had to resume taking insulin, but this was at lower doses than before transplant	-	-
Partial graft function but still insulin dependent	-	28% at 1 year (post-transplant)	Mean duration of graft function (C-peptide secretion) was 25 months, thus, despite a functioning graft, most people had to resume taking insulin (but lower doses)	-	-
Complete graft failure	13% at 1 year (post-transplant)	28% at 1 year (post-transplant)	-	-	-
Hypoglycaemia unawareness	-	-	Significantly reduced, up to 4 years from baseline	-	-

Glycaemic control	-	-	Significantly improved, up to 4 years from baseline	-	-
Hypoglycaemia fear	-	-	-	SS improvement post initial transfusion	-
QoL	-	-	-	-	SS improvement in DQoL SS improvement in only 1/8 domains of HSQ

10.3.1.4 CITR data 1999-2010 (BARTON 2012)[61] n=677 patients

The CITR is the comprehensive islet transplant registry for 27 NIDDK-funded North American and JDRF-funded European and Australian centres since 1999. The CITR consists of 81% of all allogeneic islet transplants conducted as Phase I/II trials or standard of care. In this data set/report there were:

- 214 recipients in 1999–2002 (early), 255 in mid-2003–2006, and 208 in 2007–2010 (recent)
- 423 (62%) came from North America, and 254 (38%) were reported from the European and Australian JDRF sites
- transplants comprised islet alone in 575 (85%) and IAK or simultaneous islet kidney (IAK/SIK) transplant in 102 (15%).
- no cases of islet transplantation after total pancreatectomy

Recipients

- typically aged between 18 and 65 years
- all have had type 1 diabetes for more than 5 years
- 95% had documented negative fasting C-peptide (less than 0.3 ng/mL) and
- very problematic diabetes control, including hypoglycaemia unawareness complicated by episodes of severe hypoglycaemia and/or marked glycaemic lability characterized by wide swings of blood glucose levels, often with consistently elevated HbA1clevels (more than 64 mmol/mol [8%]).

Results

- Substantial shifts in immunosuppression strategies implemented during the 12-year period:
  - the early and mid-eras dominated by the Edmonton Protocol; which used an IL-2 receptor antagonist (for example, daclizumab) for induction and a mammalian target of rapamycin (mTOR) inhibitor (for example, sirolimus), together with a calcineurin inhibitor ([CNI] for example, tacrolimus) for maintenance immunosuppression.
  - in the most recent era, there has been a shift to induction with a T-cell depleting antibody, with or without a TNF-αinhibitor (for example, etanercept) and maintenance with an mTOR inhibitor or an inosine monophosphate dehydrogenase inhibitor (for example, mycophenolic acid) combined with a CNI.
- Changes in patient characteristics over the 12-year period, suggesting more appropriate patient selection:
  - over time, recipients with C-peptide more than or equal to 0.3 ng/mL have been excluded.
  - increasingly, patients selected at older age and with longer type 1 diabetes duration.
  - requiring slightly less insulin.
  - having better kidney function, as indicated by lower serum creatinine.
  - more people using insulin pumps for insulin delivery (may explain the slightly lower daily insulin requirement).
  - more people taking lipid-lowering medications.
- Increasing levels of missing data for insulin dependence with longer follow-up (7% at 5 years, and 10-20% for other outcomes at 1-3 years).
- Mortality: low events and stable during the 12-year period.
- Life-threatening events: incidence declined with different eras.
- Insulin independence:
  - 1999-2002 era: 51, 36 and 27% (1, 2 and 3 years post-transplant)

  - 2003-2006 era: 37% (3 years post-transplant)
  - 2007-2010 era: 66, 55 and 44% (1, 2 and 3 years post-transplant)
  - SS (p=0.01) decline during 5 years in all eras.
- Durability of graft function (fC-peptide of more than or equal to 0.3 ng/ml):
  - improved significantly over the eras (p<0.001).
  - rate of graft function loss was significantly reduced if insulin independence was previously achieved (effect seen in all eras).
- Islet reinfusion (when first graft loses function completely or declining function proven by declining C-peptide levels:
  - SS decreased over 12-year period: 48% by 1 year in 2007-2010 versus 60-65% in 1999-2006.
- HbA1c: Statistically significant improvement after transplantation.
- Composite HbA1c of less than 48 mmol/mol (6.5%) or a drop by two or more percentage points:
  - Statistically significant improvement from the early era to the mid-era (p 0.03).
  - no further improvement in the most recent era, with 2–5-year success rates of 50–60% in the recent era.
- Severe hypoglycaemia:
  - baseline was more than 90% of people (all eras).
  - more than 90% remained free of SH events through 5 years of follow-up in all eras.

10.3.1.5 Integrated UK National Islet transplant programme (BROOKS 2013)[100] (n=20) islet transplant patients (case series)

Islet transplants over the first 3 years of the integrated UK islet transplant programme (April 2008 – March 2011); 16 ITA and four IAK transplant recipients. Median age was 49 (range, 44–54) years and diabetes duration was 30 (range, 17–39) years with median weight of 61.0 (range, 55.5–76.0) kg.

Inclusion criteria:

- C-peptide-negative with type 1 diabetes.
- Complicated by recurrent severe hypoglycaemia (more than or equal to 1 event over the preceding 12 months requiring assistance to actively administer carbohydrate, glucagon or other resuscitative actions) despite optimized conventional management.
- Contraindications included insulin resistance (insulin requirement of more than 0.7 U/kg to achieve HbA1cof less than 75 mmol/mol [9.0%]), body weight of more than 80 kg and any contraindications to immunosuppression therapy (including impaired renal function with isotopic GFR of less than 60 mL per minute per 1.73 m^2 or albumin excretion rate of more than 300 mg per 24 hours [unless previous renal transplant]).

Results

- Statistically significant reduction in severe hypoglycaemia (episodes per patient per year) at 12 and 24 months post-transplant (baseline = 20; 12 months = 0; and 24 months = 0.3; both p<0.001)
- Statistically significant reduction in HbA1c (baseline = 64 mmol/mol (8%); 12 months = 45 mmol/mol (6.3%); and 24 months = 44 mmol/mol (6.2%); p<0.001 and p<0.01)
- Statistically significant reduction in insulin dose used at 12 and 24 months post-transplant
- graft survival: 80% at both 12 and 24 months post-transplant
- graft survival at 3 years was 70% in patients who had and had not achieved insulin dependence
- insulin independence: 45% of patients; 3 of these 9 patients remained off insulin at 24 months

10.3.2 Whole pancreas transplantation

10.3.2.1 Current listing criteria [2015]

Simultaneous kidney/pancreas (SPK) transplant

The standard listing criteria for a SPK transplant are:

- all patients listed should have insulin-treated diabetes
- patients listed with type 2 diabetes must have a BMI of less than 30 kg/m^2
- patients listed must be receiving dialysis or have a GFR of less than 20 mls per minute

Pancreas transplant alone (PTA)

The standard listing criteria for a PTA are:

- all patients listed should have insulin-treated diabetes
- patients listed with type 2 diabetes must have a BMI of less than 30 kg/m^2
- at least 2 severe hypoglycaemic episodes in the last 24 months and be assessed by a diabetologist to have disabling hypoglycaemia

PAK transplant

The standard listing criteria for a PAK transplant are:

- all patients listed should have insulin-treated diabetes
- patients listed with type 2 diabetes must have a BMI of 30 kg/m^2
- a history of severe hypoglycaemia within the last 2 years or $HBA_{1c}$of more than or equal to 53 mmol/mol (7%)

10.3.2.2 Data from FRANK 2004[236] (study found in IPG 257); n=30 whole pancreas transplant patients (case series)

Whole pancreas transplantation

- continued functioning grafts: 83% (25/30)
- lost graft function or death: 17% (5/30)
- 1 death (11 days after transplant)

10.4 Economic evidence

Published literature

No relevant economic evaluations were identified. As this question was not aimed at assessing the effectiveness and cost-effectiveness of transplantation, but to identify the referral criteria for being considered for a pancreas transplant, or pancreatic islet cell transplantation, no economic studies could be considered relevant.

10.5 Evidence statements

10.5.1 Clinical evidence statements

None. Referral criteria and study results have been summarised in the main body of the review.

Economic

No relevant economic evaluations were identified.

10.6 Recommendations and link to evidence

The current guideline recommendations can be found at

https://www.nice.org.uk/guidance/ng17

Relative values of different outcomes	The GDG determined the impact of a whole pancreas transplant and islet cell transplantation in adults with type 1 diabetes by assessing their effect on the following clinical outcomes: **Hypoglycaemia, including severe hypoglycaemia** - Hypoglycaemia is a regular occurrence in many people on insulin-based therapies and has been associated with a reduction in quality of life for people with diabetes, and is an obstacle to improved control. Pancreas and islet cell transplantation aims to reduce the incidence of recurrent severe hypoglycaemia in an individual receiving either intervention. Particular focus was given to: • incidence of severe hypoglycaemia (hypoglycaemia event requiring help from a third party for correction), an event which has been recognised as having a significant impact on quality of life in patients with type 1 diabetes and their families. • incidence of nocturnal hypoglycaemia. **Improvement in glycaemic control** - Assessed by reduction in HbA1c. Extensive previous research has shown that an improvement in glycaemic control is associated with a reduction in microvascular and macrovascular complications. **Quality of life** – The evidence was reviewed to look at the impact of each transplant intervention on quality of life outcomes. An intervention that reduces the frequency of severe hypoglycaemia episodes and improves glycaemic control should increase quality of life. However, transplantation interventions currently require the recipient to take immunosuppression; immunosuppression carries with it both short- and long-term risks of side effects and requires constant monitoring, all of which may impact on quality of life. **Insulin independence rate** – Insulin independence can be achieved with both pancreas and islet transplantation; the data were reviewed to determine which intervention carried the best probability of achieving insulin independence. **Graft survival** – An individual undertaking the associated risks with having either intervention would need to be informed of the likely duration of graft survival before considering whether to be referred for the procedure. Note: graft survival may be indicated by biochemical measures of islet function and does not necessarily imply insulin independence. **Hospital admissions** – Recurrent severe hypoglycaemia as a consequence of impaired awareness of severe hypoglycaemia is likely to result in multiple hospital admissions. However, it must also be noted that transplant recipients are at risk of having to attend hospital for admission as a consequence of complications from the transplant procedure or side-effects from having to take long-term immunosuppression.

	Adverse events (including mortality and suddendeath) – Recurrent severe hypoglycaemia carries with it a risk of sudden death. However, transplant interventions aimed at reducing the frequency of severe hypoglycaemia episodes also carry a risk of death as a consequence of the procedure (1-3% for pancreas transplantation in the first year post-transplant) or as a consequence of long-term immunosuppression (including increased risk of renal complications, increased lifetime risk of malignancy and bone marrow suppression).
Trade-off between clinical benefits and harms	The GDG considered outcome data from UK and international transplant programmes. Data from the CITR, NHS England and previous NICE Guidance on allogeneic pancreatic islet transplantation[531]were used in writing the guidance. The original NICE guidance from 2008 was based on data obtained from the CITR in 112 recipients from 1999-2004. The procedure was recommended for individuals with loss of hypoglycaemia awareness and/or patients with diabetes on immunosuppression following renal transplantation. Both islet and pancreas transplantation achieve their goals of reducing the incidence of severe hypoglycaemia and improving glycaemic control following procedure intervention.[137,635,675] Insulin independence following islet transplantation has been reported to be between 44 and 66% at 1 year[61,137,635,675], although 76% of patients were reported to be insulin dependent again at 2 years post-transplant.[675] Complete graft failure rate was between 13 and 28% at 1 year post-transplant [137,635,675], with mean duration of graft function reported to be 25 months.[635]Significant improvement in quality of life was reported following islet transplantation (DQoL assessment).[635] The main aim of islet transplantation is to achieve a reduction in the frequency of severe hypoglycaemia. CITR has shown that improved clinical outcomes have been achieved over the last decade by more careful patient selection[61], including: • exclusion of patients with C-peptide positivity • selection of older patients with a longer duration of type 1 diabetes • avoidance of insulin-resistant patients The CITR reports that more than 90% of islet recipients are now achieving freedom from severe hypoglycaemia at 5 years post-procedure follow-up.[61] Evidence for freedom from recurrent severe hypoglycaemia following islet transplantation has been supported by UK study outcomes[100]. In that patient group, 45% achievedinsulin independence of variable duration with 1 patient out of 20 continuing insulin independence at 36 months follow-up]) HbA1c had improved to 44 mmol/mol (6.2%) at a median of 24 months follow-up. Whole-organ pancreas transplantation is associated with a greater short-term risk of morbidity and mortality than islet transplantation. One study[236] reported that 1 of 30 pancreas recipients died at 11 days post-transplant, 2 further grafts were lost from vascular thrombosis at 4 and 6 days post-transplant, one graft was lost to perigraft infection at 1 month post-operatively and a further graft was lost through rejection at 24 months post-procedure; function was therefore maintained in 83% of grafts (25/30) at 24 months post-intervention. Insulin independence was achieved in 85% of recipients and an HbA1c of 31 mmol/mol (5%) was attained at 1 year post-transplant.

	The GDG noted that islet transplantation utilised a procedure that carried a lower risk of immediate complications and mortality than pancreas transplantation[137,236,635,675]. Both procedures carry long-term risks from immunosuppression use, although data on complications from immunosuppression use are limited for islet transplantation as the procedure has only been a viable treatment option for patients with type 1 diabetes since the Edmonton trial outcomes of 2000. The GDG also recognised that despite the initial short-term morbidity and mortality risks, whole-organ pancreas transplantation was more likely to achieve insulin independence than islet transplantation, and graft function was likely to be more prolonged. However, islet transplantation might be considered for individuals experiencing recurrent severe hypoglycaemia who are not physically fit enough to undergo a major surgical procedure, or for individuals who did not wish to accept the increased short-term morbidity and mortality risks from whole-organ pancreas transplantation.
Economic considerations	This review examined referral criteria only and therefore no economic evaluation was considered appropriate for this question. The GDG acknowledged there is a cost associated with specialist referral for transplant. However, this question did not focus on whether referral is effective or cost effective. The GDG observed that both interventions were only likely to be used in a small proportion of individuals with type 1 diabetes experiencing recurrent severe hypoglycaemia that had not responded to other interventions for the management of severe hypoglycaemia. The GDG was mindful that the facilities for transplantation exist and are currently not operating at capacity. It was felt important that the right patients should be put forward for proper assessment in order to maximise the potential benefits of transplantation.
Quality of evidence	The only evidence available to the GDG was observational studies that cannot be assessed for quality by GRADE.
Other considerations	The GDG considered outcome data from UK and international transplant programmes and found that they supported the current criteria for referral to a specialist centre that can both assess and manage severe hypoglycaemia and offer transplantation options. The GDG noted that it did not have the remit to rewrite referral criteria for pancreas or islet transplantation for adults with type 1 diabetes in the UK. However, the GDG wished to highlight the availability of pancreas and islet transplantation for individuals with type 1 diabetes experiencing recurrent severe hypoglycaemia. At the time of publication, current referral criteria are available from NICE.[532]

11 Impaired awareness of hypoglycaemia [2015]

This section was updated in 2015.

Impaired awareness of hypoglycaemia (IAH) was not covered in the 2004 guideline; these evidence reviews and recommendations are new for 2015.

11.1 Identification and quantification of impaired awareness of hypoglycaemia

11.1.1 Introduction

Hypoglycaemia is one of the most common complications of the treatment of type 1 diabetes. It is defined as an abnormally low plasma glucose concentration. Cognitive function deteriorates when plasma glucose concentrations decline to less than 3.0 mmol/litre[785] . Mild hypoglycaemia results in a wide variety of symptoms, including hunger, anxiety or irritability, palpitations, sweating or tingling lips and is by definition symptomatic and noted by the patient. As plasmaglucose concentrations fall lower patients may experience weakness and lethargy, impaired vision,confusion or irrational behaviour.Severe hypoglycaemia may result in convulsions, loss of consciousness, coma. Between 4 and 10% of deaths in people with type 1 diabetes are attributed to hypoglycaemia[154]. It is likely that most people with type 1 diabetes will experience some form of hypoglycaemia within weeks or months of commencing insulin therapy and throughout their life with diabetes. Impaired awareness of hypoglycaemia (IAH) is diagnosed when the adult with type 1 diabetes has poor perception of his/her own hypoglycaemia, depending on glucose monitoring test results or other people's observations to diagnose it.In the vast majority of cases people with type 1 diabetes will perceive and successfully treat their own low blood glucose excursions with a small amount of fast-acting carbohydrate (for example, Lucozade, glucose tablets, non-diet fizzy drinks, fruit juice or high glucose, low fat confectionery such as Jelly Babies). Severe hypoglycaemia occurs when patients require treatment by a third party because they are incapable of self-management.[669] The risk for severe hypoglycaemia increases 6-fold if a person has IAH[258]Recent updates to the DVLA guidelines concerning driving and diabetes use instancesof 'severe hypoglycaemia' as one determinantof fitness to drive and absence of awareness as another.

Research suggests [162,312] that hypoglycaemic episodes can contribute to a loss of early warning symptomsduring subsequent hypoglycaemia, with symptomsbeginningto be felt at lower and lower blood glucose concentrations, and recurrent exposure to hypoglycaemia is believed to be the major factor in causing and sustaining hypoglycaemia unawareness. Lack of subjective awareness makes the early self-treatment of mild hypoglycaemia more difficult and episodes of severe hypoglycaemia more likely. Similarly, in research studies, avoidance of exposure to plasma glucose less than 3 mmol/litre has been associated with restored symptom perception[152]. Typically people with diabetes are advised to keep blood glucose levels above 4.0 mmol/litre and to treat levels below 4.0 mmol/litre in order to avoid hypoglycaemia. This advice is clinically sound but defining everything under 4 mmol/litre as hypoglycaemia can lead to over-estimation of mild hypoglycaemia, increased anxiety around hypoglycaemia and inappropriate diagnosis of IAH.

Hypoglycaemia, or the possibility of hypoglycaemia, can have a significant impact on the quality of life of people with type 1 diabetes and also of their families [439,602]. It can affect their ability to drive and their confidence in taking part in a wide variety of activities and careers. On the other hand, mild hypoglycaemia can be so commonplace for some patients that it is easy for them to underestimate its impact or to evaluate whether their hypoglycaemic excursions have become problematic.

The GDG asked these questions:

- In adults with type 1 diabetes, how is impaired awareness of hypoglycaemia/hypoglycaemia unawareness best identified and quantified?
- In adults with type 1 diabetes and impaired awareness of hypoglycaemia, what is the most effective strategy for recovering hypoglycaemia awareness?

11.1.1.1 Summary of the main impaired awareness of hypoglycaemia scores used in studies.

The following scoring systems for hypoglycaemia awareness assessment were reviewed:

Gold score[268]

This scoring system is based on the response to a single question: 'Do you know when your hypos are commencing?'. In validating this score biochemical hypoglycaemia was defined as less than 3 mmol/litre. Results are expressed by a 7-point Likert scale, where 1 = 'always aware' and 7 = 'never aware'. IAH is suggested by a value of more than or equal to 4. This score is based on results from a prospective case-control study with 60 participants and 12 months follow-up (Gold 1994); 29 participants were noted to have impaired awareness and 31 participants had normal awareness of hypoglycaemia. Participants with IAH had an increased frequency of severe hypoglycaemia episodes (more than or equal to 1 severe hypoglycaemia episodes in 66% with impaired awareness versus 26% with normal awareness; higher incidence of severe hypoglycaemia episodes per patient per year: 2.8 with impaired awareness versus 0.5 with normal awareness).

Clarke score[135]

This score is made up of 8 questions characterising an individual's exposure to episodes of moderate and severe hypoglycaemia to assess the glycaemic threshold for and symptomatic response to hypoglycaemia. The assessment gives a score where a value of more than or equal to 4 indicates IAH. The scoring system is derived from a prospective case series study in 78 subjects with 9-12 months follow-up (Clarke 1995). The Clarke includes a score for impaired awareness when hypoglycaemia is not detected until blood glucose levels are less than 2.8 mmol/litre. Frequency of severe hypoglycaemia events was increased in subjects with impaired awareness.

HYPO score

This is a composite hypoglycaemia score based on the frequency, severity and degree of IAH that provides a measure of the extent of problems with hypoglycaemia to complement an assessment of problems with glucose control.[636] The score is developed from an assessment of glucose readings collected from patients over a 4 week period (minimum of two capillary glucose readings a day), noting details of each hypoglycaemic event (glucose less than 3.0 mmol/litre), the number of occurrences of hypoglycaemia, and a completed questionnaire about the frequency and severity of hypoglycaemia episodes over the previous year (Ryan 2004). In particular, emphasis is placed on which symptoms occur and whether outside help from a third party was obtained to either recognise or treat a hypoglycaemic event. Based on data from a routine clinic and one that assessed people referred for islet transplantation and their experience of hypoglycaemia, a score of more than or equal to 433 is representative of problematic hypoglycaemia, more than or equal to1047 is indicative of very serious unawareness of hypoglycaemia.

DAFNE hypoglycaemia awareness rating

This score is a three question hypoglycaemia assessment that is used in the national DAFNE database. It asks patients to rate their awareness of hypoglycaemia by stating whether they usually recognized that they were hypoglycaemic at a blood glucose concentration of:

1. more than or equal to3 mmol/litre

2. less than 3 mmol/litre or
3. not at all.

Patients rating themselves in categories 2 and 3 were defined as having impaired awareness and had reported a mean of 3.6 severe hypoglycaemia episodes during the preceding year; compared with 0.87 in patients rating themselves as aware at blood glucose concentrations of 3 mmol/litre or higher[347]

Pedersen-Bjergaard score[636]

IAH is assessed by the question 'Can you feel when you are low?', with the respondent selecting one answer of 'always', 'usually', 'sometimes/occasionally' or 'never'. A response of 'usually' implies IAH, whilst the responses of 'sometimes/occasionally' or 'never' imply severely IAH. This scoring system was developed from a questionnaire assessing the occurrence of hypoglycaemia and aspects of hypoglycaemia unawareness in 230 participants, 47% of whom were classified as having impaired awareness (Pedersen-Bjergaard 2001). Groups with impaired awareness were found to have a 5.1 to 9.6 increased risk of severe hypoglycaemia compared with groups defined as having normal awareness.

Edinburgh Hypoglycaemia Score

The Edinburgh hypoglycaemia score[313]asks people to rank each of a number of symptoms on an analogue scale from 0 = not at all, to 7 = very severe. The reference is

11.1.2 Review question: In adults with type 1 diabetes, how is impaired awareness of hypoglycaemia best identified and quantified?

For full details see review protocol in Appendix C.

Table 81: PICO characteristics of review question

Population	Adults with type 1 diabetes
Intervention(s)	IAH according to scoring systems (specific names): • Gold score • Clarke score • Ryan score • Pedersen-Bjergaard score
Comparison(s)	• Other scoring systems • No scoring system
Outcomes	• Ability to predict severe hypoglycaemia (incidence of severe hypoglycaemia) • Ability to predict driving or work related accidents (incidence of accidents)
Study design	All study types

11.1.3 Clinical evidence

We searched for studies assessing scoring systems for identifying adults with type 1 diabetes who had IAH. Fourteenfull studies[126,135,258,259,266,268,314,335,347,366,574,636,662,703] were included in this review. The GDG also consideredseven conference abstracts[10,160,254,384,510,695,714] that met the protocol inclusion criteria, and were used for additional information.

Evidence from these are summarised in Table 82 and Table 83. See also the study selection flow chart in Appendix D, study evidence tables in Appendix Gand exclusion list in Appendix K.

All studies were non-comparative observational studies, and therefore were not able to be combined in a meta-analysis or GRADE profile, and were graded as Low quality (due to their study design). However, a summary of the quality and limitations of these studies can be found in Appendix G. The study details and the full results have been summarised in tables below.All of the data was therefore reported narratively in Table 82 and Table 83.

Table 82: Summary of fully published studies included in the review

Study	Intervention/ comparison	Population	Score system used for IAH	Outcomes
Choudhary 2010A	Prospective case-series (9-12 months follow-up) Weekly 4-point capillary home blood glucose monitoring (HBGM), 5 days of CGM and prospective reporting of severe hypoglycaemia	n=95 Type 1 diabetes adults n=74 normal awareness, n=21 IAH	Gold score ratings used to define IAH (≥4)	Patients with IAH versus normal awareness: 3 x higher incidence of severe hypoglycaemia 1.6 x higher incidence of hypoglycaemia on weekly HBGM NS differences observed with CGM
Clarke 1995	Prospective case-series (9-12 months follow-up) Hand held computer (HHC) for BG estimation	n=78 Type 1 diabetes adults n=39 IAH	Clarke score (8 questions) versus Question "to what extent can you tell by your symptoms that your sugar is low? (never, sometimes, often, always)."	n=39 with IAH Patients with IAH versus normal awareness had/were: NS difference for age, disease duration, insulin dose, or HbA1c SS less accurate in detecting BG <3.9 mmol/1 (P = 0.001) SS fewer autonomic (p = 0.006) symptoms per subject. SS fewer neuroglycopenic (p=0.004) symptoms per subject. Prospective diary records revealed that reduced-awareness subjects experienced: More moderate (P = 0.026) and severe (P = 0.0062) hypoglycaemic events. The second assessment results were similar to the first and verified the reliability of the data.
Geddes 2007	Prospective case-series (4 weeks follow-up) Compares 3 methods of IAH detection: Gold Clarke Pedersen-Bjergaard	n=140 recruited (n=80 completers) Type 1 diabetes adults IAH: Gold = 24%, Clarke = 26%, Pedersen-Bjergaard =	Gold, Clarke and Pedersen-Bjergaardscore ratings used to define IAH (≥4, ≥4, always)	IAH: Gold = 24%, Clarke = 26%, Pedersen-Bjergaard = 63% Strong association between Gold and Clarke methods for IAH (p=0.001) If Pederson used 'occasionally and never' as IAH, the % fell to 15.4% - still a poor correlation between this method and Gold or Clarke methods (rs=0.5 for both) Patients with IAH versus normal awareness had/were:

Study	Intervention/ comparison	Population	Score system used for IAH	Outcomes
	Also filled out Edinburgh Hypoglycaemia Score and 4x/day HBGM for 4 weeks	63%		SS older (using Gold and Clarke scores). NS difference for Pedersen-Bjergaardscore. SS longer duration of diabetes (using all 3 methods) NS difference in HbA1c (using all 3 methods) SS more episodes of biochemical hypoglycaemia over the 4 weeks (using Gold and Clarke scores). NS difference for Pedersen-Bjergaard score. Lower autonomic symptoms reported during biochemical hypo (using Gold and Clarke scores). NS difference for Pedersen-Bjergaard score. NS difference in self-reported neuroglycopenic symptoms (using all 3 methods). SS incidence of severe hypos in previous year (using all 3 methods).
Geddes 2008	Cross-sectional study	n=518 Type 1 diabetes adults n=101 (19.5%) IAH	Gold score ratings used to define IAH (≥4)	Patients with IAH versus normal awareness had/were: SS older (p<0.001) SS longer duration of diabetes (p<0.001) 6 x higher number of episodes of severe hypoglycaemia (per person) in preceding year p<0.001) SS lower intensity of autonomic symptoms during episodes of self-treated hypoglycaemia (p=0.004). NS difference in intensity of neuroglycopenic symptoms NS difference for HbA1c Moderate and SS association between IAH and duration of diabetes (rs = 0.21, p<0.001) and rate of SH (rs = 0.34, p<0.001).
Gimenez 2009	Prospective case-series (72h follow-up) Compares 2 methods of IAH detection during an acute induction of hypoglycaemia with regular insulin: Gold Clarke	n=20 Type 1 diabetes adults IAH: 20 on Gold score, 19 also on Clarke score.	Gold and Clarkescore ratings used to define IAH (≥4, ≥4)	IAH: Gold 20 of 20 (100%), Clarke = 19 of 20 (95%) Clarke test score was SS negatively correlated with HbA1c values (that is, lower HbA1c = higher Clarke score, thus IAH). Ability of score to detect percentageincrease in symptoms during an acute induction of hypoglycaemia: Clarke: sensitivity 100%, specificity 25%, Kappa index[a] 0.35.

Study	Intervention/ comparison	Population	Score system used for IAH	Outcomes
				CGM from the whole group revealed 18% of measurements <70 mg/dl; this was correlated with Clarke's test score and with increase in % of signs/symptoms during induced hypoglycaemia. In patients with abnormal response of symptoms during hypoglycaemia, CGM % of values <70 mg/dl was higher (23% versus 8%) than in those with a normal response (10%; p<0.028).
Gold 1994	Prospective case-control study (12 months follow-up)	n=60 Type 1 diabetes adults n=29 IAH and n=31 normal awareness.	Gold score	IAH versus normal awareness: SS more patients had 1 or more episodes of SH (66% versus 26%) SS higher incidence of SH episodes/patient/year (2.8 versus 0.5) SS more patients had greater worry/fear of hypoglycaemia, but did not modify their behaviour accordingly.
Hendrieckx 2014	Retrospective case-series	n=422 completers Type 1 diabetes adults IAH (Gold): 20.5%	Gold	IAH (Gold ≥4):= 20.5% Intact awareness (Gold = 1): 27% Most patients (52.4%) had Gold score 2 or 3. SH: 18.5% at least one event in past 6 months (mean 0.5; that is, 1 event/year) 46% of patients who reported severe hypoglycaemia episode in past 6 months also reported IAH; only 7% had intact awareness. Patients with severe hypoglycaemia were more likely to have IAH, experienced fewer symptoms of hypoglycaemia, and relied more often on others to recognise a hypoglycaemic event. Multivariate analyses: • Greater IAH was SS associated with occurrence of SH • IAH was SS associated with more frequent SH.
Hoi-Hansen 2010	Cross-sectional study 3 methods compared: Gold (A) Clarke (B)	n=470 (n=372 responders) Type 1 diabetes adults IAH: Gold = 75%, Clarke =	Gold (A) Clarke (B) Pedersen -Bjergaard (C)	Normal awareness: 75% (A), 51% (B) and41%(C) Impaired awareness/unawareness (C): 25% (A), 28%(B) and 13% were unaware (C) 46% belonged to intermediate group of impaired awareness (C)

Study	Intervention/ comparison	Population	Score system used for IAH	Outcomes
	Pedersen-Bjergaard (C)	51% and Pedersen-Bjergaard = 41%		and 21% not classifiable (B) Higher rates of severe hypoglycaemia in patients with impaired awareness (A,B)/unawareness (C)versus aware patients Patients with impaired awareness (C) had more severe hypoglycaemia than aware patients, and less severe hypoglycaemia than unaware patients. A lower rate of severe hypo was reported by aware patients classified bymethod C versus method A Fractions of patients with normal awareness without an event of severe hypoglycaemia were 0.81, 0.86, 0.91 All 3 methods of assessment of hypoglycaemia awareness are feasible in clinical practice since degree of awareness is associated with risk of severe hypoglycaemia. Method C (trisected method) identifies and intermediate group with impaired awareness and with a risk of severe hypoglycaemia that is SS different from those of aware and unaware patients.
Hopkins 2012	Retrospective case-series- data from DAFNE audit (baseline and 1 year follow-up)	• n=539 responders • Type 1 diabetes adults	IAH = those reporting symptom onset <3 mmol/litre or not at all	Pre-DAFNE: • IAH: 40%, Hypo aware: 60% • SH: 25% had ≥1 event in past 1 year; 16% ≥1 episode in past year. Post-DAFNE 62% of those who had experienced SH remained free of further episodes at follow-up 10% of those who had been free of SH in the preceding year experienced ≥1 episodes. Overall mean SH rate fell from 1.93 (range 0–99) to 0.61 (0–70) episodes/person/year after DAFNE (difference 1.15 [95% CI 0.73 to 1.57]; p<0.001) At follow-up, 43% of those with IAH at enrolment reported restoration of the ability to detect

Study	Intervention/ comparison	Population	Score system used for IAH	Outcomes
				hypoglycaemia at a blood glucose >3 mmol/litre. The rate of SH fell significantly in both groups.
Janssen 2000A	Prospective case-series (2-4 weeks follow-up) Clarke questionnaire Hand held computer to assess their recognition of hypo episodes occurring during 2-4 weeks Underwent stepped hypoglycaemic clamp, so could study response to standardised hypoglycaemia. Diagnosis of IAH was based on the self-report questions, a composite self-report score and 3 different cut-off levels for the % of accurately recognised hypo episodes during the field study. Agreement with the hypoglycaemia clamp measure was tested by kappa, sensitivity and specificity.	n=19 Type 1 diabetes adults	Clarke score	The composite self-report score agreed reasonably well with the hypoglycaemia clamp measure (kappa 0.49, sensitivity 66.7, specificity 85.7%) and showed a better agreement than the separate self-report questions. The hand help computer criterion of IAH did not agree with the hypoglycaemia clamp criterion at any of the cut-off levels tested.
Pedersen-Bjergaard 2003	Prospective case-series (1 year follow-up) Questionnaire based on Pramming and Deary studies for occurrence of hypo, aspects of hypo unawareness	n=230 Type 1 diabetes adults IAH: 47%	Pedersen - Bjergaardscore: questionnaire: can you feel when you are low? Cut-off: usually = IAH, occasionally or	Almost 90% of patients correctly recalled whether they had had SH over the previous year. Those with high recorded numbers of episodes had incomplete recall, resulting in 15% underestimation of overall rate. Question: do you recognise symptoms when you have hypoglycaemia? 40% normal awareness, 47% impaired

Study	Intervention/ comparison	Population	Score system used for IAH	Outcomes
	and sections on demographic issues and lifestyle.		never = severe IAH (unawareness).	awareness and 13% unawareness. Groups with IAH had 5.1 and 9.6 x higher rates of SH versus normal awareness groups (p<0.001).
Ryan 2004	Prospective case-series (4 weeks follow-up) Prospective monitoring of blood glucose ≥2x/day for 4 weeks. Frequency of SH over preceding year also estimated.	n=100 Type 1 diabetes adults	Hypo score IAH = median score≥850; intact awareness = median score 91.	Group with IAH had: • median 8.0 versus 2.0 episodes of hypoglycaemia per patient in previous 4 weeks (p<0.001), • 0.4 versus 0.0 SH episodes per patient in previous 4 weeks (p-value not reported).
Schopman 2011	Prospective case-control study (4 weeks follow-up) Prospective monitoring of blood glucose 4x/day for 4 weeks. Frequency of SH over preceding year also estimated.	n=38 Type 1 diabetes adults Normal awareness (n=19) patients and IAH (n=19) patients.	Gold score	IAH patients versus normal awareness: 2 x frequency of all episode of hypo over 4-week monitoring period (SS; p=0.003) NS difference in total no of symptomatic hypoglycaemic episodes. 7 x higher incidence of symptomatic hypoglycaemia (SS, p=0.001) – comprised 47% of all glucose values <3.0 mmol/litre versus 14% in normal group. Higher annual prevalence of SH: 53% versus 5% SS higher incidence of severe events (p=0.001).
Streja 2005	Prospective case-series (2-4 weeks) SMBG and clinical data collected 72hr CGMS Questionnaire	n=60 Type 1 diabetes adults HUN = 42%	Adapted Janssen questionnaire (3/5 questions answered yes = HUN)	HUN by Questionnaire:42% Best predictor of HUN was maximal duration of hypoglycaemia, as determined by CGMS (p=0.001) Detection of hypoglycaemic episodes with duration >90 minutes identified patients with HUN (sensitivity, 75%, specificity, 885) HUN was SS associated with used of ACEs or ARBs (p=0.003), and longer duration of diabetes(p=0.008)

Abbreviations: HUN, hypoglycaemia unawareness; IAH, impaired hypoglycaemia unawareness; SH, severe hypoglycaemia
(a) Kappa index of 1.0 = complete agreement.

Table 83: Summary of conference abstracts considered by the GDG

Study	Intervention/ comparison	Population	Outcomes

Study	Intervention/ comparison	Population	Outcomes
ACAMPO 2012	Conference abstract Cross-sectional study Dutch translation of the Clarke questionnaire : score ≥3 out of 5 was assumed to indicate HU. SH was assessed on the basis of the same questionnaire .	n=486 Type 1 diabetes adults	• HUN: n=158 patients (33%) and n=103 patients (21%) recalled SH in the year before the Clarke questionnaire. • HUN was associated with male sex, lower HbA1c, duration of diabetes, autonomic neuropathy and estimated GFR <60 ml/minute/1.73m^2 (all p<0.05). • After adjustments, duration of diabetes, estimated GFR <60 ml/minute/1.73m^2 and lower HbA1c were still SS associated with HUN. • SH was independently associated with the presence of autonomic neuropathy (3.62; 1.65-7.94) and the use of benzodiazepines (4.59; 1.80-11.73), but not with HbA1c or diabetes duration. • No association with SH or HUN: use of insulin analogues, insulin pump therapy, ACE inhibitors or beta-blockers Conclusion: HUN is still highly prevalent in type 1 diabetes patients despite advances in insulin therapy. Diabetes duration, lower HbA1c level and kidney dysfunction were independent risk factors for HU. Autonomic neuropathy and use of benzodiazepines were risk factors for SH. Clinicians treating patients with type 1 diabetes should be aware of the still high prevalence of HUN and its risk factors. (Table presented).
CZYEWSKA 2012	Conference abstract	n=238 Type 1 diabetes adults and young people	HUN was assessed by Clarke and Gold. HUN: CLARKE = 58 patients (24.4%), GOLD = 68 patients (28.5%). Patients split into 3 groups: Group I- patients with hypoglycaemic awareness confirmed by both tests (n = 142) Group II- patients with HUN confirmed by one test (n = 66) Group III- patients with HUN confirmed by both tests (n = 30). Patients with HUN versus awareness patients: were older (P = 0.040) had longer diabetes duration (P = 0.014) NS difference in lipid level, waist circumference, creatinine level, BMI, arterial pressure and HbA1c. More glycaemia level below 55 mg/dl (p=0.016). Performed measurements of glycaemia more frequently (p=0.049). Conclusion: Hypoglycaemia unawareness was observed in 40% type 1 diabetic patients. The severity of hypoglycaemia unawareness was associated with longer diabetes duration. The patients with hypoglycaemia unawareness had more frequent low glycaemia level.
GANDHI	Conference	n=100	HUN assessed by Clarke, Gold and Pederson and the

Study	Intervention/ comparison	Population	Outcomes
2013	abstract	Type 1 diabetes (age not given)	Edinburgh Hypoglycaemic Score, questions on causes and worry for hypoglycaemia scored on a seven-point Likert scale. Clarke score was used to assess HUN. HUN: Clarke = 18%, Gold = 19% and Pederson = 7%. HUN: were SS older (p = 0.0018) Had SS longer duration of diabetes (p = 0.0015) Had SS increased prior severe hypoglycaemic episodes (p = 0.024) Giving the insulin dose twice was increased (p = 0.011) Were SS more worried about night-time hypoglycaemia (p = 0.041) Felt significantly less empowered to avoid future hypoglycaemic episodes (p = 0.047). There was very poor correlation between the Pederson questionnaire and the other two methods used to assess HU. There was moderate agreement between the Clarke and Gold scores (kappa = 0.503). Conclusion: This report demonstrates lower prevalence of HU compared with the literature and may reflect recent improvements in type 1 diabetes management, most notably education. It highlights opportunities to improve education to avoid hypoglycaemia. The findings of this study are in keeping with a previous report suggesting that Clark and Gold questionnaires are better discriminators for HU than Pederson
KANC 2010	Conference abstract	n=114 type 1 diabetes (n=53) and type 2 diabetes insulin treated	Hypoglycaemia awareness status by Clarke's questionnaire Confirmed high internal consistency reliability of the translated questionnaires (Cronbach's alphas were 0.93, 0.94, and 0.49 for HFS, PAID, and Clarke's questionnaire, respectively). SS correlation found between HFS score and Clarke's score in general (r = 0.20, p = 0.030), type 2 diabetes (r = 0.27, p = 0.036), type 1 diabetes (r = 0.17, p = 0.217), meaning that patients with type 2 diabetes experience an increase in fear of Hypoglycaemia as their awareness decreases (but NS for type 1 diabetes). SS association of HbA1c with HFS score (r=0.23, p=0.015) and PAID score (r=0.47, p<0.001), indicating worse glucose control with increasing FoH and diabetes problems. On the contrary, four patients had very high PAID and HFS score and low HbA1c. Conclusion: In particular MDI-treated women with type 1 diabetes, bad glycaemic regulation and lower awareness of hypoglycaemia need clinical attention, focused on hypoglycaemia. Patients with excellent glycaemic control,

Study	Intervention/ comparison	Population	Outcomes
			combined with great FoH and pronounced diabetes-related problems, but should not be overlooked
MOHEET 2012 Additional info	Conference abstract	n=18 Type 1 diabetes adults with IAH (Clarke score)	History of severe HG and high total score on CQ (Clarke questionnaire/ Clarke score) is significantly related to reduced CR response to HG in patients with type 1 diabetes. Therefore, such responses on the CQ may indicate those patients with the most profound IAH, which can be of value in both the research and the clinical setting
SPEIGHT 2011	Conference abstract Patient, physician and psychologist discussions drafting new items to the Clarke Score.	n=14 Type 1 diabetes adults tested the new items of score Score = The Hypo Awareness Questionnaire	Patient input identified the need for separate questions about: hypoglycaemia when awake and asleep ways to improve specificity/acceptability. 18 items assess recall of hypoglycaemic events, blood glucose thresholds at which symptoms occur, awareness of symptoms, altered awareness, and frequency of checking blood glucose when 'feeling low'. Completion time: average 7 minute (range 5-15 minutes), shorter following each revision. Authors' Conclusion: A comprehensive, collaborative and iterative design process has generated a detailed measure of IAH with good face and content validity. The Hypo Awareness Questionnaire is likely to be useful in clinical trials and enable improved recognition of IAH together with more accurate evaluation of medical fitness for activities including driving.
TAN 2012A	Conference abstract	n=30 Type 1 diabetes	Clarke and Gold scores for IAH IAH: GOLD = 8 patients (27%) IAH versus aware patients: NS difference in HbA1c SS longer mean duration diabetes Discussed IAH during their consultation with a specialist (88% versus 64%). Conclusion: The prevalence of IAH was higher in this study than in previous work suggesting that the problem may still be underestimated. It was appropriately recognised, and treatment strategies documented for the majority, on attendance at specialist clinics.

Abbreviations: HFS, Hypoglycaemia Fear Score; PAID, Problem Areas in Diabetes

11.1.4Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix E.

11.1.5 Evidence statements

Clinical

Low quality evidence from observational studies showed that the Gold Score and the Clarke score were the best performing scores, and were equally effective at identifying IAH. These score were also good predictors of episodes of hypoglycaemia and severe hypoglycaemia in adults with type 1 diabetes.

The evidence also showed that adults with type 1 diabetes and IAH had higher rates of hypoglycaemia and severe hypoglycaemia compared with those with intact or normal hypoglycaemia awareness. People with type 1 diabetes with IAH were more likely to have a longer duration of diabetes.

Economic

- No relevant economic evaluations were identified.

11.1.6 Recommendations and link to the evidence

The current guideline recommendations can be found at

https://www.nice.org.uk/guidance/ng17

Relative values of different outcomes	The GDG reviewed the evidence for assessment of IAH to discover how it might be best identified and quantified. The aim of the review was to determine the effectiveness of current scoring systems in predicting IAH and increased risk of severe hypoglycaemia. The principal outcomes of interest are the sensitivity and specificity of the scores for predicting hypoglycaemia. Comparison of the scoring systems was undertaken by the GDG, with particular focus given to studies that assessed correlation between the scoring systems and their ability to predict severe hypoglycaemia.
Trade-off between clinical benefits and harms	The GDG considered information from 14 fully published studies as well as 7 conference abstracts. The benefits and harms of completing the scores are related almost entirely to their accuracy. Some of the scores are more complex than others and are therefore more time consuming. Correlation between scoring systems for assessment of IAH Four studies undertook comparison of scoring systems for IAH.[160,254,259,335] Three studies[254,259,335] undertook direct comparison of the Clarke, Gold and Pedersen-Bjergaard scores.[254,259,335] Gold and Clarke scores defined 18-29% of study participants as having IAH and both scores correlated well in all three studies. The Pedersen-Bjergaard scoring defined 7-15% of subjects as having IAH. However, correlation with Clarke and Gold score assessments was poor. The studies suggested that Clarke and Gold questionnaires might be better discriminators for IAH in comparison to the Pedersen-Bjergaard questionnaire. A fourth study undertook correlation of Gold and Clarke scores in 238 study participants[160]: Gold and Clarke scores defined 24% and 29% of participants as having IAH respectively, with both scores again correlating well. Scores as predictors of hypoglycaemia and severe hypoglycaemia One study[259] reported that more episodes of biochemical hypoglycaemia were predicted with use of Clarke and Gold scoring, but not with the Pedersen-Bjergaard

	score. Gold and Clarke scores predicted reduced autonomic warning symptoms during biochemical hypoglycaemia but again this was not noted with Pedersen-Bjergaard scoring. All three testing methods predicted an increased rate of severe hypoglycaemia episodes. In a second study in 518 study participants[258], the Gold score classified 101 participants as having impaired awareness: rate of severe hypoglycaemia per person was increased six-fold in this group, with lower intensity of autonomic symptoms reported. Two further studies reported that Gold scoring[662] and Clarke scoring[510] predicted Increased rates of severe hypoglycaemia in study participants. A further study of 95 adults with type 1 diabetes of at least 5 years duration found that people defined as having impaired awareness by Gold score showed increased rates of hypoglycaemia on home blood glucose monitoring by finger prick tests and an increased incidence of severe hypoglycaemia in the year following assessment, although no increase in time spent hypoglycaemic during five days of continuous glucose monitoring (CGM) was recorded.[126,266]In a study of 20 people reporting more than four non-severe hypoglycaemic episodes per week over 8 weeks, and at least 2 severe hypoglycaemic episodes in the previous 3 years, impaired awareness was found in 20 (100%) study participants by Gold score and 19 out of 20 by Clarke score. The Clarke score correlated with % time spent under 3.9 mmol/litre on 72 hours of continuous glucose monitoring[266]. Clarke scoring has also been found to correlate with clamp study findings in 19 study participants.[367]
Economic considerations	No economic evaluations regarding identification and quantification of the IAH were identified by the GDG. The GDG recognised that there were unlikely to be any substantial cost differences between the use of each of the available scoring systems, and that use of any of the scoring systems was likely to involve minimal cost. IAH is associated with an increased risk of severe hypoglycaemia (requiring help from 3rd party for correction); a reduction in the incidence of severe hypoglycaemia has been recognised as having a significant impact on quality of life in patients with type 1 diabetes. The GDG recognised that the use of scoring systems to identify individuals with IAH would be cost-effective if the identified individuals were subsequently able to undergo education or other interventions that might reduce their risk of severe hypoglycaemia.
Quality of evidence	Fourteen full studies and seven conference abstracts assessing scoring systems for identifying adults with type 1 diabetes with IAH were included for review by the GDG. Meta-analysis and GRADE were not conducted for this review as the study types and data available were not appropriate for this type of assessment. The GDG therefore made a subjective assessment on the quality of each of the available studies before reaching any conclusions on the data and concluded that the quality of the available evidence was sufficient to allow recommendations to be made.
Other considerations	The GDG observed that the Gold and Clarke scores correlated well in studies and had a high concordance with increased frequency of severe hypoglycaemia episodes. The Pedersen-Bjergaard score had less correlation with Gold and Clarke scores and not such a good concordance with prediction of severe hypoglycaemia episodes. There was little evidence reporting the use of other scoring systems but their possible use in clinical practice was considered by the GDG. The HYPO score was noted to have good concordance with frequency of severe hypoglycaemia. However, the baseline data required and the method of its interpretation for the score's calculation were considered to be too complex for regular use in clinical practice outside of the research environment. The hypoglycaemia assessment used by the DAFNE studies was felt to be a viable alternative to the Gold and Clarke

scores. However, given the greater weight of available evidence, the GDG made the recommendation of utilising the Gold score or the Clarke score for assessment of IAH in clinical practice. The GDG noted that patients make errors in completing questionnaires that could lead to their awareness status being misclassified, leading to the recommendation that scores be checked by the clinician against clinical presentation.

The GDG debated whether all adults with type 1 diabetes should be assessed for IAH or only those individuals who had previously experienced a severe hypoglycaemia episode. Annual prevalence of severe hypoglycaemia has been reported to be 30% in individuals with type 1 diabetes[239], and higher in those with IAH. The GDG recognised that measures should be taken to assess risk of hypoglycaemia and avoid the potentially dangerous consequences of a severe hypoglycaemia episode, with just one episode having potential implications regarding lifestyle choices and driving. The GDG therefore recommended that all adults with type 1 diabetes should be assessed for IAH, and that this should take place at the individual's annual care review.

The GDG noted that whilst studies often asked study participants to list their symptoms when they felt hypoglycaemic, there was not a consensus regarding the level of glucose at which hypoglycaemia symptoms might be experienced and which labelsan individual as having 'impaired awareness' of hypoglycaemia.

The GDG recognised that once hypoglycaemia resulted in cognitive impairment, this was significant as it was likely to result in a reduced ability to self-manage a hypoglycaemia episode and increase the risk of accident. The Clarke Score included assessment of symptoms at less than 3.9 mmol/litre but scored for impaired awareness of 50 mg/dl or less, which converts to a value of 2.8 mmol/litre; whilst the HYPO score assessment stated that study participants with a glucose of <3.0 mmol/litre were considered to be hypoglycaemic and asked subjects to list their symptoms at this level of blood glucose. The DAFNE questionnaire refers to a glucose level of 3.0 mmol/litre with recognition of hypoglycaemia at higher blood glucose levels constituting normal awareness. Glucose levels of <3.0 mmol/litre have also been found to be associated with the onset of cognitive impairment during glucose clamp studies[480]. The GDG concluded that if an individual reaches a glucose concentration of <3.0 mmol/litre without symptoms of hypoglycaemia, then they should be considered to have an IAH., The GDG recognised that scoring systems for the assessment of IAH might provide more detail about an individual's risk of severe hypoglycaemia episodes than a single absolute cut-off level of blood glucose for all adults with type 1 diabetes. The GDG therefore recommended the use of scoring systems for the assessment of IAH in its recommendations.

11.2 Strategies for the management of impaired awareness of hypoglycaemia

11.2.1 Introduction

Adults with IAH have a six-fold increase in risk for severe hypoglycaemia and if their unawareness is complete[258], and/or they experience more than one severe hypoglycaemia in a 12 month period, they may lose privileges such as the right to drive. Severe hypoglycaemia and hypoglycaemia unawareness also damage quality of life and cause stress not just for the person with diabetes but also for their family.[439,602] Restoring awareness of hypoglycaemia is therefore a key therapeutic goal.

Research carried out with adults with type 1 diabetes and IAH shows that avoidance of low plasma glucose concentrations leads to restoration of symptomatic responses to a subsequent episode[152]

and this has led to a recognition of the importance of always defining lower limits as well as upper limits when setting targets for self-monitoring of plasma glucose. Participants in the research were helped to avoid hypoglycaemia in daily life through very frequent contact with researchers who were healthcare professionals with experience in insulin dose adjustment. Helping adults with type 1 diabetes avoid hypoglycaemia routinely can be difficult. Anecdotally, not everyone who regained hypoglycaemia awareness during a research study was able to maintain it after the study ended.

It is important, when helping people with diabetes avoid hypoglycaemia, not to achieve that aim at the expense of a rise in glycated haemoglobin, as that replaces one problem (asymptomatic and severe hypoglycaemia) with another, increased risk of long term vascular complications. Modern methods of teaching adults with type 1 diabetes skills in flexible insulin therapy through structured education are able to reduce HbA1c and severe hypoglycaemia risk and in the case of the DAFNE programme also reduce IAH.[150,318,347,652] Exposure to such education and support in implementing its learning is thus considered the first step in treating people with IAH (see Section 7.2).However, as the DAFNE national audit shows, a significant number of people remain or have developed IAH one year after education. There are other education programmes that more specifically target hypoglycaemia.[462] Other strategies that have been shown to reduce hypoglycaemia experience include use of technologies for insulin delivery and glucose monitoring, such as insulin pumps and interstitial glucose monitoring devices, and these might be expected to help restore awareness too.Ultimately, transplantation therapies that remove the need for exogenous insulin may be the most effective treatment. However, there is evidence that some people exhibit a resistance to changing behaviour that will help avoid hypoglycaemia, with reduced ability to change treatment regimens after consultation with healthcare professionals.[689] This group may have unhelpful beliefs related to their hypoglycaemia experience.[625]

The GDG therefore asked this question:

- In adults with type 1 diabetes and impaired awareness of hypoglycaemia, what is the most effective strategy for recovering hypoglycaemia awareness?

11.2.2 Review question: In adults with type 1 diabetes and impaired awareness of hypoglycaemia, what is the most effective strategy for recovering hypoglycaemia awareness?

For full details see review protocol in Appendix C.

Table 84: PICO characteristics of review question

Population	Adults with type 1 diabetes (this covers type 1a diabetes and type 1b diabetes) with IAH • Adult is defined as aged ≥18 years • Type 1 diabetes is defined (WHO definition and NICE 2004 GL)
Intervention(s)	• Adjusting treatment/adjusting insulin regimen/less intensive glycaemic control • Pancreas/islet cell transplant • Hypoglycaemia avoidance • Adjusting monitoring of blood glucose, for example CGM • Education interventions • Psychological interventions Only intervention durations of ≥1 month will be considered
Comparison(s)	• Any • None
Outcomes	• HbA1c (continuous) • Autonomic symptoms/symptom scores during hypoglycaemia clamp study

	• Hypoglycaemia (dichotomous or continuous outcome, depending how it is reported) • Severe hypoglycaemia (dichotomous or continuous outcome, depending how it is reported) • Nocturnal hypoglycaemia (dichotomous or continuous outcome, depending how it is reported) • Hospital admissions (dichotomous or continuous, depending how it is reported) • Hypoglycaemia unawareness or awareness (dichotomous or continuous, depending how it is reported) • Quality of life – measured by DQoL, DSQoL, PAID, HADS, fear of hypoglycaemia, anxiety, depression, cognitive function (continuous) • Road traffic accidents and work related accidents
Study design	• RCTs: unit of randomisation: individual patient, cluster randomised trials • Observational studies

11.2.3 Clinical evidence

Twenty studies were included in the review[100,128,150,152,174,218,219,224,240,265,318,322,347,445,449,463,504,635,637,724], these are summarised in Table 85 and Table 86 below. See also the study selection flow chart in Appendix D, study evidence tables in Appendix G, forest plots in Appendix J and excluded studies list in Appendix K.

Five studies were RCTs or observational cohort studies[150,218,224,318,724]. Evidence from these studies is summarised in the GRADE clinical evidence profile in Appendix I. Outcomes were reported for the following interventions in patients with IAH or recurrent severe hypoglycaemia:

- Structured education and hypoglycaemia avoidance intervention (3 studies[150,218,318]): severe hypoglycaemia; nocturnal hypoglycaemia; hypoglycaemia unawareness (Gold score, Clarke score); HbA1c and symptom scores during hypoglycaemic clamp.
- Insulin regimen interventions (2 studies[224,724]): severe hypoglycaemia; HbA1c; hypoglycaemia unawareness and QOL.

Fifteen studies were observational case-series[100,128,152,174,219,240,265,322,347,445,449,463,504,635,637]. Data from these studies cannot be combined in a meta-analysis or assessed in GRADE as there is no comparison control group. Data from these studies are summarised narratively in Table 86. Outcomes were reported for the following interventions in patients with IAH or recurrent severe hypoglycaemia:

- Hypoglycaemia avoidance intervention (5 studies[152,219,240,445,463]): HbA1c; severe hypoglycaemia; hypoglycaemia unawareness (Gold score) and symptom scores during hypoglycaemic clamp.
- Educational intervention (three studies[174,322,347]): severe hypoglycaemia; IAH; HbA1c; QOL (DQol, TDQ, HADS, PAID); hospitalisation and driving incidents.
- Continuous glucose monitoring intervention (2 studies[128,637]): severe hypoglycaemia; HbA1c and hypoglycaemia unawareness (Gold score, modified HYPO score).
- Insulin regimen intervention (one study[265]): severe hypoglycaemia; HbA1c; hypoglycaemia unawareness (clarke score); symptom score during hypoglycaemic clamp and QOL (DQoL, SF-12 health survey)
- Islet transplantation intervention (four studies[100,449,504,635]): HbA1c; severe hypoglycaemia; IAH and symptom scores during hypoglycaemic clamp.

The non-comparative observational studies were not able to be combined in a meta-analysis or GRADE profile, and were graded as Low quality (due to their study design). However, a summary of the quality and limitations of these studies can be found in Appendix G. The study details and the full results have been summarised in tables below.

Table 85: Summary of included studies: RCTs and observational cohort studies

Study	Intervention	Comparison	Population	Outcomes
Structured education and hypoglycaemia avoidance				
COX 2004[150] RCT	SMBG plus HAATT (structured education designed to reduce occurrences of low BG, increase awareness and improve treatment of low BG) n=30	SMBG (standard care in Bulgaria at the time did not routinely employ SMBG) n=30	n=60 History of ≥2 episodes of SH (inability to treat oneself due to hypoglycaemic stupor or unconsciousness) in the past year.	• Severe hypoglycaemia – reported as frequency/subject/6 months (unable to put into meta-analysis as no variance reported – ANCOVA summary reported in GRADE table) • Nocturnal hypoglycaemia – reported as frequency/subject/6 months (unable to put into meta-analysis as no variance reported – ANCOVA summary reported in GRADE table)
HERMANNS 2007[318] RCT	HyPOS training programme (focusing on avoiding low BG values, causes of HU, improving detection and recognition of warning symptoms and need for treatment of low BG values). n=84	Control (Education programme aimed at optimising intensive insulin therapy without regard to hypoglycaemia problems) n=80	n=164 At least one episode of SH in the past 12 months (requiring 3rd party assistance) or IAH and tight glycaemic control (HbA1c<6.5%)	• Hypoglycaemia awareness questionnaire (HAQ; Clarke score) • Gold score • Severe hypoglycaemia – reported as frequency/patient-year • HbA1c, %, final values • QOL – PAID • QOL - ADDQoL
FANELLI 1994[218] Observational cohort study	Hypoglycaemia avoidance by change in regime and counselling. To prevent hypoglycaemia, insulin doses aimed at fasting, preprandial and bedtime BG of ~7.2-8.3 mmol/litre. n=16	Continued therapeutic regime on at entry n=5	n=21 Consistent history of frequent hypoglycaemia (BG<3 mmol/litre) in the absence of autonomic warning symptoms for at least 6 months before the study	• Autonomic symptom score during clamp, mean (SE) at 2 weeks (not reported at 3 months or 1 year) • Neuroglycopenic symptom score during clamp, mean (SE) at 2 weeks (not reported at 3 months or 1 year)
Insulin regime				
FERGUSON 2001[224] RCT (Open labelcrossov	Insulin Lispro and human NPH insulin for 6 months	Regular human insulin and human NPH insulin for 6 months	n=40 Reported a reduction in their warning	• Severe hypoglycaemia • HbA1c % • QOL (DTSQ and HFS) – unable to put into meta-analysis as no mean and variance reported –

er)			symptoms for hypoglycaemia for at least 2 years; had ≥2 episodes of SH in the 2 years preceding and self-scored on Likert scale	ANCOVA summary reported in GRADE table
THOMAS 2007[724] RCT	Education alone – re-education with relaxation of BG targets n=7	ANALOGUE; lispro/glargine n=7 continuous subcutaneous insulin infusion therapy (CSII; lispro) n=7	n=21 At least one episode of SH according to ADA criteria in the preceding 6 months. Recurrent severe hypoglycaemia confirmed in all participants. Questionnaire confirmed altered hypoglycaemia awareness in all participants (score ≥4 out of 7 on validated questionnaire)	• HbA1c % • Altered hypoglycaemia awareness (score ≥4 out of 7 on validated questionnaire), reported as number of patients • QOL(DTSQ and HFS)

Table 86: Summary of included studies: Observational case-series (not suitable for meta-analysis or GRADE)

Study	Intervention	Population	Outcomes
Hypoglycaemia avoidance			
CRANSTON 1994[152]	Hypoglycaemia avoidance (treatmentprogramme designed to achieve 3 weeks without BG<3.5 mmol/litre – achieved by diet review, advice about exercise, redistribution of insulin)	n=12 Group A: good control HbA1c<7%, n=6 Group B: poor control, swung from one extreme of hypoglycaemia to the other History of hypoglycaemia without warning. At least three BG <3mmol/litre per 2 weeks in the month before the study	• HbA1c %, mean (SD) • Group A: Before: 6.5 (0.2); After 6.9 (0.3). Reported as NS • Group B: Before: 8.2 (0.2); After 8.7 (0.3). Reported as NS • Hypoglycaemia (<3 mmol/litre) – reported as frequency/month • Group A: Before: 21; After 0 • Group B: Before:14; After 0 • Total autonomic symptoms scores during hypoglycaemia clamp • Reported as higher after intervention for both groups (data reported graphically only)
FANELLI 1993[219]	Hypoglycaemia avoidance by	n=8	• Severe hypoglycaemia

	change in regime and counselling. To prevent hypoglycaemia, insulin doses aimed at fasting, pre-prandial and bedtime BG of ~7.2-8.3 mmol/litre.	Consistent history of frequent hypoglycaemia (BG<3 mmol/litre) in the absence of autonomic warning symptoms for at least 6 months before the study	○ One year before: 2/8; three month study period: 0/8 • HbA1c %, mean (SE) ○ Before: 5.8 (0.3); After 6.9 (0.2). Reported as SS • Autonomic symptom score during clamp, mean (SE) ○ Before: 2.2 (0.9); After 5.8 (0.6). Reported as SS • Neuroglycopenic symptom score during clamp, mean (SE) ○ Before: 5.4 (1.5); After 9.4 (1.1). Reported as SS
FRITSCHE 2001[240]	Avoidance of hypoglycaemia. Target pre-prandial BG levels increased from 5.6 mmol/litre to 8.3 mmol/litre and at bedtime from 5.6 mmol/litre to 10 mmol/litre	n=10 Self-reported IAH and a history of SH as defined by DCCT (SH resulting in coma or seizure, requiring assistance from another person and treatment with glucagon or IV glucose	• Severe hypoglycaemia – reported as episodes/patient, mean (SD) ○ Four months before: 2.0 (0.5); four month study period: 0.0 (0.0) • HbA1c %, mean (SD) ○ Before: 6.8 (0.9); After 7.7 (0.9). Reported as SS • Autonomic symptom score during clamp, mean (SE) ○ Before: 1.8 (0.6); After 3.3 (0.7). Reported as SS • Neuroglycopenic symptom score during clamp, mean (SE) ○ Before: 2.2 (0.7); After 3.7 (0.7). Reported as SS
LEELARATHNA 2013[445]	Hypoglycaemia avoidance (6 months): HypoCOMPaSS education tool (individualised education session aimed at avoidance and early detection of BG <4 mmol/litre). Followed by 24-week using either MDI plus SMBG; MDI plus SMBG and RT-CGM; CSII plus SMBG; CSII plus SMBG and RT-CGM Primary goal of insulin dose	n=18 IAH (Gold score ≥4 with or without history of SH in preceding 12 months defined by ADA)	• Severe hypoglycaemia, annualised rate, median (IQR) ○ Before: 4 (0-7); After 0 (0-0). Reported as SS • Gold score, mean (SD) ○ Before: 5.2 (0.2); After 4.3 (0.4). Reported as SS • Edinburgh Hypo score during clamp study. Total AUC ○ Before: 500 (365-685); After 650 (365-1285). Reported as SS

	titration throughout the 24-week RCT period was absolute avoidance of all blood glucose levels <4 mmol/litre		
LIU 1996[463]	Hypoglycaemia avoidance by 3 months less strict glycaemic control aimed at increasing daily mean BG to 8-10mmol/litre	n=7 Recurrent hypoglycaemia (BG<3 mmol/litre more than twice a week for 5 months and at least one SH requiring assistance during the last 2 years.	• HbA1c %, mean (SE) ○ Before: 6.9 (0.3); After 8.0 (0.3). Reported as SS • Symptom scores on VAS 0-10 scale, mean (SE) ○ Sweating: Before: 1.1 (0.4); After 5.2 (1.9). Reported as SS ○ Lack of concentration: Before: 0.2 (0.2); After 4.0 (1.1). Reported as SS ○ Hunger; palpitation; tremor; fatigue: all reported as NS
Education			
DE ZOYSA 2014[174]	DAFNE-Hypoglycaemia Restoration Awareness Training (DAFNE-HART). 6 week intervention, follow-up 12 months	n=23 Persistent IAH assessed clinically and Gold score ≥4.	• Severe hypoglycaemia (<3.5 mmol/litre requiring assistance), events/patient-year, median (range) ○ Before: 3.0 (0-104); After: 0 (0-3) • HbA1c, % ○ Before: 7.8 (1.2); After: 7.8 (1.1) • Gold score, range 1-7, ≥4 = impaired awareness ○ Before: 5.6 (1.4); After: 4.5 (1.9) • Clarke score, ≥4 = impaired awareness ○ Before: 5.4 (1.2); After: 3.8 (1.8) • Ryan score, hypoglycaemia burden (<423 considered to indicate hypoglycaemia not a major clinical concern) ○ Before: 948 (831); After: 372 (466) • Anxiety, HADS (score >8 indicates clinically relevant psychological distress) ○ Before: 5.9 (5.0); After: 6.0 (5.7) • Depression, HADS (score >8 indicates clinically relevant psychological distress) ○ Before: 5.2 (4.6); After: 5.1 (4.7) • PAID, score ≥40 indicates clinically relevant psychological distress ○ Before: 30.7 (22.6); After: 24.7 (20.5)
HERNANDEZ 2008[322]	Self-awareness educational intervention (reported at 6, 12 and 18 months – outcomes reported here as end-of-study, 18	n=23 Previously diagnosed with HU by an endocrinologist and verified with the Clarke score	• Severe hypoglycaemia, number of events ○ Before: 13.3 (17.4); After 7.1 (11.6). Reported as NS • QOL – The Diabetes Questionnaire (TDQ) ○ Before: 75.3 (7.8); After 79.7 (7.0). Reported as SS • QOL – DQoL

	months)		○ Before: 93.3 (18.7); After 120.9 (22.3). Reported as SS • Hospitalisation, number of events ○ Before: 0.8 (2.2); After 0.2 (0.4). Reported as NS • Driving incidents, number of events ○ Before: 0.3 (0.7); After 0.1 (0.5). Reported as NS
HOPKINS 2012[347]	DAFNE (Dose adjustment for normal eating) – 5 day course focusing on adjustment of insulin for carbohydrate intake and reflective use of home BG monitoring data. Follow-up 1 year	n=215 (only including subgroup of patients with impaired awareness before intervention) Those reporting symptom onset at BG <3 mmol/litre or not at all were considered to have IAH.	• Number of patients with IAH (reporting symptom onset at BG <3 mmol/litre or not at all) ○ Before: 215/215 (100%); After: 97/215 (45%) • Severe hypoglycaemia – reported as episodes/patient- year, mean (SD) ○ Year preceding: 3.6 (13.6); Year post-DAFNE: 1.3 (5.9)
Monitoring			
CHOUDHARY 2013[128]	CGM for 12 months (in addition to usual CSII or MDI)	n=35 Ongoing problematic hypoglycaemia leasing to limitation of daily activities and Gold score >4 despite structured education with or without CSII	• Severe hypoglycaemia – reported as episodes/year, mean (SD) ○ Before: 8.1 (13); After 0.6 (1.2). Reported as SS • HbA1c %, mean (SD) ○ Before: 8.1 (1.2); After 7.8 (1.0). Reported as SS • Gold Score (range of values 1-7), mean (SD) ○ Before: 5.0 (1.5); After 5.0 (1.9). Reported as NS
RYAN 2009[637]	CGM for 2 months (in addition to MDI)	n=16 Elevated baseline HYPO-score >75th percentile for type 1 diabetes population (>423) and had at least one SH within the last year	• Modified HYPO score (higher scores = worse), mean (SE) ○ Before: 857 (184); After: 444 (92) • HbA1c %, mean (SE) ○ Before: 8.4 (0.3); After 8.2 (0.3)
Insulin regime			
GIMENEZ 2010[265]	CSII (reported at 6, 12 and 24 months – outcomes reported here as end-of-study, 24 months)	n=20 Presenting more than 4 mild hypoglycaemia events per week (in the last 8 weeks) and more than 2 SH events (in the last 2	• Severe hypo – reported as episodes/patient/year, mean (SD) ○ Before: 1.3 (0.4); After 0.1 (0.2). Reported as SS • HbA1c %, mean (SD) ○ Before: 6.6 (1.1); After 6.3 (0.9). Reported as NS • Clarke score, number of patients with HU

		years)	(score≥4) ○ Before: 19/20; After: 3/20 • Clarke score, mean (SD) ○ Before: 5.5 (1.2); After: 1.6 (2.0). Reported as SS • Hypoglycaemia symptom score during clamp, mean (SD) ○ Before: 31.6 (16.4); After: 62.3 (23.6). Reported as SS • QOL, DQoL ○ Reported as SS better for all four subscales after intervention • SF-12 health survey, mean (SD) ○ Before: 34.1 (3.9); After 37.0 (2.9). Reported as SS
Islet transplantation			
BROOKS 2013[100]	Islet transplantation	n=20 Recurrent severe hypoglycaemia (≥1 event over the preceding 12 months requiring assistance to actively administer carbohydrate, glucagon or other resuscitative actions) despite optimized conventional management.	• Severe Hypoglycaemia, number of patients ○ Baseline 12 months: 20/20 (100%); During 24 month follow-up: 8/20 (40%) • Severe hypoglycaemia, episodes/patient-year, median (IQR) ○ Before: 20 (7-50); 12 months: 0 (0-1); 24 months: 0.3 (0-1.6) • HbA1c %, median (IQR) ○ Before: 8.0 (7.0-9.6); 12 months: 6.3 (5.8-7.1); 24 months: 6.2 (5.7-8.4) • Gold score, range 1-7, ≥4 = impaired awareness, median (IQR) ○ Before: 6 (5-7); 24 months: 3 (1.5-4.5)
LEITAO 2008[449]	Islet transplantation	n=31 Having islet transplantation (not all patients classified as having HU before intervention, 87% had HU before)	• Clarke score, number of patients with HU (score≥4) ○ Before: 27/31 (87%); After: 4/31 (13%) • Clarke score, mean (SD) ○ Before: 5.29 (1.51); After: 1.35 (1.92)
MEYER 1998[504]	Islet transplantation	n=3 Multiple episodes of protracted SH requiring hospitalisation and glucagon or IV glucose	• HbA1c %, mean (SD) ○ Before: 8.0 (0.5); After 8.2 (0.3). Reported as NS • Severe hypoglycaemia, number of patients ○ Before: 3/3; After: 0/3 • Autonomic symptom score during clamp, mean (SD) ○ Before: 2.3 (1.5); After 7.0 (1.7) • Neuroglycopenic symptom score during clamp, mean (SD) ○ Before: 2.7 (2.5); After 5.0 (1.7)
RYAN 2005[635]	Islet transplantation	n=65	• Problematic hypoglycaemia (frequent recurrent episodes of hypoglycaemia,

		Having islet transplantation (not all patients classified as having HU before intervention). 80% classified as having problematic hypoglycaemia before intervention (frequent recurrent episodes of hypoglycaemia, usually associated with HU and more recently quantified with HYPO score ≥1047).	usually associated with HU and more recently quantified with HYPO score ≥1047): ○ Before: 52/65 (80%); After: reported to improve significantly post-transplant

Table 87: Clinical evidence summaries: structured education and hypoglycaemia avoidance versus standard care

Outcome	No. of studies	Imprecision	GRADE rating	Absolute difference	Control event rate (per 1000)	Control event mean (continuous outcomes)
Hypoglycaemia unawareness ≤6months: HAQ (Clarke)	1	Serious	VERY LOW	MD 0.7 lower (1.3 to 0.1 lower)	-	3.0
Hypoglycaemia unawareness ≤6months: Gold Score modified VAS	1	Serious	VERY LOW	MD 0.8 higher (0.2 to 1.4 higher)	-	5.3
Severe Hypoglycaemia ≤6months: events/patient-year	1	Serious	LOW	MD 0.3 lower (1 lower to 0.4 higher)	-	1.2
Severe Hypoglycaemia ≤6months: events/patient/6 months	1	Very serious	VERY LOW	Unable to calculate MD[a,b]	-	1.7
Nocturnal Hypoglycaemia ≤6months: events/patient/6 months	1	Very serious	VERY LOW	Unable to calculate MD[a,c]	-	1.6
HbA1c % (final values) ≤6months	1	No serious imprecision	MODERATE	MD 0.1 higher (0.18 lower to 0.38 higher)	-	7.1
Quality of Life ≤6months: PAID	1	Very serious	VERY LOW	MD 0.7 higher (3.2 lower to 4.6 higher)	-	23.3
Quality of Life ≤6months: ADDQoL	1	No serious imprecision	LOW	MD 0.1 lower (0.3 lower to 0.1 higher)	-	1.1
Autonomic symptom score during clamp ≤6months	1	Serious	VERY LOW	MD 5.0 higher (3.0 to 7.0 higher)	-	1.9
Neuroglycopenic symptom score during clamp ≤6 months	1	Serious	VERY LOW	MD 3.6 higher (1.14 to 6.06 higher)	-	6.1

(a) SD not given, therefore, unable to calculate MD and 95% CI
(b) Data given: SE and avoidance 0.4, Control 1.7; p=0.03
(c) Data given: SE and avoidance 0.8, Control 1.6; p=0.06

Table 88: Insulin Lispro versus regular Human Insulin

Outcome	No. of studies	Imprecision	GRADE rating	Absolute difference	Control event rate (per 1000)	Control event mean (continuous outcomes)
Severe Hypoglycaemia ≤6 months, number of patients	1	Very serious	VERY LOW	0 fewer per 1000 (from 197 fewer to 300 more)	545 per 1000	-
HbA1c % ≤6months	1	Serious	VERY LOW	MD 0.2 lower (0.64 lower to 0.24 higher)	-	9.3
Quality of Life ≤6 months: DTSQ	1	Very serious	VERY LOW	Unable to calculate MD[a,b]	-	Unable to calculate[a,b]
Quality of Life ≤6 months: HFS	1	Very serious	VERY LOW	Unable to calculate MD**(a)(b)**	-	Unable to calculate[a,b]

(a) Mean values and SD not given therefore unable to calculate MD and 95% CI
(b) Data given: No differences between Lispro and human insulin

Table 89: Education and relaxation of BG targets versus analogue insulin lispro/glargine

Outcome	No. of studies	Imprecision	GRADE rating	Absolute difference	Control event rate (per 1000)	Control event mean (continuous outcomes)
HbA1c % ≤6months	1	Serious	LOW	MD 0.7 higher (0.2 lower to 1.6 higher)	-	7.6
Altered hypoglycaemia awareness, number of patients ≤6months	1	Very serious	VERY LOW	285 fewer per 1000 (from 497 fewer to 514 more)	571 per 1000	-
Quality of Life ≤6months: DQOL	1	Serious	VERY LOW	MD 12 lower (26.38 lower to 2.38 higher)	-	70
Quality of Life ≤6months: HFS	1	Very serious	VERY LOW	MD 2 lower (23.88 lower to 19.88 higher)	-	83

Table 90: Clinical evidence summary: Education and relaxation of BG targets versus CSII

Outcome	No. of studies	Imprecision	GRADE rating	Absolute difference	Control event rate (per 1000)	Control event mean (continuous outcomes)
HbA1c % ≤6months	1	Serious	LOW	MD 0.9 higher (0.15 lower to 1.95 higher)	-	7.4
Altered hypoglycaemia awareness, number of patients ≤6 months	1	Very serious	VERY LOW	142 fewer per 1000 (from 360 fewer to 789 more)	429 per 1000	-
Quality of Life ≤6months: DQOL	1	Serious	VERY LOW	MD 16 lower (34.97 lower to 2.97 higher)	-	74
Quality of Life ≤6months: HFS	1	Serious	VERY LOW	MD 17 higher (1.25 to 32.75 higher)	-	64

11.2.4 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix E.

11.2.5 Evidence statements

Clinical

RCT and cohort study evidence

Structured Education and Hypoglycaemia Avoidance versus Standard Care

Evidence that was mostly low and very low quality from single studies showed a clinical benefit at less than or equal to 6 months of structured education and hypoglycaemia avoidance compared with standard care in people with type 1 diabetes and IAH for severe hypoglycaemia (events/patient-year), and for both autonomic and neuroglycopenic symptom scores during clamp. However the evidence showed no clinical difference for the outcomes of hypoglycaemia unawareness (in terms of HAQ- Clarke, and Gold modified VAS), severe hypoglycaemia and nocturnal hypoglycaemia (both measured by events/patient/6 months), HbA1c, and QoL (measured by PAID and by ADDQoL)

Insulin Lispro versus Regular Human Insulin

Very low quality evidence from a single study showed no clinical differenceat less than or equal to 6 months between insulin lispro and regular human insulin in people with type 1 diabetes and IAH for the outcomes of severe hypoglycaemia (number of patients), HbA1c, and for QoL (measured by DTSQ, and HFS)

Education and relaxation of BG targets versus analogue insulin lispro/glargine

Low and very low quality evidence from a single study showed a clinical benefit at less than or equal to 6 months of education and relaxation of BG targets compared with insulin lispro/glargine in people with type 1 diabetes and IAH for QoL (DQOL). However the evidence showed clinical harm of education and relaxation of BG targets for HbA1c, and the number of patients with altered hypoglycaemia awareness. There was no clinical difference between the two interventions for QoL (HFS).

Education and relaxation of BG targets versus CSII

Low and very low quality evidence from a single study showed a clinical benefit at less than or equal to 6 months of education and relaxation of BG targets compared with CSII in people with type 1 diabetes and IAH for: QoL (DQOL). However the evidence showed clinical harm of education and relaxation of BG targets for HbA1c, and the number of patients with altered hypoglycaemia awareness, and for QoL (HFS).

Observational case-series evidence

Hypoglycaemia avoidance programmes

Low quality evidence from several case-series showed consistently that, compared with baseline, hypoglycaemia avoidance programmes in people with type 1 diabetes who had IAH resulted in improved hypoglycaemia awareness in terms of symptom scores, reduction in the rate of severe hypoglycaemia, and reduction in Gold and Clarke scores. However there were increases in HbA1c levels.

Education programmes

Low quality evidence from several case-series showed consistently that, compared with baseline, education programmes (particularly those aimed at improving awareness) in people with type 1 diabetes who had IAH, resulted in improved hypoglycaemia awareness in terms of reporting symptom onset at BG of less than 3 mmol/litre or not at all, reduction in the rate of SH, improvement in several (but not all) QoL scores and reduction in Gold and Clarke scores.

CGM

Low quality evidence from two case-series showed that, compared with baseline,monitoring using CGM in people with type 1 diabetes who had IAH, resulted in a small reduction in HbA1c, reduction in the rate of SH, and improved hypoglycaemia awareness in terms of HYPO score. However there was no difference in terms of Gold score for improved awareness.

CSII

Low quality evidence from a single case-series showed that compared with baseline, insulin therapy using CSII in people with type 1 diabetes who had IAH, resulted in a reduction in HbA1c, reduction in the rate of SH, and improved hypoglycaemia awareness in terms of worse symptom scores, and lower Clarke score and Gold scores. There was also improvement in QoL measures.

Islet transplantation

Low quality evidence from several case-series showed that, compared with baseline, islet transplantation in people with type 1 diabetes who had IAH or recurrent SH, resulted in a reduction in HbA1c, reduction in the rate and number of people experiencing SH or problematic hypoglycaemia, and improved hypoglycaemia awareness in terms of symptom scores, and lower Clarke and Gold scores.

Economic

No relevant economic evaluations were identified.

11.2.6 Recommendations and link to evidence

The current guideline recommendations can be found at

https://www.nice.org.uk/guidance/ng17

Relative values of different outcomes	The GDG reviewed the evidence for the most effective strategy for recovery of IAH in adults with type 1 diabetes. Only interventions with an evidence base to reflect an effect of ≥1 month duration were reviewed The following outcomes were considered: • Recovery of hypoglycaemia scores/autonomic/neuroglycopenic warning symptoms, reflecting an objective improvement in hypoglycaemia awareness. • Reduction in the incidence of severe hypoglycaemia. The GDG acknowledged that even if interventions could not restore awareness of hypoglycaemia, they might still be able to reduce incidence of severe hypoglycaemia. When contemplating the impact of interventions on clinical outcomes, particular focus was given to: • A reduction in the incidence of severe hypoglycaemia (requiring help from 3rd party for correction), which has been recognised as having a significant impact on quality of life in individuals with type 1 diabetes. • A reduction in the incidence of nocturnal hypoglycaemia. • Change in glycaemic control, assessed by HbA1c. Extensive previous research has shown that an improvement in glycaemic control is associated with a reduction in microvascular complications. Any therapy that achieves a reduction in the frequency of hypoglycaemia and improvement in awareness of hypoglycaemia without worsening glycaemic control would be beneficial. **Improvement in quality of life.** It would be anticipated that a reduction in the incidence of severe hypoglycaemia would result in an improvement in quality of life. However, in order to achieve a reduction in the rate of severe hypoglycaemia, some lifestyle constraints or greater regularity of glucose monitoring might be required. In addition, transplant interventions require immunosuppression therapy, which can produce side-effects and impact on quality of life by their effect on the immune system. Reduction in the incidence of hospital admissions. Ultimately, the aim of any intervention would be to reduce the incidence of severe hypoglycaemia episodes, and this might be reflected in a reduction in the incidence of hospital attendances for the treatment of severe hypoglycaemia. Reduction in the incidence of road traffic accidents and work-related incidents as a consequence of hypoglycaemia.
Trade-off between clinical benefits and harms	**Evidence for hypoglycaemia avoidance by relaxation of blood glucose control:** A number of research studies reported that if hypoglycaemia is avoided by intensive supervision of patients' insulin regimens, hypoglycaemia awareness can be re-established with time.[152,218,219,240,463]However, the GDG noted that this achievement was sometimes at the expense of an elevation in mean blood glucose reflected by increased HbA1c. There are a number of currently available interventions which report improvement in hypoglycaemia awareness without deterioration in glycaemic control. **Evidence for structured education interventions:** Three RCTs used structured education interventions for IAH and reported a reduction in the frequency of severe hypoglycaemia episodes and an improvement in hypoglycaemia awareness following attendance by adults with

type 1 diabetes.

Hypoglycaemia Anticipation, Awareness and Treatment Training (HAATT) is a structured education programme designed to reduce occurrence of low blood glucose in adults with type 1 diabetes. An RCT in 60 participants[150] reported that incidence of severe hypoglycaemia per subject reduced from 2.0 to 0.4 episodes and frequency of nocturnal hypoglycaemia from 1.1 to 0.8 episodes in individuals receiving HAATT education, whilst no change in clinical outcomes was reported for controls not receiving the education. In addition, improved awareness of symptoms accompanying hypoglycaemia was reported in the trial.

HyPOS training[318]was a structured education programme focusing on avoidance of low blood glucose levels, causes of IAH, improvement in detection and recognition of hypoglycaemia warning symptoms and recognition of the need to treat low blood glucose levels. An RCT in 164 participants showed that education resulted in an improvement in Clarke and Gold scores for hypoglycaemia awareness and a reduced incidence of severe hypoglycaemia; no change in HbA1c or quality of life scores was observed.

Four observational studies of education programmes provided further support for their use as an intervention in the management of individuals with IAH. A self-awareness educational intervention in 23 participants with IAH showed that incidence of severe hypoglycaemia and hospitalisation could be reduced, even if hypoglycaemia symptoms, HbA1c and quality of life remained unchanged[322].

DAFNE (Diabetes Adjustment for Normal Eating) education has been shown to reduce the incidence of severe hypoglycaemia in attendees and improve hypoglycaemia awareness, with 43% of those entering the programme with impaired awareness reporting recovered awareness one year later and an overall improvement in the prevalence of impaired awareness[347]. The DAFNE-HART study (Dose Adjustment For Normal Eating Hypoglycaemia Awareness Restoration Training)[174] was a pilot study in 23 participants with IAH persisting following other structured education (DAFNE) who underwent a six week education intervention with additional psychotherapeutic interventions aimed at reducing their incidence of hypoglycaemia. At reassessment one year later, Gold, Clarke and HYPO scores improved and incidence of severe hypoglycaemia was reduced, quality of life as measured by the PAID score improved, whilst HbA1c and anxiety and depression HADS scores were unchanged.

The HypoCOMPaSS education tool for avoidance of hypoglycaemia in patients with IAH has been shown to produce an improvement in autonomic and neuroglycopenic warning symptoms during clamp studies, with increased self-awareness of hypoglycaemia, an improvement in Gold scores and a reduction in the incidence of severe hypoglycaemia[445].

Evidence for Insulin analogue use and CSII pump therapies:

An RCT in 40 participants comparing lispro insulin and neutral protamine hagedorn (NPH) insulin use with regular human insulin and NPH use over six months reported that use of the analogue insulin lispro had no impact on severe hypoglycaemia rate, HbA1c, or quality of life in study participants[224]. A further RCT compared lispro and glargine analogue use to lispro CSII, whilst a third intervention group received education and relaxation of glucose targets. Whilst treatment with insulin analogue therapies and CSII improved HbA1c and reduced incidence of severe hypoglycaemia, there was no difference between the two treatment strategies and no impact on hypoglycaemia awareness or quality of life[724]. A fall in severe hypoglycaemia rate also occurred in the group treated by

education and relaxation of glucose targets alone, but the mean rate remained higher as did HbA1c, although the trend did not reach significance in this small study (7 subjects per group).

An observational study reported that 24 months CSII therapy reduced Clarke score, improved autonomic scoring during a hypoglycaemic clamp, decreased the incidence of severe hypoglycaemia and improved quality of life alongside maintenance of a stable HbA1c in 20 study participants[265].

Evidence for Insulin analogue use and CSII pump therapies:

An RCT in 40 participants comparing lispro insulin and neutral protamine hagedorn (NPH) insulin use with regular human insulin and NPH use over six months reported that use of the analogue insulin lispro had no impact on severe hypoglycaemia rate, HbA1c, or quality of life in study participants[224]. A further RCT compared lispro and glargine analogue use to lispro CSII, whilst a third intervention group received education and relaxation of glucose targets. Whilst treatment with insulin analogue therapies and CSII improved HbA1c and reduced incidence of severe hypoglycaemia, there was no difference between the two treatment strategies and no impact on hypoglycaemia awareness or quality of life[724]. A fall in severe hypoglycaemia rate also occurred in the group treated by education and relaxation of glucose targets alone, but the mean rate remained higher as did HbA1c, although the trend did not reach significance in this small study (7 subjects per group).

An observational study reported that 24 months CSII therapy reduced Clarke score, improved autonomic scoring during a hypoglycaemic clamp, decreased the incidence of severe hypoglycaemia and improved quality of life alongside maintenance of a stable HbA1c in 20 study participants[265].

Evidence for CGM usage:

A study in 16 participants with IAH reported a reduction in modified HYPO scoring after 2 months CGM use[637]. However, a larger observational study assessing impact of CGM in 35 participants over 12 months showed that whilst a reduction in the frequency of severe hypoglycaemia episodes was achieved alongside a small reduction in HbA1c (8.1 to 7.8 %), no impact on Gold score was achieved[128].

Evidence for transplant interventions:

Early observational studies in islet transplant recipients reported that autonomic and neuroglycopenic symptoms were improved during a hypoglycaemic clamp in post-transplant recipients[504]. Subsequent larger studies in islet transplant recipients reported a reduction in HbA1c and frequency of severe hypoglycaemia alongside an improvement in awareness of hypoglycaemia assessed by HYPO score[635], Clarke score[100,449] and Gold score[100].

The GDG were aware of an observational study that did not meet the review protocol inclusion criteria (too short follow-up time), but they thought it was useful for their consideration, as no other suitable evidence on pancreas transplantation was found. The study was conducted in 13 pancreas transplant recipients and matched controls with IAH assessed responses to a stepped hypoglycaemic clamp protocol[392]. Successful pancreas transplantation improved adrenaline response and normalised hypoglycaemia symptom recognition in recipients with established autonomic neuropathy.

The GDG recognised that both pancreas transplantation and islet transplantation were viable treatments for the restoration of hypoglycaemia awareness, and that

	both interventions might also improve HbA1c and reduce frequency of severe hypoglycaemia. However, the risk of complications from immunosuppression therapy and its possible impact on quality of life led the GDG to recommend the use of transplant interventions only in individuals experiencing recurrent severe hypoglycaemia episodes with ongoing IAH despite efforts with alternative interventions.
Economic considerations	No economic evaluations regarding strategies for the management of IAH were identified by the GDG. Cost-effectiveness of structured education, analogue insulin therapies, CSII and CGM have been considered in Chapter 7. The likely high cost of transplant interventions and the ongoing need for post-operative immunosuppression contributed to the GDG decision to recommend transplant interventions only if alternative strategies for the management of IAH had been unsuccessful. Discussion on referral for transplant interventions is reported in chapter 18.
Quality of evidence	Twenty studies were included in this review. Six studies were RCTs or observational cohort studies. Evidence from these studies was GRADE assessed. The quality of this evidence for the structured education RCTs[150,318,652] was Moderate to Very low; for the insulin regimen RCT[224]it was Very low; for the studies on education and relaxation of blood glucose targets it was Low to Very low[218,724]. Fifteen studies were observational case-series. Meta-analysis and GRADE were not conducted for these studies as they were not appropriate for this type of assessment as there were no comparison control groups. The GDG noted that many of the studies were small in size, making it hard for study outcomes to achieve significance. However, the GDG were satisfied that recommendations could be made from the available evidence regarding interventions for the management of individuals with IAH.
Other considerations	The GDG noted that in both the HAATT and HyPOS training programmes, participants had not received any previous formal structured education before their participation in the education programmes. However, the GDG recognised that educational interventions aimed specifically at individuals with IAH could improve clinical outcomes in adults with diabetes, even if they had previously received other forms of structured education.

11.2.7 Research recommendations

26. For adults with type 1 diabetes, what are the optimum technologies (such as insulin pump therapy and/or continuous glucose monitoring, partially or fully automated insulin delivery, and behavioural, psychological and educational interventions) and how are they best used, in terms of clinical and cost effectiveness, for preventing and treating impaired awareness of hypoglycaemia?

Why this is important

Impaired awareness of hypoglycaemia renders adults with type 1 diabetes susceptible to sudden unexpected deteriorations of conscious level and irrational behaviour, and increases their risk of severe hypoglycaemia 6-fold. Impaired awareness of hypoglycaemia and severe hypoglycaemia creates barriers to many aspects of daily living, and can cause enormous stress for family and friends. Severe hypoglycaemia can also cause fear of hypoglycaemia great enough to prevent a person

achieving the glucose targets that are associated with minimal risk of complications. Impaired awareness of hypoglycaemia results from overexposure to hypoglycaemia in daily life, and awareness can be much improved by avoidance of hypoglycaemia. Developing technologies in glucose monitoring and insulin delivery have not been rigorously tested in adults with type 1 diabetes and impaired awareness of hypoglycaemia. Research is needed formally to document the extent to which existing technologies can help the adult with type 1 diabetes and impaired awareness of hypoglycaemia to avoid hypoglycaemic episodes and regain awareness for occasional episodes. Research is also needed to develop new technologies. Research is also needed into how to engage adults with type 1 diabetes and impaired awareness of hypoglycaemia with treatment strategies designed to improve awareness.

11.3 Prevention, problems related to hypoglycaemia, and management of symptomatic hypoglycaemia [2004]

This section of the guideline was not updated by the GDG in 2015. Content and recommendations are from the 2004 guideline. The blood glucose awareness training section originally featured in 2004 has been removed as it has been superseded by new evidence reviewed by the 2015 GDG (see Chapter 8). The original content can be found in Appendix S.

11.3.1 Rationale

Hypoglycaemia is, for most people using insulin therapy, an inevitable consequence of the erratic absorption of insulin from subcutaneous tissue after depot injection or infusion, coupled with absence of feedback to insulin need when changes in planned activity or eating occur once the injection has been given. Hypoglycaemia is usually unpleasant, often becomes a source of fear, and can be an embarrassment as well as a safety risk. Accordingly while careful choice of insulin regimen (Section 9.2) informed by self-monitoring (Section 9) is important in ameliorating this problem, other preventative measures are of importance.A higher level of optimised management is needed when hypoglycaemia and its related problems do occur.

11.3.2 Evidence statements

Management of hypoglycaemia

Canadian clinical practice guidelines reported four studies supporting the use of 15 g glucose (monosaccharide) (orally) for the treatment of moderate hypoglycaemia.[787] Two studies within the guidelines explored a 20 g oral glucose dose for recovery of blood glucose levels. Recovery was slower following treatment with milk and orange juice. The use of glucose gel also delivered slower recovery in the latter study and required swallowing to have a significant effect. A further study showed no support for buccal administration of glucose (**Ia**).

One study within the Canadian guidelines[787] reported on the special needs of people taking alpha-glycosidase inhibitors when treating hypoglycaemia, recommending the use of glucose (dextrose) tablets, or milk or honey if these are unavailable (**IV**).

Nocturnal hypoglycaemia

A bedtime snack may be needed to avoid nocturnal hypoglycaemia. Two studies from a systematic review showed prepared corn starch snack bars have some benefit in overnight reduction of hypoglycaemia, but the number of events were not significantly reduced (**Ia**).[787]

Hypoglycaemia unawareness

Canadian clinical practice guidelines[787] report one paper on the link between incidence of prior hypoglycaemic episodes and worsening in the defect of the hormonal responses to hypoglycaemia, leading to a reduction in the self-detection of hypoglycaemia. Eight papers report the benefits of strict avoidance of hypoglycaemia in improving recognition of severe hypoglycaemia or the responses of counter regulatory hormones (**Ia**).

Long term complications of hypoglycaemia

Evidence on the impact of hypoglycaemia on cognitive function is not clear. Two prospective studies reported within the Canadian guidelines , which did not find association between intensive diabetes management and cognitive function.[787] However, six retrospective studies found subjects with recurrent hypoglycaemia performed more poorly in a range of intellectual tests (**IIa**).

Medical intervention of hypoglycaemia

Two randomised studies compared the use of glucagon and dextrose in the treatment of severe hypoglycaemia.One study compared intramuscular administration of 1 mg glucagon with 50 ml 50 % IV dextrose in people with hypoglycaemic coma.[571] A second study compared intravenous administration of 1 mg glucagon versus 50 ml 50 % dextrose in people with hypoglycaemic coma.[139] Both studies showed a significantly slower recovery to a normal level of consciousness in the glucagon treated group (**Ib**).

Two glucagon-treated patients in each study (7 and 4 % respectively) and two dextrose-treated patients in the second study (4 %) required additional administration of 12.5 g IV dextrose following failing to recover consciousness after 15 minutes.In the first study average duration of hypoglycaemic coma was not different between the two treatment groups (**Ib**).

No correlation was seen between time taken to recovery of consciousness and initial plasma glucose concentration or duration of hypoglycaemia in either of the studies. Side effects were similar among the treatment groups (**Ib**).

These two small studies suggest that intravenous glucose gives a clinically non-significant advantage over intra-muscular glucagon in time to recovery of consciousness in people with type 1 diabetes in hypoglycaemic coma (**Ib**).

11.3.3 Health economic evidence

No health economic evidence on the prevention or management of hypoglycaemia was identified in the literature review.

11.3.4 Consideration

The group noted this was an area of considerable importance to people with type 1 diabetes, but that prevention of hypoglycaemia was considered appropriately under insulin therapy recommendations, and secondarily under education and lifestyle issues.The Group noted issues related to absorption and ingestion of free carbohydrate in people with decreased conscious

level.They were concerned that recurrent hypoglycaemia was properly considered in a medical context, and not simply attributed to lifestyle problems secondary to insulin therapy.

Hypoglycaemia unawareness was also noted to be an important issue, and be partially reversible and capable of useful management, as now is nocturnal hypoglycaemia (it was noted that the recommendations on insulin therapy and clinical monitoring addressed other aspects of such management).No useful hard evidence was available for cognitive decline occurring in people with type 1 diabetes, but the possibility of recurrent severe hypoglycaemia being a contributory factor was felt worth mentioning.

The group noted that the ease and safety of administration of glucagon compared to IV glucose (risk of extravasation) meant that in most situations it was the treatment of choice. While it was recognized that there were groups of people to whom the identified studies do not apply (starvation, alcohol toxic), and that these people would not be expected to respond well to glucagon, it was agreed that the best means of detecting this was by absence of a response to glucagon at 10 minutes.Safe follow-up management after either therapy should include oral carbohydrate and awareness of risk of relapse.Users of glucagon injections need appropriate education and training.

11.3.5 Recommendations [2004]

The current guideline recommendations can be found at

https://www.nice.org.uk/guidance/ng17

12 Ketone monitoring and management of diabetic ketoacidosis (DKA)

This section was updated in 2015.

The 2015 GDG updated self-monitoring and in hospital monitoring of ketones.The 2004 content that has been superseded by the 2015 update can be found in Appendix S.Management of DKA was not in the scope for the 2015 update and therefore the original recommendations and content from CG15are reproduced in this chapter.

12.1 Ketone monitoring [2015]

12.1.1 Introduction

Ketosis and ketonuria reflect a greater degree of insulin deficiency than hyperglycaemia alone. The presence of ketones indicates that insulin concentrations are too low not only to control blood glucose concentrations but also to prevent the breakdown of fat (lipolysis). Because ketones are acid substances, high ketone concentrations in the blood may create acidosis. Diabetic ketoacidosis (DKA) is a medical emergency and in its established state carries a 0.7–5% mortality in adults.[459,476,784]

High ketones in the blood are associated with high levels of fatty acids and together create insulin resistance. The patient with significant ketonaemia will require more insulin than usual to control the blood glucose.

Traditionally, ketonaemia has been assessed by urine testing. This has been applied in three main settings: it is recommended as part of guidance for patient self-management of acute illness at home, when patients are advised to increase their usual corrective insulin doses in the presence of significant ketonuria; in the assessment of patients presenting to emergency services with hyperglycaemia, where presence of ketonuria may influence management decisions, including need for admission and in the management of established DKA, where resolution of ketonuria is an important indication of recovery. However, not all ketone bodies are detected by urine testing. For example, beta-hydroxybutyrate (β-OHB) is not detected with current strip tests and if there is a high β-OHB:acetoacetate ratio, urine testing may give a falsely low estimate of ketosis. Furthermore, after an episode of ketoacidosis, where measurement of blood ketones may provide a more accurate assessment of re-insulinisation than blood glucose measurements alone, urine tests, measuring lipid soluble acetone, may continue positive for 48 hours as acetone leaks from fat tissue although ketogenesis and lipolysis have stopped.

Recent advances in technology have included the development of faster, more accurate blood tests for ketones, including strip and meter tests for measuring ketonaemia as β-OHB from a finger prick blood sample. There is a need to assess the evidence base for the use of blood ketone measurement, both laboratory- and strip-based, in three settings:

- Use of self-assessment of blood ketones as part of home monitoring when hyperglycaemia is detected and the patient is feeling unwell to see if it can improve a patient's ability to manage intercurrent illness at home, reduce hospital admissions and/or reduce the severity of ketoacidosis when someone presents to the emergency services.
- Use of blood rather than urine ketone measurement in the assessment of patients presenting to emergency services with hyperglycaemia.
- Use of blood rather than urine ketone measurement in the inpatient management of established ketoacidosis to reduce morbidity and length of stay in either high dependency care and/or the hospital.

The new review questions included in this chapter are:

- In adults with type 1 diabetes (including atypical ketosis-prone diabetes), does patient self-monitoring of blood (and urine) ketones reduce the incidence of DKA and hospital admissions?
- In adults with type 1 diabetes, does inpatient monitoring of blood ketones by the healthcare professional reduce the length of hospital stay, exposure to IV insulin and the development of in-hospital complications:
  - in patients with suspected DKA?
  - in patients admitted with DKA and/or those that get it in hospital?

The evidence and text from the previous guideline, CG15, that has been superseded by this update is in Appendix S.

12.1.2 Review question: In adults with type 1 diabetes (including atypical ketosis-prone diabetes), does patient self-monitoring of blood (and urine) ketones reduce the incidence of DKA and hospital admissions?

Table 91: PICO characteristics of review question - self-monitoring

Population	Adults with type 1 diabetes
Intervention/s and comparison/s	• Blood ketone versus urine ketone measurements • Any or no comparison
Outcomes	• Hospital admissions – for DKA if specified • Duration of admission/length of hospital stay • DKA • HbA1c • Hypoglycaemia • Quality of life – measured by PAID, anxiety • Severity of acidosis at admission - duration of acidosis and degree of acidosis
Study design	All study types

12.1.3 Review question: In adults with type 1 diabetes, does inpatient monitoring of blood ketones by the healthcare professional reduce the length of hospital stay, exposure to IV insulin and the development of in-hospital complications:

- **in patients with suspected DKA?**
- **in patients admitted with DKA and/or those that get it in hospital?**

Table 92: PICO characteristics of review question - inpatient monitoring

Population	Adults with type 1 diabetes and DKA
Intervention/s	Blood Ketone monitoring
Comparison/s	• Urine ketone • No monitoring
Outcomes	• Length of hospital stay (continuous) • In-hospital complications of the admission – for example, cerebral oedema, mortality, serious electrolyte imbalance (dichotomous) • Exposure to IV insulin (dichotomous) • Sensitivity of DKA diagnosis • Specificity of DKA diagnosis • How often admission occurs

Population	Adults with type 1 diabetes and DKA
	• Hypoglycaemia • Quality of life (continuous)
Study design	All study types

12.2 Clinical evidence

We searched for studies published since the original type 1 diabetes guideline (2003 onwards).

Five studies were included in the review [47,66,298,430,710] One of the studies was a randomised controlled trial (RCT)[430]. All other studies were non-comparative observational studies, and therefore were not able to be combined in a meta-analysis or GRADE profile, and were graded as Low quality (due to their study design). However, a summary of the quality and limitations of these studies can be found in Appendix G. Evidence from these studies has therefore been summarised narratively, with an overview in Appendix I. See also the study selection flow chart in Appendix D, and study evidence tables in Appendix Gand exclusion list in Appendix K.

One study, the RCT [430], looked at ketone self-monitoring. All other studies involved inpatient ketone measurement (point of care testing in the emergency department).

There were no data reported in any of the studies for the following outcomes:

- length of hospital stay
- in-hospital complications of the admission
- quality of life
- hypoglycaemia

The terms β-OHB and β-HBA have been used throughout the review, according to the terminology reported in the studies. These are alternative acronyms representing the same ketone, beta-hydroxybutyric acid.

Table 93: Summary of studies included in the review (self-monitoring)

Study	Intervention/ comparison	Frequency of ketone monitoring	Setting	Population	Follow-up	Outcomes/results
LAFFEL 2006[430]	RCT Blood vs. urine ketone (β-OHB) monitoring	No. of checks overall was not significantly different between groups (1866 blood vs. 1798 urine checks). Frequency of checks during hyperglycaemia was similar. Frequency of checks during sick days SS higher in	Sick day management (home monitoring)	n=123 type 1 diabetes Children, adolescents and young people	6 months	Blood β-HBA is best Monitoring of blood (capillary) β-HBA resulted in less ER use, hospitalisations and greater change in HbA1c than with urine β-HBA monitoring HbA1c change from baseline: no significant difference between groups or within groups

Study	Intervention/ comparison	Frequency of ketone monitoring	Setting	Population	Follow-up	Outcomes/results
		blood vs. urine group (91% vs. 61%; p<0.001)				Patient preference: blood ketones (easier to perform) VERY LOW quality[a]

(a) Quality rating from GRADE table, see Appendix I for details.

Table 94: Summary of studies included in the review (inpatient monitoring)

Study	Intervention/ comparison	Frequency of ketone monitoring	Setting	Population	Follow-up	Outcomes/results
ARORA 2011[47]	Ketone (β-OHB) measurement in blood and urine Observational study (prospective case series)	Not reported	ED patients Point of care testing	n=516 Blood glucose ≥250 mg/dL	2 years	Blood β-HBA is best Blood (capillary) β-HBA was as sensitive and more specific than urine β-HBA for detecting: DKA (98/79 vs. 98/35) VERY LOW quality[a]
BEKTAS 2004[66]	Ketone (β-HBA) measurement in blood and urine Observational study (prospective case series)	Weekly	ED patients Point of care testing	n=139 Diabetic newly diagnosed or known Adults	6 months	Blood β-HBA is best Blood (capillary) β-HBA was more sensitive and specific than urine β-HBA for detecting: DK (91/56 vs. 82/54) DKA (72/82 vs. 66/78) VERY LOW quality[a]
HARRIS 2005[298]	Ketone (β-OHB) measurement in blood and urine Observational study (retrospective case series)	Not reported	ED patients Near patient testing	n=50 Hyperglycaemia Blood glucose >11 mmol/litre	n/a	Blood β-OHB (>3 mmol/litre) is best Blood (capillary) β-OHB >3 mmol/litre was as sensitive and more specific than urine β-OHB for detecting: DKA (100/88 vs. 100/52) Patients requiring IV insulin treatment (100/100 vs. 100/65) VERY LOW quality[a]
TABOU	Ketone (β-	Frequency	ED	n=529	32	Blood β-OHB is best

Study	Intervention/ comparison	Frequency of ketone monitoring	Setting	Population	Follow-up	Outcomes/results
LET 2007[710]	OHB) measurement in blood and urine Observational study (retrospective case series)	not mentioned, but nurses instructed to measure as often as possible, and both blood and urine samples were always taken together in order for comparison.	patients Point of care/near patient testing	Hyperglycaemia Blood glucose >13.75 mmol/litre	months (retrospectively in patients records)	Blood (capillary) β-OHB was significantly better than urine β-OHB for predicting: ketoacidosis hospitalisation hospitalisation for ketoacidosis VERY LOW quality[a]

(a) Data is from case series, mostly of retrospective design. The quality has been rated as VERY LOW because these study designs are associated with a high risk of bias.

Table 95: Clinical evidence summary: Blood β-HBA versus urine β-HBA ketone measurement (less than or equal to 6 months)

Outcomes	Number of studies	Imprecision	GRADE rating	Absolute difference Blood ketones	Control event rate (per 1000 patients) Urine ketones
HbA1c	1 study (n=123)	Serious	VERY LOW	MD 0.7 higher (0.12 to 1.08 higher)	8.3 final value in urine group
ER use	1 study (n=123)	Serious	VERY LOW	101 fewer per 1000 (from 172 fewer to 55 more)	230
Hospitalisation	1 study (n=123)	Very serious	VERY LOW	83 fewer per 1000 (from 118 fewer to 43 more)	131

12.3 Economic evidence

Published literature

No relevant economic evaluations comparing either self-monitoring of blood ketones with urine ketones, or hospital-monitoring of blood ketones with urine ketones were identified.

Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided below to aid consideration of cost-effectiveness.

Table 96: Unit costs for self-monitoring of ketones

Self-monitoring ketone tests	Usage	Cost	Quantity	Cost per unit
Ketostix	Urine test	£3.00[a]	50	£0.06
Mission Ketone	Urine test	£2.50[a]	50	£0.05
FreeStyle Optimum ß-Ketone Test Strips	Blood test	£20.63[a]	10	£2.06
Optimum Xceed	Monitor	Free[b]	1	Free[b]
GlucoMen LX Ketone Test Strips	Blood test	£20.32[a]	10	£2.03
GlucoMen LX	Monitor	Free[b]	1	Free[b]

(a) Electronic Drug Tariff[540]
(b) GDG opinion – Monitors are given away free by medical devices companies. Normal cost ranges around £10 to £15

Table 97: Unit costs for in-hospital ketone monitoring

In-hospital ketone monitoring tests	Usage	Cost	Quantity	Cost Per Unit
Biochemistry Blood Test	Blood test	£1.26[a]	1	£1.26
FreeStyle Optimum ß-Ketone Test Strips	Blood test	£20.63[a]	10	£2.06
GlucoMen LX Ketone Test Strips	Blood test	£20.32[a]	10	£2.03
Ketostix	Urine test	£3.00[b]	50	£0.06
Mission Ketone	Urine test	£2.50[b]	50	£0.05
Nurse time	Administer test	£40 an hour[c]	5 minutes	£3.33

(a) NHS Reference Cost[177]
(b) Electronic Drug Tariff[540]
(c) PSSRU 2011[158]- 14.3 – Cost of a band 5 nurse on a standard day ward (plus qualification cost)

Table 98: Pooled average cost of non-elective inpatient care for management of DKA

Age range	Average	Lower quartile	Upper quartile
Under 69 years	£828	£611	£953
70 and above years	£1,532	£1,102	£1,775

Source: NHS Reference Costs[177]. This includes excess bed days.

Table 99: Pooled average cost of non-elective excess bed care days for management of DKA

Age range	Average	Lower quartile	Upper quartile
Under 69 years	£230	£184	£263
70 and above years	£207	£174	£249

Source: NHS Reference Costs[177]

12.3.1 Evidence statements

Clinical

Self-monitoring of β-HBA ketones: blood capillary versus urine

Very low quality evidence from one RCT (n=123) showed:

- clinical benefit of blood monitoring in reducing both ER use and hospitalisations
- no clinical benefit of blood monitoring for HbA1c
- patients preferred blood measurements and found them easier to perform

In the case of ER use and hospitalisations the direction of the estimate of effect favoured blood measurement, with no impact on HbA1c.

Inpatient monitoring

Low quality evidence from four observational studies (n=50 to n=529) showed that point-of-care testing of blood (capillary) β-OHB or β-HBA (in people admitted to the emergency department) was better than urine β-OHB or β-HBA in terms of:

- sensitivity and specificity of detecting DK and detecting DKA.
- patients requiring IV insulin treatment.
- predicting ketoacidosis and hospitalisation

Economic

No relevant economic evaluations were identified.

12.3.2 Recommendations and link to evidence

The current guideline recommendations can be found at

https://www.nice.org.uk/guidance/ng17

Relative values of different outcomes	To determine whether ketone monitoring might be beneficial to individuals with type 1 diabetes, the GDG reviewed the evidence for the use of capillary blood ketone measurement in adults with type 1 diabetes in three clinical settings: Patient self-assessment of capillary blood ketones as part of home-monitoring during acute illness, when hyperglycaemia is detected and the patient is feeling unwell. Ketone monitoring here might improve the patient's ability to manage intercurrent illness at home, with the possibility of reducing hospital admissions.It could also ensure that patients present to emergency services at the appropriate time, reducing the severity of ketoacidosis at presentation to emergency services Comparison of capillary blood ketone measurement versus urine ketone measurement undertaken by healthcare staff at the time of patient presentation to the emergency services with hyperglycaemia, to determine whether one might be superior in determining the need for patient admission to hospital. Comparison of blood ketone measurement versus urine ketone measurement in the inpatient management of established ketoacidosis, with the aim of determining which might lead to morbidity reduction and decreased length of stay in hospital in patients with established DKA.

	Based on assessment from these three clinical settings, the following outcomes for the use of ketone monitoring were assessed: Mortality and morbidity – High ketone levels in the blood result in acidosis, and DKA is a medical emergency that in its established state carries a 0.7 to 5 % mortality[459,476,785]. Ketone testing should allow earlier diagnosis and management of ketosis in individuals with type 1 diabetes and therefore, prevention of complications from DKA. Emergency admission rates to hospital – Early identification of ketosis in individuals with type 1 diabetes might allow corrective measures to be taken and subsequent treatment at home, potentially avoiding the need for presentation as a medical emergency to healthcare services. Access to ketone testing may allow more effective self-management of intermittent illness associated with hyperglycaemia and subsequent morbidity may be reduced, especially if timely referral to emergency services is enabled. Assessment of ketonaemia in hospital – Ketonaemia assessment might influence clinical decision making, enabling earlier diagnosis and management of established DKA. Ketone testing might guide insulin dosing in the management of ketoacidosis, and could conceivably reduce admission times for DKA. Sensitivity and specificity of capillary blood strips versus urine testing for ketones assessment - Ketone testing has traditionally been assessed by urine testing, although, not all ketone bodies are detected by this method of testing. β-OHB is not detected with current urine test strips, and there is the possibility that urine testing can give a falsely low estimate of ketosis. Recent advances in technology have included the development of capillary blood testing strips for ketonaemia, which measure β-OHB from a finger prick blood sample – The evidence was reviewed to assess their sensitivity and specificity in comparison with urine ketone sticks. Ease of capillary blood testing versus urine testing for ketones assessment. Ease of test use is likely to determine frequency of use by both patients and healthcare staff; patients are more likely to be compliant with testing, and healthcare professionals are more likely to adopt the test in management-driven protocols if it is easy to use.
Trade-off between clinical benefits and harms	Mortality and morbidity The GDG looked for published outcomes on whether monitoring for ketones had any impact on electrolyte imbalances, cerebral oedema and mortality during the management of ketoacidosis, but no studies were available for review following evidence searches. Emergency admission rates to hospital A single study from the USA showed that the use of blood rather than urine ketone monitoring during home management of intercurrent illness was associated with a reduced attendance rate to the Emergency Room. Although this difference did not achieve statistical significance, the GDG considered this to be of substantial clinical benefit and an important clinical outcome favouring the use of blood ketone monitoring in this setting.[430] Assessment of ketonaemia in hospital Four studies[46,66,298,710] showed that capillary blood ketone testing might have advantages over urine ketone testing, and that they could be used as a rapid bedside test to measure accurately blood concentrations of ketones in an emergency department setting. The studies suggested that this might be useful for making early management decisions in patients presenting to emergency departments with suspected DKA.

	One study[610] showed that length of hospital stay for the management of DKA was reduced from 3.0+/-1.4 days to 1.8+/-0.7 days by the introduction of capillary blood ketone monitoring to an inpatient DKA management protocol. The GDG observed that this protocol followed the Joint British Diabetes Associations (JBDS) DKA management protocol[650], and were wary of what influence the combined aspects of the protocol, as opposed to ketone measurement alone, might have had on influencing duration of admission in this study. However, the GDG also recognised that one of the main monitoring tests used in the JBDS protocol was the use of blood ketone monitoring to dictate management decisions, and therefore, it was likely that blood ketone monitoring did influence the duration of hospital admission in this study. Sensitivity and specificity of capillary blood strips versus urine testing for ketones assessment Capillary blood ketone assessment was found to be more sensitive than urine testing in two studies[46,66], and more specific in three studies[46,66,298], while a further study concluded that blood ketones were able to better predict ketoacidosis, hospitalisation and hospitalisation for ketoacidosis management than urine ketones assessment[710]. Ease of capillary blood testing versus urine testing for ketones assessment Patients in one study expressed a preference for ketone monitoring over urine ketone monitoring[430]. As a patient testing for ketones is likely to be already testing their blood for glucose levels, no additional finger pricking is required. The GDG recognised that more frequent measurements of blood ketones were relatively easy to undertake in comparison to urine ketone monitoring.
Economic considerations	No relevant economic evaluations comparing either self-monitoring or hospital-monitoring of blood ketones with urine ketones were identified. In the absence of UK cost-effectiveness analysis, the GDG considered the relevant unit costs of blood and urine monitoring to reach its own conclusion regarding cost-effectiveness. Home monitoring Blood ketone test strips have a higher initial cost (£20.32 for a pack of 10) than urine ketone test sticks (£2.50 for a pack of 50). However, blood ketone test strips have a longer shelf-life (12-18 months) compared with urine test sticks (3 months). As individuals with type 1 diabetes are likely to test for ketones on an infrequent basis, it is possible that only a fraction of the ketone testing strips or sticks might be used from a provided container before they have passed their expiry date. This wastage will be greater for urine sticks, which partially offsets the lower unit cost. The GDG considered that companies making test strips should provide a lower number of strips or sticks per container to reduce the risk of wastage. The clinical review showed that blood strip ketone testing rather than urine ketone monitoring during home management of intercurrent illness was associated with a reduced attendance rate to the Emergency Room in individuals with type 1 diabetes. This was considered clinically significant by the GDG and they recognised that allowing adults with type 1 diabetes access to home blood strip ketone monitoring could have substantial cost-saving implications if it resulted in a reduction in hospital admission rates for the management of DKA. The GDG acknowledged that there may be additional cost implications in that individuals would need education from healthcare staff on how to test for blood ketones and how to interpret the result. Presentation to emergency services and hospital monitoring Given the cost of individual blood ketone test strips, the GDG was keen that capillary

	blood testing did not replace the use of urine testing when screening for ketones. This was with the aim of preventing capillary blood ketone testing becoming ubiquitous amongst healthcare professionals even when suspicion of ketosis is low. The biochemistry blood test for ketones assessment costs £1.26 per unit, which is cheaper than capillary blood strip ketone testing. However, the GDG recognised that in clinical practice the laboratory-measured result would be available less readily than capillary blood ketone results when making management decisions for insulin infusion rates in the management of DKA. For the use of capillary blood ketones for inpatient management of DKA, the GDG were presented with the cost of the average length of hospital stay of 3.4 days for the management of DKA (Hospital Episode Statistics 2011-12). The GDG found that provided discharge was safe and would not lead to a recurrence of DKA, capillary blood ketone monitoring would have to reduce length of stay in hospital by more than 0.074 days (or 100 minutes) in order to be cost-saving in comparison to urine ketone monitoring. The GDG observed that one study in the clinical review had shown that switching to a protocol using capillary blood ketone testing in place of urine ketone testing as per the JBDS protocol had reduced length of hospital stay by 1.2 days, and therefore, capillary blood ketone monitoring was likely to be cost-effective for use in the inpatient management of DKA. However, in making its recommendation, the GDG wanted to state explicitly that blood ketone monitoring should only be used as part of an approved protocol for the management of DKA, rather than being used in isolation.
Quality of evidence	Six studies were identified for the review. Only one of the studies was a RCT, and this assessed self-monitoring of ketones at home and its impact on emergency admission rates[430]. The population participating in this study was young (age ≤22 years - a mixture of children, young people and young adults) and therefore, caution was taken in interpreting the results from this study and applying the results to the adult population with type 1 diabetes. The GRADE quality of the study was 'Very low', and the GDG expressed concerns about the effect of the study protocol impacting on the final result. Individuals in the trial underwent training on blood ketone monitoring, and had 24 hour access to advice from a physician, and therefore, may have been better able to manage intercurrent illness for reasons other than just ability to monitor ketonaemia. The study also specifically excluded individuals with a previous history of high admission rates for DKA, who would arguably be the target group for assessing the effectiveness of home ketone monitoring. The other studies for the evidence review were non-comparative observational studies, and therefore, could not be assessed by meta-analysis or GRADE assessment. All five studies assessed the impact of ketone monitoring on inpatient management[46,66,298,610,710]. These studies were given a 'Low quality' rating by the GDG, and therefore, conclusions were drawn with caution when interpreting the data.
Other considerations	Members of the GDG recognised that the most recent national guidance for DKA management (JBDS guidelines) advised the use of capillary blood ketone testing to facilitate management decisions, and that this guidance was being used in hospitals across the country. The GDG recognised that the quality of the available evidence regarding capillary blood ketone testing was low, and that there were no RCT data to support the use of capillary blood ketone strips in the emergency department setting. The GDG therefore made a recommendation that research into whether the use of blood ketone strips improves clinical outcome should be undertaken. Patient members on the GDG expressed a preference for access to capillary blood ketone monitoring over urine ketone monitoring, as it provided a means of testing

	for ketones that was of greater convenience and the evidence suggested that it provided a more accurate result.

12.3.3 Research recommendations

27. In adults with type 1 diabetes, what is the clinical and cost effectiveness (particularly in terms of morbidity, reduction in admission rates, and length of stay) of using blood capillary ketone strips compared to urine ketone strips for the management of DKA?

28. In adults with type 1 diabetes, what is the clinical and cost effectiveness (particularly in terms of morbidity, reduction in admission rates, and length of stay) of using blood capillary ketone strips compared to urine ketone strips for the prevention of DKA?

29. In adults with type 1 diabetes, what is the clinical and cost effectiveness (particularly in terms of pre-empting admissions) of self-monitoring blood ketones compared to urine ketones?

12.4 Management of DKA [2004]

The management of DKA is a topic which has attracted considerable attention over 40 years because it can carry a high fatality risk if suboptimally managed. If optimally managed, the fatality and morbidity rates are very low. The topic is not easily addressed within a general diabetes guideline, being large enough for a guideline of its own. The approach below is to address some broad principles and specific topics of contention, rather than present a detailed protocol.

12.4.1 Evidence statements [2004]

Insulin therapy

Continuous versus intermittent insulin therapy for DKA was evaluated in one small randomised study.[586] Insulin was administered as bolus injections (50 U per 2 hours) compared with continuous insulin infusion (10 U per hour) and low-dose continuous insulin infusion (2 U per hour) with an initial loading dose. To reduce plasma glucose concentrations, continuous infusion is as effective as intermittent insulin therapy at 10 U per hour, with reduction to 5 U per hour when plasma glucose is less than 300 mg/100 ml. DKA recovery rate was significantly reduced following the very low dose continuous infusion regimen (Ib).

Another small study showed that low doses of insulin given by intermittent intramuscular (IM) injection or by constant intravenous (IV) infusion after an initial IV loading dose are similarly effective in controlling DKA.[640] Time to recovery of DKA and total insulin dose required did not differ between the two treatment groups (Ib).

A comparison of different possible routes of insulin delivery in treating DKA showed similar efficacy for IV, IM and subcutaneous administered insulin therapy.[230] No significant differences were seen for the time to metabolic recovery or total insulin dose or fluid replacement requirements. Patients receiving IM insulin were most likely to require an additional insulin loading dose to achieve an adequate initial response. In this report, a significantly higher rate of decrease in glucose and ketone bodies was observed in the first 2 hours following IV insulin, but these differences were not maintained over the rest of the recovery period (Ib).

No significant differences in recovery rates were seen following the administration of human and porcine insulin for the treatment of DKA in a prospective trial with a small study population of people with both type 1 and type 2 diabetes (Ib).[702]

Continuation of insulin administration past the usual cut-off point of near-normoglycaemia versus conventional insulin regimen (rehydration, electrolyte replacement and insulin at 5 U per hour to near-normoglycaemia, that is blood glucose less than or equal to 10 mmol/litre, and then at a reduced rate until clinical recovery) in one small study, significantly increased the resolution of ketosis, measured as duration of elevated blood 3-hydroxybutyrate levels, and acidosis (Ib).[776]

Bicarbonate therapy

IV sodium bicarbonate therapy added to the treatment regimen for DKA was shown in a randomised trial with small sample size to increase recovery of arterial pH and bicarbonate levels in the first 2 hours, but did not effect pCO_2 or blood glucose levels.[248] All patients in the bicarbonate group developed hypokalaemia (Ib).

One study compared the effect of two different IV bicarbonate doses (adjusted to initial arterial pH) on the recovery rate of DKA, with placebo.[514] No significant differences were seen between the groups treated with bicarbonate or placebo (Ib).

In agreement with these studies, one small trial showed that IV bicarbonate therapy had no additional beneficial effect when compared with standard DKA therapy without bicarbonate supplementation (IIa).[756]

No significant differences were seen after the addition of phosphate therapy to treatment for DKA in a small trial.[229] A protective effect against hypophosphataemia was seen following phosphate treatment compared with placebo, but only on the first day of treatment (Ib).

An additional paper also reported no evidence of clinical benefit of phosphate therapy compared with placebo (Ib).[781]

Somatostatin therapy

One small study concluded that addition of the somatostatin analogue, octreotide, to low-dose insulin therapy reduced the time taken for correction of ketonuria.[794] However, no such effect was seen on the recovery rate of hyperglycaemia and acidosis (Ib).

12.4.2 Health economic evidence [2004]

The health economic searches found only one US-based costing study.[373] As such, no specific health economic guidance can be provided here.

12.4.3 Considerations [2004]

DKA management was noted to be based on a mixture of types of evidence, pathological, pharmacokinetic, clinical outcomes, cohorts and trials.

It was noted that DKA management is:

- quite detailed
- often performed under the supervision of diverse groups of specialists
- dependent on careful monitoring if catastrophic outcome is to be avoided

There was broad consensus on issues of management, which largely seem to revolve around ameliorating the acidosis and hyperglycaemia without inducing the possibly fatal complications of cerebral oedema, hypokalaemia or aspiration pneumonia. Moderation in the speed and methods of

correcting dehydration, hyperglycaemia and ketosis is combined with a high intensity of the monitoring of the changing condition of the patient.

The group noted that there was no evidence at all for the use of bicarbonate in any situation, and that the consensus recommendations for its use below a pH of 6.9 were poorly grounded in either clinical experience or any kind of evidence.

The group noted that the nature of insulin pharmacokinetics and pharmacodynamics suggested that the detailed studies of ways of starting insulin infusions had no logical basis.

Clinical experience of management in adults suggested that acute respiratory distress syndrome ('fluid on the lung') was seen not infrequently in addition to cerebral oedema. While the evidence that either of these could be ameliorated by using lower rates of saline replacement was not good, nor was there any impression that in the non-shocked patients such lower rates were harmful. Accordingly they are recommended.

Members of the group had seen examples of glucose concentration escape after reaching near-normal glucose levels, and felt that the evidence-based lesson of the Belfast paper (that these insulin-resistant patients require continued administration of higher rates of insulin than other patients on insulin infusions) was worth noting.[776]

12.5 Recommendations [2004]

The current guideline recommendations can be found at

https://www.nice.org.uk/guidance/ng17

13 Associated illness [2004]

13.1 Introduction

This chapter was a section of the 'Management of Late Complications' chapter in the 2004 guideline CG15. It has been moved to a separate chapter to separate associated illnesses from complications.The 2015 GDG did not update associated illness; 2004 evidence is reproduced verbatim in this chapter.

13.2 Rationale [2004]

Type 1 diabetes is an auto-immune disease associated with genes which modulate the immune response. Other auto-immune diseases are similarly associated, and manifestation of some of them can be sub-clinical while interacting with aspects of food absorption or metabolism. The evidence for routine screening for thyroid dysfunction was reviewed in 2015; recommendations concerning screening for other autoimmune conditions (Addison's disease, pernicious anaemia, premature ovarian failure) has not been reviewed or updated from 2004.

13.3 Evidence statements [2004]

Latent pernicious anaemia

Using a microbiological method to measure cobalamin concentration, one study from Australia found reduced cobalamin concentration in six out of 371 people with type 1 diabetes.[168,170] Four of the patients showed no clinical signs of pernicious anaemia, the fifth was mildly anaemic and the sixth patient was not available for further testing. This medium-sized study with methodological limitations gave a prevalence of latent pernicious anaemia of 11 per 1000 in people with type 1 diabetes (III).

Prevalence of coeliac disease

Using immunoglobulin A (IgA) class anti-endomysial antibodies (EmAb) detected by immunofluorescence (test) and histological confirmation of coeliac disease by small intestinal biopsy partial or total villous atrophy, a medium-sized study showed in an unselected sample at an outpatients clinic that the prevalence of coeliac disease in the sampled population was 6.4% and that EmA were highly predictive of the presence of coeliac disease on biopsy (DS).[711]

A larger study, but with potential methodological limitations, found that in a two-step screening process of anti-gliadin antibodies (GA) detected by enzyme-linked immunosorbent assay (ELISA) assay and IgA class EmAb detected by immunofluorescence, the predictive value of GA was moderate, with a high false-positive rate for IgA-GA.[686,687] Prevalence of coeliac disease in type 1 diabetes to be up to 2.6% and that after 30 years diabetes duration, the prevalence of coeliac disease was >6%. The study also found that EmAb were highly predictive of the presence of coeliac disease on biopsy (DS).

The frequency of coeliac disease-specific serologic markers and the prevalence of coeliac disease in families of patients with type 1 diabetes were evaluated in a medium-sized study using a two-step screening process.[486] The screening programme included circulating islet cell antibodies (ICA), anti-glutamic acid decarboxylase antibodies and GA, and then IgA class EmAb detected by immunofluorescence. This study found the prevalence of biopsy-proven coeliac disease to be 1.3% among patients with type 1 diabetes and zero among controls, or family. Of screening assays, only EmAb were highly predictive of the presence of coeliac disease (DS).

Another diagnostic study using IgA class EmAb compared people with type 1 diabetes with adults with coeliac disease as true positives (as determined by intestinal biopsy) and controls (healthy and diseased) as true negatives (as determined by intestinal biopsy).[649] The prevalence of biopsy-proven coeliac disease among adults with type 1 diabetes was 3.13%. This study showed IgA class EmAb had high specificity in detecting coeliac disease in people with type 1 diabetes (DS).

Red cell distribution width

Using red cell distribution width (RDW) as a screening test against EmAb and diagnostic duodenal biopsy as reference tests for coeliac disease one very small, methodologically-limited study demonstrated the poor specificity of RDW in predicting coeliac disease in people with type 1 diabetes.[375,376] Given the potential methodological limitations, this evidence was not used to support any recommendations in this area (DS).

13.4 Health economic evidence [2004]

The health economic searches found no relevant papers for the treatment of those with type 1 diabetes suffering from concurrent disease.

13.5 Considerations [2004]

While auto-immune conditions are probably more common in people with type 1 diabetes than in the general population, the group did not feel that this should lead to any formal system of surveillance for the development of such conditions.

13.6 Recommendations

The current guideline recommendations can be found at

https://www.nice.org.uk/guidance/ng17

14 Arterial risk control

This section was updated in 2015.

The 2015 GDG updated the evidence for aspirin for the primary prevention of cardiovascular disease.All other aspects of this chapter are the work of the 2004 GDG and were not updated.

14.1 Aspirin for the primary prevention of cardiovascular disease [2015]

14.1.1 Introduction [2015]

Type 1 diabetes substantially increases the risk of a cardiovascular (CV) event. Although recent data show that absolute CV mortality rate has fallen in recent years, the age-adjusted incidence rate ratio remains elevated at 2.3 for men and 3.0 for women.[464] CV disease is the commonest cause of death in people with type 1 diabetes over the age of 40 years and regular assessment and active management of each individual's CV risk is essential.

Although good management of CV risk in type 1 diabetes is imperative, updating the 2004 sections of this chapter for the 2015 version was not prioritised (with one exception).This does not reflect the importance of the topic, rather the fact that several of the original questions have been updated by other pieces of NICE guidance. In the section "Interventions to reduce risk and to manage CVD", the evidence and recommendations on lipid-lowering measures have been reviewed and new guidance published as CG181 'Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease'. Evidence pertinent to people with type 1 diabetes was considered separately by the GDG developing CG181, where available, and the relevant recommendations have therefore been taken to replace those from the 2004 type 1 diabetes guideline. Similarly, the evidence on blood pressure management has been updated for people with type 1 diabetes and renal impairment in CG182 "Chronic kidney disease: early identification and management of chronic kidney disease in adults in primary and secondary care", and the relevant recommendations replace those from 2004 for people with type 1 diabetes.

The only review question addressed by the 2015 type 1 diabetes GDG refers to the role of aspirin as a primary preventative agent. Low-dose aspirin (75-600 mg per day) has been shown to reduce the incidence of CV disease in people at high risk for other reasons, particularly if they have had a previous event.[40] However, its consumption is associated with an increased risk of haemorrhage and some of the data supporting its use come from the pre-statin era. In the non-diabetic population, the therapeutic ratio is such that aspirin is only recommended as secondary prevention. Because of the high risk of CV disease in the type 1 diabetes population, it is important to assess the potential benefit of aspirin for primary prevention in this population specifically, and to review the risk:benefit ratio.

The updated review question in this chapter is:

- In adults with type 1 diabetes, is aspirin an effective anti-platelet agent for the primary prevention of cardiovascular events?

The evidence and text from the previous guideline, CG15, that has been superseded by this update is in Appendix S.

14.1.2 Updated review question: In adults with type 1 diabetes, is aspirin an effective anti-platelet agent for the primary prevention of cardiovascular events?

For full details see review protocol in Appendix C.

Table 100: PICO characteristics of review question

Population	Adults with type 1 diabetes
Intervention/s	Aspirin
Comparison/s	• Placebo • Usual care/no intervention • Low-dose versus high-dose
Outcomes	• Mortality – all-cause (dichotomous/time-to event) • Mortality – CV (dichotomous/time-to event) • MI – all-cause (dichotomous/time-to event) • MI – fatal (dichotomous/time-to event) • MI – non-fatal (dichotomous/time-to event) • Stroke – all-cause (dichotomous/time-to event) • Stroke – fatal (dichotomous/time-to event) • Stroke – non-fatal (dichotomous/time-to event) • Quality of life – measured by SF-36, DQoL, DSQoL (continuous) • Adverse events – bleeding or gastrointestinal complications (dichotomous) • HbA1c(continuous) • Hypoglycaemia - preferably severe hypoglycaemia if reported (dichotomous or continuous outcome, depending how it is reported)
Study design	Randomised controlled trials (RCTs)

14.1.2.1 Clinical evidence

We searched for randomised trials comparing the effectiveness of aspirin versus placebo or usual care as a prophylactic treatment with the aim of preventing the development of CV events in adults with type 1 diabetes.

Two studies were included in the review (Hansen 2000[294] and ETDRS 1997[212]). Evidence from the included studies are summarised in the clinical GRADE evidence in Appendix I. See also the study selection flow chart in Appendix D, forest plots in Appendix J, study evidence tables in Appendix Gand exclusion list in Appendix K.

Due to the scarcity of relevant studies found in the electronic literature search, a hand search of the literature was also conducted, based on references to studies, meta-analyses and guidelines that were referred to in the original NICE 2004 guideline (CG15)[529], and the SIGN diabetes guideline (2010)[668]. All studies referred to in these documents (apart from Hansen 2000[294] and ETDRS 1997[212]) were excluded from this review because they looked at the wrong populations – they were either type 2 diabetes, mixed population with no type 1 diabetes subgroup analysis, or did not have diabetes.

Because very few studies were found to answer this question, and our review sought to assess the impact of aspirin on the **primary** prevention of CV events in adults with type 1 diabetes, we decided to contact the authors of the large ETDRS study, in order to obtain specific data for type 1 diabetes adults who had no documented history of a CV event (that is, aspirin used for primary prevention of CV events). The original ETDRS study had looked at the efficacy of aspirin for both primary and secondary prevention, in a combined population of type 1 diabetes and type 2 diabetes. The authors supplied us with unpublished data[213] for the subpopulation of type 1 diabetes adults who had not previously had any CV events, and these data have been included in the review (for the outcomes they provided us– CV events, CV mortality, MI and stroke). However, for the outcomes of all-cause mortality and life-table 5-year results, we have used the data provided in the published paper (based on a mixed population of type 1 diabetes adults with and without a history of CV events – that is,

both primary and secondary prevention). These data have therefore been downgraded in GRADE for indirectness.

Table 101: Summary of studies included in the review

Study	Intervention/ comparison	Population	Follow-up	Outcomes	Comments
ETDRS 1992[212,213]	Aspirin (650 mg) vs. placebo	n=1393 (unpublished data) or n=1130 (published data)[a] type 1 diabetes with diabetic retinopathy; 25% had proliferative retinopathy, 49% had a history of CV disease or previous CV event§	5 years follow-up (average)	• Mortality (all-cause) • Mortality (CV) • MI (fatal/non-fatal) • Stroke (fatal/non-fatal)	HIGH-DOSE ASPIRIN
HANSEN 2000[294]	Aspirin (150 mg) vs. placebo	n=16 type 1 diabetes with persistent low-level (micro) albuminuria; 41% had proliferative retinopathy	4 weeks treatment 6 months follow-up	• HbA1c • Dyspepsia • Adverse events	LOW-DOSE ASPIRIN

(a) The ETDRS study population consisted of both type 1 diabetes and type 2 diabetes adults, who had previous CV events (that is, secondary prevention) or no previous CV event (that is, primary prevention). Data included for this review were taken from the published paper and some of the outcomes were provided to us by the study authors. The data from the study authors is specifically for the population relevant to this review (type 1 diabetes adults who did not have a previous CV event - that is, primary prevention).

(b) History of CV disease was defined as history of any of the following: coronary artery disease, congestive heart failure, MI or intermittent claudication. Patients reporting any of the following drug use were also considered to have CV disease history: long-term antianginal agents, beta-blockers, vasodilators, digitalis, antiarrhythmic agents, diuretics or other antihypertensive agents. Patients with a systolic blood pressure of more than or equal to 160 mmHg were also considered to have CV disease history.

Outcomes

In keepingwith the small number of published studies included, no suitable conference abstracts were found.

There were no data reported in any of the studies for the following outcomes:

- quality of life
- hypoglycaemia

Table 102: Clinical evidence summary: Aspirin versus placebo (less than or equal to 6 months)

Outcomes	No. of studies	Imprecision	GRADE rating	Absolute difference Aspirin	Control event rate (per 1000 patients) Placebo
HbA1c	1 study (n=17)	Very serious	VERY LOW	MD 0.1 lower (0.67 lower to 0.47 higher)	8.5 final value in control group
Dyspepsia	1 study (n=17)	Very serious	VERY LOW	40 more per 1000 (from 230 fewer to 1000 more)	333
Adverse events	1 study (n=17)	Very serious	VERY LOW	Not reported and not estimable – study indicates there was no difference between groups	

Table 103: Clinical evidence summary: Aspirin versus placebo (more than 6 months)

Outcomes	No. of studies	Imprecision	GRADE rating	Absolute difference Aspirin	Control event rate (per 1000 patients) Placebo
Mortality (all-cause)	1 study (n=1130)	Serious	MODERATE	16 fewer per 1000 (from 36 fewer to 14 more)	68
Mortality (CV)	1 study (n=1393)	Very serious	LOW	10 fewer per 1000 (from 26 fewer to 17 more)	56
CV events	1 study (n=1393)	Very serious	LOW	10 fewer per 1000 (from 33 fewer to 23 more)	90
MI (fatal and non-fatal)	1 study (n=1393)	Serious	MODERATE	14 fewer per 1000 (from 32 fewer to 14 more)	68
Stroke (fatal and non-fatal)	1 study (n=1130)	Very serious	LOW	7 more per 1000 (from 6 fewer to 33 more)	18

14.1.2.2 Economic evidence [2015]

Published literature

No relevant economic evaluations comparing the relevant interventions were identified, either in this update or in the original guideline.

Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided below to aid consideration of cost effectiveness.

Table 104: Unit costs

Drug	Dose	Cost	Pack size	Cost per tablet
Aspirin	75 mg	76p	28	3p
Aspirin	300 mg	31p	32	1p

Source: BNF64[378]

Table 105: Cost of cardiovascular-related complications

	At Time of Event		Annual thereafter
Complication	Fatal	Non-Fatal	
Ischaemic heart disease	-	£3,337	£1,103
MI	£1,690	£6,434	£1,060
Heart failure	£3,721	£3,721	£1,304
Stroke	£4,963	£3,936	£744

Source: Waugh N, Cummins E, Royle P, Clar C, Marien M, et al. *Newer agents for blood glucose control in type 2 diabetes: systematic review and economic evaluation. Health Technol Assess 2010;14(36)*[764].

Note: *Updated to 2010/11 prices using PSSRU 2011*[158]

Table 6: Pooled average cost of gastrointestinal bleeds

Group	Average cost	Lower quartile	Upper quartile
Elective			
Elective inpatient	£1,694	£709	£2,060
Elective excess bed days	£243	£170	£301
Non-elective			
Non-elective inpatient	£2,313	£1,683	£2,625
Non-elective excess bed days (long stay)	£220	£172	£264
Non-elective excess bed days (short stay)	£455	£308	£527

Source: *NHS Reference Costs*[177]

14.1.3 Evidence statements [2015]

Clinical

Aspirin versus placebo (less than or equal to 6 months)

Very low quality evidence from one study showed no clinical difference for:

- HbA1c (n=17)
- dyspepsia (n=17)

In the case of HbA1c, the direction of the estimate of effect favoured aspirin, whereas for dyspepsia, it favoured placebo.

Very low quality evidence from one study showed no difference[b] for:

- adverse events (n=17)

Aspirin versus placebo (more than 6 months)

Evidence from one study showed no clinical difference for:

- mortality – all-cause (Moderate quality evidence; n=1130)
- mortality - CV (Low quality evidence; n=1393)
- CV events (Low quality evidence, n=1393)
- MI – fatal and non-fatal (Moderate quality evidence; n=1393)
- stroke – fatal and non-fatal (Low quality evidence; n=1130)

In the cases of mortality (both all-cause and CV), CV events and MI, the direction of the estimate of effect favoured aspirin, whereas for stroke, it favoured placebo.

Economic

No relevant economic evaluations were identified.

14.1.4 Recommendations and link to evidence

The current guideline recommendations can be found at

https://www.nice.org.uk/guidance/ng17

Relative values of different outcomes	The important (critical) outcomes are mortality and CV events. The GDG also felt that adverse events, particularly those affecting the gastrointestinal tract (for example, dyspepsia and bleeding), were important and had to be taken into consideration when balancing the benefits and harms of aspirin. The outcomes of HBA_{1c} and hypoglycaemia are less important for this question, although it is appropriate to consider whether they are affected by aspirin.
Trade-off between clinical benefits and harms	The GDG was interested in balancing the prevalence of dyspepsia and gastrointestinal bleeding against any reduction in CV events. There was a paucity of studies in people with type 1 diabetes. Within the data available, there was little

b *Data required for calculating clinical difference or direction of effect was not reported, so this is based on statistical difference.*

	robust evidence from the type 1 diabetes population to suggest either benefit or harm from the therapy; all the 95% Confidence Intervals crossed the line of no difference, and when looking at the clinical importance of the effect sizes based on the absolute differences, none of the outcomes showed a clinically important effect. In addition to looking at type 1 diabetes-specific evidence, the GDG considered the data from the general population because, although the risk of a CV event is much higher in a person with type 1 diabetes than in those without diabetes, there is no obvious reason why people with type 1 diabetes should respond differently to the beneficial or harmful effects of aspirin in primary prevention. The GDG noted thatcurrent guidance from the MHRA[502] suggests that the harms of aspirin for primary prevention outweigh the benefits. It was also decided to contact authors of studies that had been initially excluded in the review because they were of a mixed type 1 diabetes and type 2 diabetes population, to request data for the type 1 diabetes subpopulation. None of these authors responded with any additional data. We also contacted the authors of the ETDRS study, because this study looked at the effects of aspirin for both primary and secondary prevention, and the authors provided some primary prevention-specific data which showed no clinical benefit of aspirin in reducing/preventing CV mortality, CV events or MI in adults with type 1 diabetes at an average of 5 years follow-up.
Economic considerations	No economic evidence was found. The GDG considered the low cost of aspirin and its potential side effects vs. the high cost of CV complications. Due to the low costs involved in treatment with aspirin, the clinically effective option is likely to be the cost effective one. Since the clinical data showed that there was no clinical benefit of aspirin for reducing/preventing CV mortality, CV events and MI in adults with type 1 diabetes at an average of 5 years follow-up, the GDG did not consider the use of aspirin to be cost-effective for primary prevention in adults with type 1 diabetes.
Quality of evidence	The evidence quality was considered as Very low for the ≤6 months data (based on the Hansen 2000 study) because there was very serious imprecision and the study design had a number of methodological flaws. The outcomes at >6 months were rated as Moderate to Low (based on the ETDRS study), because, although the study design was considered to be robust, the imprecision varied from serious to very serious. The main published ETDRS study also included a mixture of people who had previous CV events as well as those who had not, and so was considered both primary and secondary prevention. This was therefore downgraded for indirectness. However, for some of the outcomes in our review (CV events, CV mortality, MI and stroke), we were able to obtain unpublished data from the authors, which was for people with type 1 diabetes who had no previous history of CV disease (that is, the primary prevention data). This was therefore considered as more robust and relevant evidence, and was not downgraded for indirectness.
Other considerations	None.

14.1.5 Research recommendations

30. In adults with type 1 diabetes, what is the clinical and cost effectiveness of aspirin and other anti-platelet agents who are at high risk for vascular disease (for example, smokers, those with renal disease, those with other evidence of vascular disease)?

14.2 Identification of arterial risk [2004]

14.2.1 Rationale [2004]

People with type 1 diabetes are generally recognized to be at greatly increased risk of arterial disease (CVD) in middle age. While the literature on arterial risk factors and markers in the general population is large, it would not appear to follow that the findings can be simply carried over to people with type 1 diabetes. Similarly, the tools used to quantify arterial risk in the general population are known not to work well in people with type 2 diabetes, and seem even less likely to be valid in type 1 diabetes.

14.2.2 Evidence statements [2004]

Arterial risk factors

The Scottish Intercollegiate guidelines identify specific risk factors for CVD, such as cigarette smoking, dyslipidaemia, hypertension, hyperglycaemia, obesity and microalbuminuria (**IV**).[668]

The guideline reports on non-randomised studies showing that smoking is an independent arterial risk factor in people with diabetes.[668] Additional observational studies reported dyslipidaemia. An increased concentration of LDL cholesterol or total cholesterol has also been identified as an independent risk factor for arterial morbidity and mortality, and each 1.0 mmol/litre reduction of LDL cholesterol represents a 36% reduction in the risk of CVD (**IIa**).

Two controlled but not randomised studies reported within the guideline demonstrated the positive relationship between hypertension and risk of arterial death, with a progressive increase in risk with rising systolic pressure.[668] Each 10 mmHg reduction in systolic pressure is associated with a 15% (95% CI, 12 to 18) reduction in risk of arterial death over 10 years (**IIa**).

The link between glycaemia and arterial morbidity and mortality was also reported in two studies reviewed in the SIGN guideline 174. In one study, each 1.0% reduction in HbA1c was associated with a 21% (95% CI, 15 to 27) reduction in the risk of diabetes-related death and a 14% reduction for myocardial infarction (MI) over 10 years. (**IIa**)

Evidence for the other risk factors is sparse. In the SIGN guidelines, no studies were identified for linking obesity as an independent risk factor in established diabetes.[668] One observational study reported microalbuminuria as an independent marker associated with doubling in arterial risk, but, there is insufficient evidence to determine whether reducing albumin excretion rate specifically reduces arterial morbidity or mortality. (**IIa**)

A meta-analysis aimed at defining risk factors for CVD from studies in people with diabetes showed that, adjusted for age, both total mortality and death from all vascular causes increased significantly with total cholesterol level and systolic blood pressure, and decreased with the percentage of women.[385] Duration of diabetes and mean HbA1c were not considered to be associated with mortality. However, this meta-analysis did not contain a critical appraisal of included studies or details of approaches used to ensure study quality before inclusions and should, therefore, not be used as the basis for clinical recommendations. (**IIa**)

Screening tests

One systematic review examined 67 studies, addressing both screening for the primary detection of arterial risk factors and treatment of lipid abnormalities in asymptomatic people both with and without diabetes.[585] Reliability and effectiveness of each screening strategy for identifying lipid

disorders was investigated, and showed that total cholesterol measurements generally have good reliability, with an analytic variability of less than or equal to 3% and a mean total biologic variability of the order of 6%. A total cholesterol level within 10% of the true value can be determined with two separate measurements, which do not differ significantly between fasting or non-fasting venous blood. (**III**)

Evidence within this systematic review 176 for HDL cholesterol showed a higher analytical (6%) and biological (7.5%) variation than total cholesterol, however, two or three values were required to estimate true HDL cholesterol levels to within 10% to 15%. Variations were also found between non-fasting and fasting blood samples as HDL cholesterol is 5% to 10% lower in the non-fasting state, suggesting that non-fasting measurements may slightly overestimate coronary heart disease risk, but not enough to make accuracy of screening unacceptable. (**III**)

Additional studies within this systematic review considered triglyceride screening. Values measured varied by 20 to 30% between fasting and non-fasting states.[585] LDL cholesterol is calculated from total and HDL cholesterol, as well as triglyceride measurements and application of the Friedewald equation. However, this equation has been found to be inaccurate at triglyceride levels greater than or equal to 4.5 mmol/litre when special techniques must be employed (for example, ultracentrifugation). (**III**)

Also considered in this systematic review was the comparable accuracy of total and HDL cholesterol from capillary blood samples.[585] These were found to be less reliable without proper attention to calibration and proper testing techniques. One study found that a Framingham-based coronary risk model was the best predictor of ischaemic heart diseasemortality. Guidelines reported in the review concluded that the LDL:HDL cholesterol and the total:HDL cholesterol ratios performed equally well in determining arterial outcomes, and the least accurate screening test was that of measuring total cholesterol alone. (**III**)

Other studies included in this review assessing characteristics of the screening tests showed that the non-fasting total cholesterol alone is the easiest to perform for the patient and provider.[585] The total:HDL cholesterol ratio is easy for patients to obtain and for providers to interpret and performs equally accurately as the LDL:HDL cholesterol ratio strategy. However, one study in the review demonstrated that risk-based algorithms, which directly incorporate age, other risk factors and measures of total and HDL cholesterol, are the most accurate approach to screening. These processes are difficult to access and so supplemental tables, such as the Sheffield table, can improve the feasibility of a risk-based strategy. (**III**)

There was no evidence from this systematic review to inform the question of appropriate frequency of screening.[585] National guidelines recommend a 5-year interval for people with previous normal results and more frequent screening in those with borderline values. (**IV**)

Prediction of arterial risk

Six studies all published by the same group addressed the relative specificity and sensitivity of the different methods for predicting arterial risk (Sheffield, modified Sheffield, Joint British Guidelines, Canadian, Framingham categorical, New Zealand and Joint European guidelines, but not including the UKPDS risk engine).

One study comparing the Sheffield tables with the computer-calculated Framingham equation revealed a low sensitivity and specificity for the Sheffield tables (35% [95% CI, 28 to 42] and 98% [95% CI, 97 to 99], respectively).[63] The old tables only included patients with a systolic blood pressure of less than 160 mmHg, and a cholesterol greater than 5.5 mmol/litre. Adopting these exclusion criteria led to a substantial reduction in the number of patients eligible for screening without improving detection of risk assessment. (**DS**)

Another evaluation[249] studied all seven guidelines against the calculated Framingham equation in 906 people with diabetes, showing that Modified Sheffield tables have higher sensitivity (95% versus 37%) with a slight reduction in specificity (90% versus 97%) compared with the original tables, with a slightly better positive predictive value than the original version (80% versus 71%). The Joint British tables have good specificity (99%), but low sensitivity (77%). However, the tables perform well at the lower CHD risk of greater than or equal to 15% over 10 years (specificity, 92%; sensitivity, 96%). Canadian tables perform poorly at more than or equal to 30% risk, and only slightly better at the greater than or equal to 15% level of risk (specificity, 100%; sensitivity, 5%; and 85% and 98%, respectively). The Framingham categorical tables have a lower specificity (83%) for the identification of high-risk individuals (although risk is greater than or equal to 27%, not greater than or equal to 30%) and this deteriorates for identification of those at more than or equal to 15% risk (specificity, 77%). New Zealand tables had a sensitivity of 69% and specificity of 88% at a greater than or equal to 20% level of risk. At the more than or equal to 10% level of risk, specificity deteriorates to 58%. The Joint European tables have a sensitivity of 89% for risk levels greater than or equal to 20%, but specificity of only 71%. This means that 1 in 4 patients would be incorrectly identified as having a risk above the 20% threshold. (**DS**)

A further study from the same investigators assessed the PROCAM programme against that of the Framingham equation.[250] Only 56% of the study population were eligible for evaluation with PROCAM. This evaluation also systematically underestimates risk in comparison with the Framingham equation at low levels of absolute risk, but overestimates at higher risk levels. (**DS**)

The sensitivity and specificity of various risk prediction tables and charts was also investigated in one comparative study.[380] Compared with the Framingham equation, the Sheffield tables had a low sensitivity (40% eligible for cholesterol-lowering treatment would be identified), but with high specificity and thus, low false-positive rates. The New Zealand tables had similar sensitivities and specificities to the Sheffield tables, but a 10% level of risk prediction of 5-year CVD risk threshold specificity is significantly lower than the Sheffield tables. The European tables have better sensitivity than the Sheffield and New Zealand tables, but specificity is significantly worse than other risk assessment levels leading to an equally low sensitivity. The joint British Societies table has significantly better specificities at greater than or equal to 15% and greater than or equal to 30% 10-year CHD risk than the modified Sheffield tables. Sensitivity is generally low, but high at the 15% 10-year CHD/10% five-year CVD risk level. Canadian tables are not reliable at greater than or equal to 30% risk, but are comparable with the modified Sheffield tables at 154% risk threshold. The Framingham equation had the best performance with sensitivity and specificity comparable to that of the modified Sheffield and joint British Society methods, respectively. (**DS**)

14.2.3 Consideration

The Group recognised the very considerable difficulties in reaching conclusions from the evidence in this area. Very little direct information pertaining to people with type 1 diabetes can be ascertained, whilst the importance of the issue is emphasized by the very high early CVD risk run by people with type 1 diabetes. Nevertheless, certain subgroups are known to be at particularly high risk (people with raised urinary albumin excretion), while others combine type 1 diabetes with combinations of classic risk factors typical of the metabolic syndrome and known to be predictors of high arterial risk in people with type 2 diabetes and indeed non-diabetic populations. A further group of people will combine type 1 diabetes with a single arterial risk factor or risk marker, while others will have type 1 diabetes but appear low risk otherwise.

Accordingly, the important factors for surveillance are markers of urinary albumin excretion (most important), other classical risk factors, including full lipid profile, and risk markers, such as age, family history, and some ethnic groups. In accordance with the principle of unified organization of care, monitoring of these factors annually is to be recommended, but it was recognized that in low-risk

individuals, technology might become capable of programming longer review intervals for serum lipids.

The group recognized that different ways of using information from a full lipid profile (calculated LDL and HDL separately, calculation of total cholesterol:HDL ratio and calculation of non-HDL cholesterol) are in use. While the group preferred the first of these, as not mixing lipid abnormalities of different pathogenesis and being a better route to using the treatments for different lipid disorders rationally, it was recognized that there was not good evidence to suggest supporting one approach over the others.

The group could find no confidence in any risk table, engine or equation when applied to people with type 1 diabetes.

14.2.4 Recommendations [2004]

The current guideline recommendations can be found at

https://www.nice.org.uk/guidance/ng17

14.3 Interventions to reduce risk and to manage arterial disease [2004]

14.3.1 Rationale [2004]

Prevention of arterial risk in people with type 1 diabetes, through attention to blood glucose control (insulin therapy, patient education, nutrition and self-monitoring) is considered elsewhere in this guideline, and blood pressure management is considered in Section 14.4, below. However, in the general population (at much lower risk) and in people with type 2 diabetes, other therapies are known to reduce the risk of arterial events. Therefore, the current section deals with these approaches as applied to people with type 1 diabetes.

14.3.2 Evidence statements [2004]

Lipid-lowering therapy

The Scottish intercollegiate guidelines identify a role for lipid-lowering drugs in reducing ischaemic heart disease events, but not all-cause mortality in people with no known CVD, compared with placebo (Ia).[668]

SIGN guidelines on lipids and the prevention of ischaemic heart disease detail studies targeted at people with type 2 diabetes.[665] However, secondary prevention trials of lipids reported in the guideline have shown significant reduction in CVD in both type 1 and type 2 diabetes. These guidelines recommend the loss of weight, reduction of intake of saturated fat, increased consumption of fruit and vegetables, regular exercise and the introduction of a lipid-lowering drug treatment for primary prevention of arterial problems in high-risk people with diabetes. The guidelines also report a study raising concern about underestimating diabetic ischaemic heart disease risk, particularly in people with type 1 diabetes (Ia).

The SIGN guidelines report on a number of therapeutic studies.[668] The CARE study demonstrated a significant reduction in coronary events with pravastatin versus placebo, although, the magnitude of effect was lower than in the 4S study. The LIPID study also showed a trend to reduction in recurrent coronary events, but the numbers of people with diabetes in this study were too low to demonstrate statistical significance. The VA-HIT study showed significant secondary prevention of coronary events

in men with diabetes aged less than 74 years, taking a fibrate (gemfibrozil) for a mean follow-up of 5.1 years (Ia).

Three RCTs reported on the positive effect of pravastatin on arterial outcomes in people with diabetes.[269,604,634] One study reported a significant change in total and LDL cholesterol, HDL cholesterol and triglycerides versus placebo.[634] After 24 weeks, the reduction in total cholesterol from baseline was 22%, LDL cholesterol 26%, and triglycerides decreased by 2%, accompanied by an increase in HDL cholesterol of 14%. Pravastatin was well tolerated throughout the study (Ib).

Similar results were seen in the further two trials. One study reported reductions in LDL cholesterol and VLDL cholesterol of 30% and 13%, respectively, with pravastatin compared with placebo, and significant increases in HDL cholesterol at 8 and 16 weeks.[604] The final study was in a majority of sulfonylurea-treated people with type 2 diabetes, and pravastatin reduced total and LDL cholesterol by 19% and 27%, respectively, in the diabetes group.[269] Compared with placebo, pravastatin caused a 13% decrease in triglycerides and a 4% increase in HDL cholesterol in people with diabetes. Results were similar to those in people without diabetes, and were unaffected by adjustment for age and gender (Ib).

The SIGN management of CVD in diabetes guidelines[668] cite results from the Scandinavian Simvastan study, which contained 204 people with diabetes (of a study population of 4444), and demonstrated that cholesterol-lowering therapy was highly effective compared with placebo in those undergoing revascularisation procedures, especially in those with diabetes (risk reduction 55% versus 32% in non-diabetes) (Ia).

Two RCTs reported the effect of simvastatin in people with diabetes. Total and LDL cholesterol levels and the ratio between LDL and HDL cholesterol were decreased following treatment in one study of 25 people with diabetes, whereas no difference was seen following placebo; no between group comparison was made.[648] The second study, containing 26 people with type 1 diabetes, also reported a significant reduction in the plasma concentrations of total cholesterol, LDL cholesterol and apolipoprotein B after 12 weeks of simvastatin treatment, whereas no changes were observed after placebo treatment (Ib).[345]

One study reported the effect of bezafibrate on arterial outcomes in 36 people with type 1 diabetes.[782] However, there are some potential methodological limitations in this study, which does not make this evidence a reliable basis for a clinical recommendation (Ib).

Antiplatelet therapy as secondary prevention [2004]

The North of England guidelines on aspirin for the secondary prophylaxis of vascular disease in primary care reported a pooled risk ratio by combining the meta-analysis of the Antiplatelet Collaborative Group with trials published after 1990 to establish the impact of antiplatelet therapy on subsequent MI, stroke and vascular death.[542] This provided strong evidence for a general protective effect of aspirin as antiplatelet therapy in patients at raised vascular risk. Few studies were found containing comparisons of aspirin and alternative antiplatelet agents to enable comparison of their relative effectiveness (Ia).

For evidence relating specifically to people with diabetes the North of England guidelines identified 8 trials contributing to an overall estimate of risk difference for arterial morbidity of 1.2% with aspirin compared with placebo or other antiplatelet agent.[542] These trials were homogeneous with a pooled incidence rate difference (by random effects model) of a 0.3% reduction in the risk of MI, stroke or vascular death from antiplatelet therapy for 1 year. This is not a statistically significant difference, and in summary, authors state that aspirin given to patients with diabetes appears to have a small and statistically uncertain effect upon the risk of experiencing a subsequent vascular event. They also suggest that the similar relative risk for MI, stroke and vascular death found in diabetes trials and

other trials of patients at raised vascular risk, indicates that patients with diabetes alongside other indications of vascular risk are likely to benefit from routine aspirin therapy (Ia).

American Diabetes Association guidelines indicate that meta-analysis and large-scale collaborative trials in men and women with diabetes support the view that low-dose aspirin therapy should be prescribed as a secondary prevention strategy if no contraindications exist.[29] The guidelines also point to substantial evidence suggesting that low-dose aspirin therapy should be used as a primary prevention strategy in men and women with diabetes who are at a high risk for arterial events.

The meta-analysis of 145 prospective controlled trials of antiplatelet therapy by the Antiplatelet Trialists Group reported in the ADA guidelines showed a trend toward increased risk reductions with doses of aspirin of ≤325 mg per day, but the difference was not statistically significant.[29] An estimated 38±12 vascular events per 1000 patients with type 1 diabetes would have been prevented if they were treated with aspirin as a secondary prevention strategy (Ia).

The ADA guidelines also reported on the HOT study, which showed a reduction in arterial events following aspirin therapy compared with placebo of 15% and a 36% reduction in MI.[29] This study also showed that fatal bleeding, including intracerebral bleeding, were equal in the aspirin and control groups, whereas non-fatal minor bleeding episodes were more frequent in patients receiving aspirin. The US Physicians Health study reported in the same guideline compared aspirin (325 mg per day) with placebo in male physicians (without diabetes), resulting in a 44% risk reduction in MI among the treated group. In a subgroup of people with diabetes, there was a reduction in MI from 10% to 4%, yielding a relative risk of 0.39 for men with diabetes randomised to aspirin therapy (Ia).

The ADA guidelines also addressed the safety of aspirin use and reported several prospective randomised studies in which a trend for an increase in haemorrhagic stroke followed aspirin therapy, although this has not reached statistical significance (Ia).[29]

Contraindications reported include allergy, bleeding tendency, anticoagulant therapy, recent gastrointestinal bleeding and clinically active hepatic disease (Ib).[29]

Relative risk of MI reported by the ETDRS group, in which roughly 48% of men and women with diabetes had a history of CVD, was lowered significantly in the first 5 years in those randomised to aspirin therapy (Ib).[212]

In the management of people with diabetes and new or established vascular disease, the SIGN guidelines refer to a meta-analysis of platelet inhibitor therapy demonstrating a 31% reduction in non-fatal reinfarction, a 42% reduction in non-fatal stroke and a 13% reduction in arterial mortality (Ia).[668]

One meta-analysis of 6 randomised, double-blind, placebo-controlled trials showed a significant pooled reduction in mortality following treatment with platelet glycoprotein inhibitors.[624] The most marked benefit was seen in patients undergoing percutaneous coronary intervention. A significant reduction in composite death or MI at 30 days was also seen following treatment in people with diabetes. However, potential methodological limitations of the trials included would not permit this analysis to be used as an evidence base to inform recommendations in this area (Ia).

Also reported in the SIGN guideline is a substudy analysis of a large RCT demonstrating that the addition of clopidogrel to aspirin over 3 to 12 months reduces the risk of fatal or non-fatal MI or stroke by 20% in patients with a past history of coronary heart disease presenting with acute coronary syndromes (without electrocardiographic ST elevation).[668]This risk reduction was however associated with an additional risk of bleeding (Ia).

The ADA guidelines also report from the CAPRIE study which showed that clopidogrel was slightly more effective than aspirin in reducing the combined risk of stroke, MI or vascular death in people with and without diabetes (effect sizes not stated) (Ia).[29]

Management of arterial disease [2004]

One RCT reviewed in the ADA guideline showed that thrombolytic therapy reduced mortality after acute MI in subjects with diabetes by ≤42% with no increase in risk of bleeding or stroke, and should not be withheld due to concern about retinal haemorrhage in patients with retinopathy.[29] This study also demonstrated that the indications and contraindications for thrombolysis in patients with diabetes are the same as those without (Ia).

The SIGN guideline reports on the results of the beta-blocker adrenergic pooling project study, which demonstrated that diabetes is not a contraindication to the use of beta-blockers, and that these reduce mortality, sudden cardiac death and reinfarction when given after acute MI[668] The guideline also cites the 1995 Collaborative Group on ACE inhibitor trials meta-analysis of nearly 100,000 patients which showed that receiving therapy with an ACE inhibitor within 36 hours of acute MI for ≥4 weeks, reduced mortality post MI. The majority of benefits occurred within the first few days when mortality was highest, benefiting patients at a higher risk to a greater absolute extent (Ia).

Three large trials (AIRE, SAVE and TRACE studies) also reviewed within the SIGN guideline have shown consistent reductions in mortality when ACE inhibitor therapy is given to people after acute MI with clinical evidence of heart failure or a reduced ejection fraction[668] A fourth study (SOLVD) demonstrated an absolute risk reduction for mortality of 4.5% in patients with diabetes and chronic heart failure given an ACE inhibitor compared with placebo over a mean follow-up of 4.5 years (Ia).

A predefined subgroup analysis of 3577 people over 55 years with diabetes (the majority of whom had type 2 diabetes) in the large multinational HOPE RCT 191 showed the effect of ramipril on arterial outcomes in people with diabetes. The rate of the combined primary outcome of MI, stroke or arterial death was significantly lower in the ramipril groups than in those receiving placebo; total mortality was reduced by 24%. Adjustment for changes in systolic and diastolic blood pressures did not change the magnitude of the effect (Ib).

Other results from the HOPE study in which patients aged over 55 years, with and without diabetes, who were randomised to receive 400 IU vitamin E for an average follow-up of 4.5 years, showed no effect of antioxidant over placebo.[795] Primary outcomes of MI, stroke or arterial death, or secondary outcomes of hospitalisations for angina or heart failure, were similar following treatment with vitamin E and placebo. No differences were observed in the frequency of outcomes in people with diabetes in the two treatment groups (Ib).

Management of acute stroke [2004]

SIGN guidelines state that the clinical presentation of stroke in people with diabetes is similar to that in people without diabetes.[668] There is little evidence specific to people with diabetes let alone specific to type 1 diabetes, suggesting that the management of stroke should be similar to that in people without diabetes.

14.3.3 Health economic evidence [2004]

Whilst economic analyses have been conducted on trials of lipid-lowering agents, no evaluation has specifically considered Type 1 diabetes. Three papers were identified within the health economic literature dealing with mixed diabetic populations.[284,285,381] An economic analysis of simvastatin using the 4S trial data suggests that it would provide cost-effective mortality reduction in the UK amongst a similar population.[381] A second cost-effectiveness paper351 also suggests that the simvastatin may be cost-effective in the UK for those aged 40 to 70 years with elevated cholesterol even if they have not been diagnosed with arterial disease. A third paper based outside the UK suggests that the benefits of simvastatin to diabetics with elevated lipid levels and arterial disease outweigh the benefit to those with elevated lipid levels and no prior arterial disease.[284]

As the GDG has no confidence in any existing risk table, engine or equation when applied to those with Type 1 diabetes, the degree to which models that make use of such equations can be relied upon is extremely limited.

14.3.4 Consideration [2004]

The data on arterial risk management in people with type 1 diabetes are few, though it is noted that studies in people with and without type 2 diabetes point to clinically effective interventions for those groups. In the absence of quantitative risk assessment and noting the economic evidence placed before the group it seemed clear that interventions in people with type 1 diabetes must be recommended considering their semi-quantitative CVD risk: high, moderate or no risk.

Given the high arterial risk of many people with type 1 diabetes, smoking was considered to be particularly disadvantageous.

14.3.5 Recommendations [2004]

The current guideline recommendations can be found at

https://www.nice.org.uk/guidance/ng17

14.4 Blood pressure [2004]

14.4.1 Rationale [2004]

Blood pressure is an accepted arterial risk factor. Some drugs used in blood pressure management have been suggested as having metabolic effects or interacting with insulin therapy. Accordingly, blood pressure management in people with type 1 diabetes might be different from people who do not have diabetes. However, those with developing diabetic kidney disease may have different needs again, and are considered separately.

14.4.2 Evidence statements [2004]

Drug therapy

A significant amount of research has been conducted into the treatment of hypertension in recent years. Primary endpoints for this research are the reduction of arterial and microvascular complications by the reduction of blood pressure to within target levels.

Three sets of national clinical guidelines have been published in the two years prior to2004: Canadian,[489] American,[29] and Scottish[666] – presenting rigorous systematic reviews of evidence in this area to date.

The UKPDS RCT (in people with type 2 diabetes) showed that lowering blood pressure in people with diabetes reduces the risk of macrovascular and microvascular disease (Ib).[17]

British Hypertension Society guidelines recommend a threshold for initiating antihypertensive treatment in people with diabetes at less than 140/90 mmHg.[601] Target blood pressure for this group of people is advised at less than 140/80 mmHg unless nephropathy or proteinuria (more than 1 g per 24 hours) is present when this target is lowered to less than 130/80 mmHg and less than 127/75 mmHg, respectively. The guidelines also recommend that blood pressure reduction and ACE inhibitors can be employed to reduce the rate of decline in renal function in people with hypertension and diabetic nephropathy (IV).

British Hypertension Society guidelines suggest that treatment should essentially be the same in people with type 1 and type 2 diabetes.[601] Several studies are cited which provide evidence for the safety and efficacy of ACE inhibitors, dihydropyridine calcium channel blockers, low-dose thiazide diuretics and beta-adrenergic blockers in the treatment of hypertension in people with diabetes. The guidelines recommend that the choice among these drug classes should be determined using the criteria set out for people without diabetes (IV).

The large multicentre randomised ALLHAT trial showed no superiority of a calcium channel blocker (amlodipine) or an ACE inhibitor (lisinopril) over a thiazide diuretic (chlorthalidone) in preventing major coronary events or in increasing survival in older people both with and without type 2 diabetes.[7] This RCT of long duration found that lisinopril therapy had a 15% higher risk for stroke and a 10% higher risk of combined CVD compared with chlorthalidone in a mixed population with 36% of people with diabetes.[7] The 6-year absolute risk difference for combined CVD was 2.4%, which included a 19% higher risk of heart failure and 10% higher risk of hospitalised/fatal heart failure (not statistically significant), also a 11% higher risk for treated angina and 10% higher risk of coronary revascularisation were statistically significant outcomes. Patients assigned to amlodipine had a 38% higher risk of heart failure, a 6-year absolute risk difference of 2.5% and a 35% higher risk of fatal heart failure compared with those on chlorthalidone. Further long-term outcomes reported in this study showed that diuretic was superior to the calcium channel blocker in preventing major coronary events or increasing survival, although, their effect on overall CVD prevention was comparable. Diuretic treatment was superior to ACE inhibitor lowering of blood pressure and in preventing aggregate arterial events (mainly stroke, heart failure, angina and coronary revascularisation) in both people with and without type 2 diabetes (Ib).

Two meta-analyses of RCTs cited in the Scottish guidelines, demonstrated that thiazides, beta-blockers, ACE inhibitors and calcium channel blockers are all effective in lowering blood pressure and reducing the risk of arterial events (Ia).[666]

A large RCT of the use of an angiotensin II receptor antagonist compared with a beta-adrenergic blocker in people with diabetes (predominantly type 2 diabetes) found that the angiotensin II receptor antagonist significantly reduced the risk of arterial mortality or stroke, and MI over four or more years of follow-up (Ia).

RCTs reported within the SIGN guidelines state that combination therapy is often required to reach target blood pressure, either with the same class of drug, or in combination with another type of drug.[666] The superiority of one combination regimen over another has not been examined or documented in type 1 diabetes (Ia).

Several trials report the benefit of ACE inhibitors in producing highly significant and clinically important reductions in endpoints of MI, stroke and arterial death.

Multiple trials and systematic reviews have consistently demonstrated substantial benefits from ACE inhibitors in people with type 1 diabetes, with hypertension and diabetic nephropathy.[29,489,664,667] In diabetic nephropathy, these antihypertensives reduce progression from micro- to macroalbuminuria and to end-stage renal disease compared with placebo as reported in a well-developed systematic review (Ia).[489]

Two sets of SIGN guidelines recommend ACE inhibitors as first-line therapy in patients with microalbuminuria due to their additional benefit on renal function, based on a review of RCT-based evidence (Ia).[666,667]

Adverse effects of ACE inhibitors described in clinical trials and found to be problematic in clinical use include a persistent cough (IV).

The ADA technical review[29] and one RCT in the Canadian guidelines[489] suggest that if ACE inhibitors are prescribed, serum creatinine and potassium levels should be measured at baseline and 1 to 2 weeks after initiation (Ia).

The UKPDS showed apparent equivalence of beta-blockers (atenolol) with ACE inhibitors (captopril) to moderate blood pressure in people with diabetic nephropathy; this study was in people with type 2 diabetes and had insufficient power to show any change of clinical significance (Ia).[668]

Three randomised studies have shown similar reductions in proteinuria in diabetic antihypertensive patients with beta-blockers and ACE inhibitors as reported in a systematic review (Ia).[29]

Concern around the blunting of recovery from hypoglycaemia by beta-blockers was not confirmed in a large randomised study on people with type 2 diabetes, but caution is urged when prescribing to insulin-treated people with a history of severe hypoglycaemia (Ia).[29]

There is no robust evidence to recommend the use of alpha-blockers as first-line treatment in antihypertensive therapy. One ongoing multicentre trial is reported in a systematic review as having discontinued the alpha-blocker arm of the study due to increased incidence of arterial events in this treatment group (Ia).[29]

A recent meta-analysis suggests that dihydropyridine calcium channel blockers may be equivalent in protecting against stroke, but less effective in reducing MI and coronary events than ACE inhibitors, beta-blockers or diuretics (Ia).[29]

One randomised study found no difference between dihydropyridine calcium channel blockers and other antihypertensive drugs with respect to diabetic nephropathy.[225] In addition, the American guidelines urge caution as it is difficult to compare trials studying different calcium channel blockers due to their diverse pharmacological effects (Ia).[29]

Evidence for the use of thiazide diuretics is not as robust as for other antihypertensive therapies.[489] Treatment has been associated with hypokalaemia, hyponatraemia, volume depletion, hypercalcaemia and hyperuricaemia. Two retrospective studies reported in the American guidelines suggested increased arterial mortality, and other studies have shown that thiazides may not be as effective in subjects with significantly decreased renal function (IV).[29]

Target blood pressure

Two large multicentre trials included in a systematic review showed an improvement in arterial and microvascular outcome in patients randomised to lower target blood pressures compared with those with less intensive blood pressure lowering.[489] Evidence supports a treatment goal of a diastolic blood pressure of less than 80 mmHg (Ia).

No evidence exists on the appropriate target systolic blood pressure for people with type 1 diabetes. Consensus recommendations from the Canadian Hypertension Recommendations working group is that systolic blood pressure should be less than 130 mmHg (IV).[489]

The SIGN hypertension guidelines note that RCTs use target blood pressures of less than 130/80 mmHg in major outcome trials or 125/75 mmHg when proteinuria of more than 1 g per 24 hours is present (IV).[666]

Behavioural therapy

A rigorous systematic review performed in the production of the American Diabetes Association guidelines on the treatment of hypertension in diabetes reported one meta-analysis of RCTs showing that dietary management with moderate sodium restriction has been effective in reducing blood pressure in individuals with essential hypertension.[29] However, this has not been tested in a diabetic

population. No evidence exists for the significant benefit of magnesium supplementation or calcium supplementation in people with diabetes (Ia).

Weight reduction has also been shown in a systematic review of non-RCTs to reduce blood pressure independently of sodium intake and to improve glucose and lipid levels (IIa).[29]

Smoking cessation, moderation of alcohol intake and mild physical activity have been recommended by the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure to reduce blood pressure (IV).[29]

The American Diabetes Association guidelines recommend that patients with a systolic blood pressure of 130–139 mmHg or diastolic blood pressure of 80–89 mmHg should be given lifestyle or behavioural therapy as first-line treatment for a maximum of 3 months, based on evidence from large-scale RCTs (Ia).[29]

14.4.3 Health economic evidence [2004]

The health economic literature on type 1 diabetes does not assess the cost-effectiveness of ACE inhibitors in lowering blood pressure in isolation. The effect of ACE inhibitors in lowering blood pressure is linked in these studies to its effects in delaying kidney damage, and the GDG felt that no recommendations in regard of blood pressure lowering alone could be drawn from the existing evidence.

14.4.4 Consideration [2004]

The finding of raised blood pressure in people with diabetes is felt to be of different significance in the presence of nephropathy, if features of the metabolic syndrome are present, or in the absence of these findings. Other risk factors (age, ethnic group, family history and smoking) will be relevant in the last group, in whom it was felt management should echo that of non-diabetic people of the same age, but regarding the diabetes as a further substantial risk factor (formal risk calculation was considered above under CVD surveillance, and is not recommended). The combination of raised blood pressure and nephropathy, or features of the metabolic syndrome is, however, known to be very high risk indeed for premature CVD in early middle age. Accordingly, intervention levels and targets should be lower and more strictly applied than for the person with 'simple' hypertension. Very many suggestions for intervention levels based on evidence have been put forward by other groups, with (allowing for the gradual evolution of evidence) considerable coherence. The group assessed all the available recommendations in this area and reached a consensus based on small differences between these.

The problems of motivating professionals and people with diabetes to manage blood pressure appropriately, despite the clear arterial and macrovascular protection to be gained, were noted to be multifactorial. Accordingly, recommendations emphasising intervention levels, targeting, informed discussions and patient-held record cards were discussed. The problem of potential and minor side effects inhibiting the achievement of major clinical gains was felt to be worth mentioning. It was noted that lifestyle interventions have a role in blood pressure management (considered in more detail in other parts of this guideline).

14.4.5 Recommendations [2004]

The current guideline recommendations can be found at

https://www.nice.org.uk/guidance/ng17

15 Inpatient management

This section was updated in 2015.

The 2015 GDG updated inpatient management in relation to insulin replacement (intravenous regimens and dose-adjustment devices). Other aspects of inpatient management were not updated and the content from CG15 is included.

15.1 Introduction [2015]

Diabetes control in hospital is complicated by the stress of the primary condition, the relative immobility of the bed-bound patient, and the change in usual food intake and daily routine. Usual insulin regimens are designed around mealtime insulin requirements, superimposed on a background insulin replacement to control endogenous glucose production – both these hyperglycaemic processes are altered during hospitalisation. The management of type 1 diabetes during hospitalisation aims to maintain near-normoglycaemia, despite these often unpredictable factors. Hyperglycaemia should be avoided, as it is associated with abnormalities of fluid and electrolyte balance, increased risk of infection and poorer outcomes. Hypoglycaemia should also be prevented as it can be associated with impaired brain function and cardiac arrhythmias. However the degree of glucose control associated with best outcome (that is, the target glucose ranges) and the regimens for achieving them remain controversial.

Protocol-driven management of glucose during hospitalisation is associated with better control and improved outcomes, such as shorter ICU stay[65], with evidence to support the ability of intravenous infusion regimens to improve glucose control and important outcomes after major surgery.[246]Some studies in critical care show better outcomes when blood glucose control is kept near-normal, between 4.4 and 6.1 mmol/litre with intravenous insulin regimens[253,745,760], but the benefits may be outweighed by a high risk of hypoglycaemia unless very well managed.[252,596]

The pharmacodynamics of intravenous insulin, with its rapid onset and offset of action, allows it to be adaptable to the changing physiology of the sick patient, titrated easily, and without a dosage threshold (8). Furthermore, insulin has minimal side effects except for hypoglycaemia.

Intravenous insulin regimens are reactive however (that is, the insulin infusion rate is adjusted after the glucose has moved away from target) and for all non-critically ill patients, who are eating, a basal/bolus insulin regimen is the preferred method of glycaemic control with appropriate corrective doses. Care must be taken to accommodate the unpredictable eating and diagnostic testing schedules that in-patients may face, which make the patient more susceptible to hypoglycaemia or hyperglycaemia.

An appropriate target range should be established for each patient group.

There are many protocols and guidelines governing in-patient insulin management, which include common themes such as the use of soluble insulin for continuous insulin infusion, titration of insulin dose against blood glucose and stepping down to normal therapy (for example, the NHS Diabetes and Joint British Diabetes Societies Inpatient Care Group guidance[182]).

Continuous infusion of soluble insulin is suggested for critically ill ICU patients, pre- and postoperative patients, peripartum women with hyperglycaemia, severe hyperglycaemia with metabolic decompensation (diabetic ketoacidosis and hyperosmolar non-ketotic states), and any patient in whom tight glycaemic control is clinically indicated. Paper-based and increasingly computer-based insulin infusion algorithms, some of which can be automated, are available to help clinicians achieve optimal glycaemic control.

Conversion from IV to SC insulin commonly occurs when the critical illness resolves and the patient is ready to begin eating or is in a stable condition with enteral nutrition.

This chapter addresses this question:

- In adults with type 1 diabetes who have been admitted to hospital (elective and emergency), what are the most effective intravenous insulin dose-adjustment devices and regimens for optimal diabetic control?

15.1.1 Review question: In adults with type 1 diabetes who have been admitted to hospital (elective and emergency), what are the most effective intravenous insulin dose-adjustment devices and regimens for optimal diabetic control?

For full details see review protocol in Appendix C.

Table 106: PICO characteristics of review question

Population	Adults admitted to hospital with type 1 diabetes (this covers type 1a diabetes and type 1b diabetes) • Adult is defined as aged ≥18 years • Type 1 diabetes is defined (WHO definition and NICE 2004 GL) as:
Intervention/s	• IV insulin Note: only UK licensed interventions and doses will be considered
Comparison/s	• Subcutaneous insulin • Each other (different regimens) • Each other (different devices) • No comparison Note: only UK licensed interventions and doses will be considered
Outcomes	Outcomes • Achieving target BG levels (may be measured differently in studies) • Hypoglycaemia - preferably severe hypoglycaemia if reported (dichotomous or continuous outcome, depending how it is reported) • Time spent out of target glucose (Hypoglycaemia/Hyperglycaemia) • Duration of IV treatment • In-patient stay • In-patient mortality • Infection rate/wound healing • Quality of life – measured by SF-36, DQoL, DSQoL (continuous)
Study design	RCTs, observational studies • Unit of randomisation: individual patient

15.1.2 Clinical evidence

Six studies were included in the review [130,145,356,492,592,761]. Evidence from these are summarised in Table 107 andTable 108, and in the clinical evidence profiles below inTable 109**,** Table 110and Table 111**.** See also the study selection flow chart in Appendix D, forest plots in Appendix J, study evidence tables in Appendix G, GRADE tables in Appendix Iand exclusion list in Appendix K.

Five studies reported data on IV insulin regimes during surgery. One study was an RCT comparing IV insulin versus SC insulin during surgery[130]. Data were reported for the following outcomes: achieving blood glucose targets; mild hypoglycaemia; duration of inpatient stay. One retrospective cohort

study was identified comparing IV insulin, CSII continuation and CSII suspension during surgery[145]. Data were reported for the following outcomes: achieving blood glucose targets; severehypoglycaemia. The remaining three studies were case-series and the results are summarised in Table 107.

One study[761]reported data on IV insulin for inpatients with DKA, and this study was a case-series.

All the non-comparative observational studies (case-series), were not able to be combined in a meta-analysis or GRADE profile, and were graded as Low quality (due to their study design). However, a summary of the quality and limitations of these studies can be found in Appendix G. Study details and the full results have been summarised narratively.

No data were reported on the following outcomes:

- Time spent out of target glucose (hypoglycaemia/hyperglycaemia)
- Duration of intravenous (IV) treatment
- In-patient mortality
- Quality of life

Table 107: Summary of studies included in the review: Surgery

Study	Intervention	Comparison	Population	Outcomes
RCTs				
CHRISTIANSEN 1988 RCT	IV infusion of glucose, insulin and potassium (GIK) for 24 hours	Pre-op SC insulin (Concomitant glucose infusion for 24 hours)	n=20 Adults Insulin-dependent diabetics admitted for minor surgery Follow-up = 3 days (op day and 2 days post-op)	IV GIK was better than SC insulin for: Achieving target BG levels (5-10 mmol/litre) during 3 days (reported as % BG values within target range; 48% versus 26%, reported as p<0.01) Achieving target BG levels (5-10 mmol/litre) during infusion period (reported as % BG values within target range; 67% versus 28%, reported as p<0.0001) SC insulin was better than IV GIK for: Hypoglycaemia, no. of patients with ≥1 BG level <5 mmol/litre (6/10 versus 4/10) No difference between groups for: Inpatient stay, median (range) 5(1-10) versus 5 (2-7)
Observational Studies				
CORNEY 2012 Retrospective cohort	IV infusion n=20 (convert from SCII to IV infusion pre-op)	1. CSII n=53 (continue CSII with supplemental SC or IV insulin if required) 2. Suspend	n=99 cases (75 unique individuals • Adults 85-90% type 1 diabetes • Elective surgery CSII	IV and CSII continuation was better than CSII suspension for: % with intra-op target BG, % intra-op hypoglycaemia and % intra-op hyperglycaemia only reported graphically (no data). Comparison reported as P=0.034.

Study	Intervention	Comparison	Population	Outcomes
		CSII n=19 (with or without SC or IV insulin boluses)	Follow-up = inpatient stay	No difference between groups for: Severe hypoglycaemia (intra-op blood glucose<40 mg/dl or loss of consciousness): 0/20 versus 0/53 versus 0/19 QUALITY rating = LOW (see GRADE tables in AppendixI)
HUSBAND 1986 Prospective case-series	IV infusion of GIK	None	n=128 (n=41 IDDM) • Mainly adults • Elective surgery Follow-up = 3 days (op day and 2 days post-op)	Achieving target blood glucose levels (pre-op: 5-10 mmol/litre): 26/41 Achieving target blood glucose levels (op day: 5-12 mmol/litre with no hypoglycaemia <3 mmol/litre): 31/41 Mean BG values, mmol/litre: Pre-op: 8.2 (3.0); Post-op: 9.6 (3.4); op day: 8.9 (2.3); post-op day 1: 9.4 (1.9); post-op day 2: 10.2 (2.8) Hypoglycaemia on op-day, no. of patients with blood glucose level <5 mmol/litre: 4/41 Hyperglycaemia on op-day, no. of patients with BG level >12 mmol/litre: 6/41 VERY LOW QUALITY[a]
MCCAVERT 2010 Prospective case-series	IV infusion of GIK	None	n=69 (n=35 type 1 diabetes) • Elective (n=21) or emergency (n=14) surgery Follow-up = 3 days (op day and 2 days post-op)	Achieving target blood glucose levels (6.1-10 mmol/litre), mean % of patients over 3 days: elective 25.9%; emergency 22.7% No hypoglycaemic episodes were reported Wound infection: elective 2/21; emergency 1/14 Peritonitis: elective 1/21; emergency 0/14 Septicaemia: elective 0/21; emergency 2/14 VERY LOW QUALITY[a]
POPPE 2004 Retrospective case-series	Perioperative IV insulin protocol	None	n=50 type 1 diabetes (n=12, subgroup data only for the following outcomes) • Surgical procedure as inpatient Follow-up = first 24 hours of infusion	% of levels in the hyperglycaemic range (>12mmol/litre): 49.7% Mean BG level: 12.1 (1.1) mmol/litre VERY LOW QUALITY[a]

(a) Data is from case-series, mostly of retrospective design. The quality has been rated asVery lowbecause these study designs are associated with a high risk of bias.

Table 108: Summary of studies included in the review: Inpatients with DKA

Study	Intervention	Comparison	Population	Outcomes
WAGNER 1999 Prospective case-series	IV insulin infusion 'Very low-dose insulin application'	None	n=65 Adults and young people with type 1 diabetes Severe ketoacidosis, admitted to ICU	Achieving target blood glucose levels - reported as mean (range) BG mg/dl at each time point: admission 606(86-1191); after 1 hour 468(96-1075); after 4hr 376(66-1003); after 8 hours 283(107-738); after 12 hours 251(89-614) VERY LOW QUALITY[a]

(a) Data is from case-series. The quality has been rated as Very low because this study design is associated with a high risk of bias.

Table 109: Clinical evidence summary: IV insulin versus SC insulin during surgery

Outcome	Number of studies	Imprecision	GRADE rating	Absolute difference	Control event rate (per 1000)	Control event rate for continuous outcomes
Mild hypoglycaemia	1 (n=20)	Very serious	VERY LOW	200 more per 1000 (from 160 fewer to 1000 more)	400 per 1000	n/a
Duration of inpatient stay	1 (n=20)	Very serious	VERY LOW	Median 0 higher	n/a	Median 5 days

Table 110: Clinical evidence summary: IV insulin versus continuation of CSII (with supplemental SC or IV insulin if required) during surgery

Outcome	Number of studies	Imprecision	GRADE rating	Absolute difference	Control event rate (per 1000)	Control event rate for continuous outcomes
Severe intra-op hypoglycaemia	1 (n=73)	none	LOW	0 more per 1000	0 per 1000	n/a

Table 111: Clinical evidence summary: IV insulin versus suspension of CSII (with or without IV or SC insulin bolus) during surgery

Outcome	Number of studies	Imprecision	GRADE rating	Absolute difference	Control event rate (per 1000)	Control event rate for continuous outcomes
Severe intra-op hypoglycaemia	1 (39)	none	LOW	0 more per 1000	0 per 1000	n/a

15.1.3 Economic evidence [2015]

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow diagram in Appendix E.

Unit costs

Unit costs of different insulin preparations that can be delivered intravenously or subcutaneously are reported in Appendix Q to aid consideration of cost-effectiveness.

15.1.4 Evidence statements [2015]

Clinical

IV insulin versus SC insulin during surgery

Very low quality evidence from one RCT (n=20) showed no clinical benefit of iv insulin for:

- Mild hypoglycaemia
- Duration of inpatient stay

In the case of mild hypoglycaemia, the direction of the estimate of effect favoured SC insulin, and for inpatient stay, both groups had the same median duration.

Very low quality evidence from one RCT (n=20) showed benefit[c] of iv insulin for:

- percentage of BG values within target range during all 3 days and during infusion period.

IV insulin during surgery versus continuation of CSII (with supplemental SC or IV insulin if required) during surgery

Low quality evidence from one cohort study (n=73) showed no clinical difference between IV insulin for:

- Severe intra-operative hypoglycaemia

The direction of the estimate of effect did not favour either group as there were zero events in each arm.

Low quality evidence from one cohort study (n=73) showed no difference between IV insulin and CSII for:

- Percentage of patients achieving the intra-operative target BG
- Percentage of patients with intra-operative hypoglycaemia
- Percentage of patients with intra-operative hyperglycaemia

IV insulin versus suspension of CSII (with or without IV or SC insulin bolus) during surgery

Low quality evidence from one cohort study (n=39) showed no clinical difference between IV insulin for:

- Severe intra-operative hypoglycaemia

c Data required for calculating clinical difference or direction of effect was not reported, so this is based on statistical difference.

The direction of the estimate of effect did not favour either group as there were zero events in each arm.

IV infusion

Low quality evidence from three case series' showed that for IV infusion:

- Most patients (more than 60%) achieved target blood glucose levels preoperatively and on operation day (one study, n=128).
- Approximately 20% of patients achieved target blood glucose levels over 3 days (one study, n=69)
- Very few (approximately 10%) patients had hypoglycaemia on operation day (one study, n=128).
- Very few (approximately 15%) patients had hypoglycaemia on operation day (one study, n=128).
- There were no hypoglycaemic events (one study, n=69)
- There was a low incidence of infection (one study, n=69)
- Most patients (approximately 50%) had blood glucose levels within the hyperglycaemic range (one study, n=50).

Inpatients with DKA

- Very low quality evidence from one study (n=65) showed that mean blood glucose levels decreased over time with IV insulin infusion.

Economic

No relevant economic evaluations were identified.

15.1.5 Recommendations and link to evidence

The current guideline recommendations can be found at

https://www.nice.org.uk/guidance/ng17

Relative values of different outcomes	In order to establish the best means of treating a person with type 1 diabetes when admitted to hospital with a medical or surgical emergency, or for a non-urgent surgical procedure, the GDG sought evidence with the following critical outcomes: • Maintenance of stable plasma glucose levels within an acceptable range. Closely linked to this is the question of what is the best blood glucose target range.There is evidence from a number of emergency situations, including common conditions such as acute coronary syndromes and COPD exacerbations, that those with elevated blood glucose have worse clinical outcomes • Mortality. No papers covering this important outcome were found • Hypoglycaemia and severe hypoglycaemia (requiring help from 3rd party for correction) In addition the GDG agreed to look at data on: • Quality of life • Infection rates • Duration of intravenous treatment (IV lines are a risk factor for hospital-acquired infection) • Length of hospital stay
Trade-off between	There are essentially three ways of controlling plasma glucose levels when a person

clinical benefits and harms	is too unwell to manage this with their usual regimen. The first is to administer short-acting subcutaneous (s/c) insulin in variable amounts, depending on the current plasma glucose concentration. Basal insulin may be continued. Any necessary intravenous fluids are given separately. The second and third are to use intravenous insulin infusion either as: • A variable rateintravenous insulin infusion (VRIII), commonly referred to as a "sliding scale", in which an insulin infusion is adjusted regularly on the basis of frequent bedside plasma glucose measurements with intravenous glucose, potassium and other fluids given separately, • Addition of short-acting insulin to a bag of glucose solution administered intravenously at a constant rate. Potassium is usually also added, and the amount of both this and the insulin in any bag can be varied, the latter according to frequent bedside plasma glucose measurements. This is often referred to as a GKI infusion. Both intravenous methods are in use around the UK. Only one RCT comparing these two methods was found[131]. This showed better control of blood glucose levels using GKI. There was no difference in the hypoglycaemia incidence, or in length of stay in hospital. The 5 other papers considered were case-series, but only 3 of these allowed comparison of sliding scales with GKI. There were no significant differences between the 2 methods in either blood glucose control or hypoglycaemia. One study reported infection rates, but in this study some of the patients received VRIII in error, and the GDG did not feel that any value could be placed on the reported difference in infection. Rather than always using VRIII or GKI, some anaesthetists do not give any insulin at onset of surgery but monitor blood glucose and start treatment if this rises. One study[145] included an arm in which this approach was evaluated. Blood glucose control in this arm of the study was poorer than with either VRIII or GKI.
Economic considerations	No health economic evaluations were identified and therefore unit costs were considered. The GDG also considered whether there were any differences in cost related to the need for monitoring blood glucose with the two regimens. However, this consideration would not affect many of these patients since those requiring major surgery, and some of the medical emergencies, would require HDU or ICU monitoring anyway. The GDG concluded that the cost effectiveness of different strategies was driven by other considerations such as convenience and safety.
Quality of evidence	Overall the quality of evidence was considered Very low. The only RCT was small, and the GDG felt that the dose of insulin used in the VRIII arm of the study was too low. The case series were also relatively small, with low event rates. In addition, one of those which allowed comparison between the 2 regimens was a retrospective series[592]. There is also an issue with the age of some of the studies since the insulins used in these have been superseded, and the results may not be applicable to present-day practice. No studies were found covering acute medical emergencies, and any conclusions for that situation were necessarily based on extrapolation from the studies of elective surgery, plus GDG experience and consensus.

Other considerations	The GDG were concerned about the lack of data and considered whether there was any useful information to be obtained from papers in mixed population of type 1 and type 2 diabetes, many of which are in the list of excluded studies. Clearly less importance could be attached to these but the GDG noted: • Abelev 2011[12] showed shorter length of hospital stay with GKI versus subcutaneous insulin • Furnary 2006[245] in the USA looked at mortality rates for cardiac surgery when a switch from s/c insulin to intravenous was made, and showed a marked decrease. • However, the GDG were unsure how well intravenous regimens had been used in the Furnary study, and noted the paper by Golightly (2006)[272] which demonstrated how poorly these were implemented in many instances • Gan (2009)[251] also considered patients undergoing cardiac surgery and showed that arrhythmia incidence increased once the blood glucose level was >8 mmol/litre. • Simmons (1994)[685] showed higher rates of adverse events with GKI than s/c insulin Some GDG members reported that use of GKI was not permitted in their hospital because of safety concerns around injecting insulin into bags of fluid. The GDG also noted the NICE clinical guideline 130[534] which considered the management of hyperglycaemia in the context of acute coronary syndromes. The TA concluded that the blood glucose should be maintained below 11 mmol/litre during the acute illness. Of note, the TA was not confined to type 1 diabetes, but rather looked at management of all people with an elevated blood glucose irrespective of any diagnosis of diabetes. The GDG were in agreement that if people with diabetes are eating reasonably normally then their usual insulin regimen is the best way of controlling diabetes during an admission, and this should be possible for lesser surgical procedures or less severe medical emergencies. They also agreed that if a person is able to administer their own usual insulin, and are willing to do this, then this is the safest way of managing insulin during an admission. In more severe circumstances the GDG did not feel that there was sufficient evidence to recommend GKI over the VRIII, or vice-versa. They concluded that it was more important that hospitals have a clear protocol in place, using one or the other of these methods, but that stopping insulin in type 1 diabetes and waiting to see if the plasma glucose rises is not acceptable. They also agreed that there were some circumstances in which intravenous insulin would be preferred to the s/c route. Regarding optimal plasma glucose levels, the GDG could not find any reason why control should be less tight during an intercurrent illness or surgical procedure than at other times. They also noted the (extrapolated) evidence from cardiac surgery regarding adverse effects of a plasma glucose >8 mmol/litre. They therefore agree to recommend a target range of 5-8 mmol/litre. The GDG were aware of a National Patient Safety Agency alert[537]encouraging empowerment of patients to self-administer insulin if willing and able to, and this informed recommendation 127.

15.1.6 Research recommendations

31. In adults with type 1 diabetes, what is the clinical and cost effectiveness (particularly in terms of optimal blood glucose control, patient-reported outcomes and experience, length of stay, and short-term complications) of closed loop insulin delivery systems and automated insulin dose

advisors during in-hospital care, and could the development of new systems and technologies improve on current clinical outcomes?

15.2 Inpatient management [2004]

15.2.1 Rationale [2004]

People with Type 1 diabetes often find that time in hospital, or other institutional care, is stressful. The delicate equilibrium they may have established with their insulin therapy can be destroyed by the change in routine, change in nutrition and the effects of illness and procedures. They find too often that the expertise they bring to their diabetes management is underused by staff with less knowledge of the condition than themselves. Special insulin regimens may be needed to cope with procedures which interfere with eating patterns, or which cause enough metabolic stress to otherwise disturb control of diabetes. In some acute situations there is evidence that special insulin management may improve the outcomes of other medical conditions.[534]

The overwhelming majority of admissions of people with diabetes are for non-diabetes related medical and surgical conditions. Indeed the problems discussed above are likely to be greater when care is outside the responsibility of the multidisciplinary diabetes team. Accordingly the evidence search and recommendations are intended to cover hospital and other institutional care across all specialties. However, some aspects of continuing self-care will self-evidently not be relevant during extreme critical illness.

The principles espoused are seen as applying, in general, to other institutional care (prisons, residential and nursing homes) as well as hospital care.

15.2.2 Evidence statements [2004]

Multidisciplinary team care

One study showed a significant reduction in length of stay in hospital following supervision by a diabetes specialist nurse.[167] Significant differences were also seen in patient satisfaction and diabetes knowledge, although not for readmission frequency, referral rates or quality of life (Ib).

A cohort study showed a significant reduction in length of stay in medical and surgery wards in patients with diabetes following the introduction of a diabetes nurse advisor (IIa).[117]

A prospective randomised study examining the impact of a specialist diabetes team on inpatient management demonstrated a significant increase in documentation of instructions for blood glucose monitoring, insulin administration, received education and nutritional consultation.[414] Patients were significantly less likely to be readmitted within three months following supervision by a specialist diabetes team (Ia).

15.2.3 Health economic evidence [2004]

One UK-based study suggested that the provision of a hospital-based diabetes specialist nurse lowered the cost per patient admission without producing a significant difference in readmission, quality of life or patient satisfaction.[167]

15.2.4 Consideration [2004]

The evidence supporting the benefit of specialist multidisciplinary team advice in giving healthcare and cost gains to inpatients outside specialist diabetes wards was felt to be conclusive. Professional and patient members of the group were sadly familiar with the failure of some wards to use the

expertise of people with diabetes, and the distress this can cause when care becomes suboptimal as a result. This was noted to be particularly the case in relation to nutritional intake and insulin therapy.

15.2.5 Recommendations [2004]

The current guideline recommendations can be found at

https://www.nice.org.uk/guidance/ng17

16 Management of complications

The 2015 GDG updated treatment of gastroparesis, insulin-induced neuropathy and monitoring for thyroid disease.The evidence and text from the previous guideline, CG15, that has been superseded by these updated sections is in Appendix S.Other complications were not updated; the original content from 2004 has been presented.

16.1 Eye disease [2004]

16.1.1 Retinopathy surveillance programmes

16.1.1.1 Rationale

Diabetes eye damage is the single largest cause of blindness before old age. The success of laser therapy in the treatment of sight-threatening retinopathy is an accepted part of ophthal-mological care and has not been assessed for this guideline. Appropriate issues which need to be addressed are, however, how people with developing retinopathy can be selected for ophthalmological referral in time for optimal treatment, and whether preventative therapy other than good blood glucose and good blood pressure control can be useful in people with type 1 diabetes. This section deals with the structure and success of surveillance programmes, while the methods used for detection of early retinopathy, the use of alternative preventative therapies and referral guidelines to ophthalmology are considered below.

16.1.1.2 Evidence statements

The SIGN guideline suggested from two comparative studies that screening is effective at detecting unrecognised sight-threatening retinopathy.[667] Onset of pre-proliferative retinopathy was identified in one study 3.5 years after diagnosis of type 1 diabetes in post-puberty patients, and within two months of onset of puberty (IIa).

There are discrepancies in the recommended optimal frequency of testing for diabetic retinopathy. Annual review was considered appropriate by consensus in two guidelines.[357,358,667] Testing for other diabetic complications takes place annually, and this is considered an appropriate schedule for retinopathy screening (IV).

The NICE guidelines for type 2 diabetes reached consensus on a more frequent need for screening (three to six months) in patients who experienced worsening of lesions or scattered exudates more than one disc diameter from the fovea or in a person with changes in blood glucose control suggesting higher risk of progression of retinopathy (NICE).[528,545]

Further research is needed in increasing this screening interval for low-risk patients. Evidence from non-randomised controlled studies considered in a systematic review found that patients with no retinopathy at baseline have a less than 1% chance of developing any retinopathy within two years (IIa).[667]

Evidence from patient focus groups and the grey literature suggests that success of screening depends on continued consistently high levels of uptake. Patients expressed importance in discussing fear of blindness and benefits of attending regular screening. Explanations of techniques and technologies for screening including new technologies under investigation were requested. The need for eye drops and transient effects on vision should also be communicated. Multiple patient reminders did not improve attendance at screening sessions. A range of education methods is needed to encourage non-attendees (IV).

SIGN guidelines cite cohort studies with high risk of potential confounding in their design and expert opinion indicating that patients prefer screening to be performed at a site convenient to them.[667] Low vision clinics and community self-help groups can improve the quality of life and functional ability of patients with visual impairment. Community support, low vision aids and training, and assistance to register as blind/partially sighted should be provided to people with diabetes and visual impairment (IV).

16.1.1.3 Health economic evidence

The health economic searches produced nine papers of potential interest to the guideline that fall into three distinct sets. The first set of five papers present US and Swedish simulations of the cost-effectiveness of the screening for and treatment of diabetic retinopathy using a similar model structure.[223,223,369-372,372,372,372,372] All these papers consider retinopathy screening at a yearly or more frequent interval. Three of the papers relate to a government perspective within the US, where the cost of federal benefits for blindness is argued to be greater than the costs of a yearly (or more frequent) screening regimen for those with retinopathy.[370-372,372,372,372] A fourth paper relates the model to Sweden, where it is argued that retinopathy screening is cost-saving to the government.[223] A final paper, also US based, considers only medical costs (a health insurer standpoint) and finds a cost-effectiveness ratio of $1,996 per QALY (1990 prices) for the yearly screening of those without retinopathy and a six-monthly screening for those with retinopathy.[369,372]

Two other related papers consider national retinopathy screening using an alternative model.[153,153,591,591]In one of these papers, only minimal glycaemic control is assumed (HbA1c at 10%) when evaluating retinopathy, whilst the other gives insufficient details of the model or alternative strategies to allow analysis. Both papers appear to produce findings consistent with the cost-effectiveness of screening for and treatment of diabetic retinopathy.

None of the above papers consider the potential role of digital photography in detecting diabetic retinopathy at low marginal cost.

Two papers consider the screening methods used in dispersed or isolated populations.[77,77,475,475] Of these, one relates to a mixed population with a very low proportion of type 1 diabetes,[475] whilst the other uses highly-specific cost estimates.[77] As no large dispersed or isolated subgroup exists within the UK, the results of these papers are not relevant for the guideline.

16.1.1.4 Consideration

Members of the group recognised that some people with long-standing stable eye condition (and unchanging metabolic and blood pressure control) did not necessarily justify annual eye surveillance, but that currently the practicalities and knowledge base for identification and selection and recall of such people meant that a universal minimum recommendation of annually was the correct judgement. More frequent assessment of some individuals with changing retinopathy was noted to be cost-effective as they would otherwise have to be referred to ophthalmologists. The group were aware that future developments in the evidence base may allow for longer intervals between assessments for low-risk individuals. The importance of education of people with diabetes as to the purpose of the surveillance was agreed, while the issue of convenience of site was noted to have significant cost consequences.

16.1.1.5 Recommendations

The current guideline recommendations can be found at

https://www.nice.org.uk/guidance/ng17

16.1.2 Screening tests for retinopathy

16.1.2.1 Rationale

The success of laser therapy in the treatment of sight-threatening retinopathy is an accepted part of ophthalmological care and has not been assessed for this guideline. The appropriate issue to be addressed is, but how people with developing retinopathy can be selected for ophthalmological referral in time for optimal treatment. This section deals with the methods used for detection of early retinopathy, the structure of surveillance programmes having been covered in the previous section, while other therapy issues are covered in 9.3.

16.1.2.2 Evidence statements

Ophthalmoscopy

Direct ophthalmoscopy does not usually meet the required standards for retinopathy screening and review.[528,545]Sensitivity achieved by GP and optometrist screening with ophthalmoscopes is very low (NICE).[303,528,545]

Ultra-wide angle screening laser ophthalmoscope

Little evidence is available in this area. One comparative study conducted on healthy individuals reported in a systematic review is of limited applicability clinically (Ia).[303]

Slit lamp biomicroscopy

A diagnostic study quoted in a systematic review found that slit lamp biomicroscopes with dilated indirect ophthalmoscopy used by properly-trained individuals can achieve sensitivities similar to retinal photography, with a lower technical failure rate (DS).[303]

A systematic review concluded that slit lamps are always needed for those not amenable to digital photography (IV).[303]

Retinal photography

Retinal cameras have the highest level of accuracy of any practical screening method, and provide permanent images for quality control.[18] Retinal photography is more effective than direct ophthalmoscopy and can regularly achieve a sensitivity of 80% (DS).[667]

Photography is more accurate at detecting the presence of microaneurysms than ophthal- moscopy and may be of use in milder disease states (Ib).[18]

A low percentage of retinal photographs are ungradeable, although this may be improved by digital imaging. Accuracy is not dependent on the type of professional involved, but data from non-randomised controlled studies underlines the need for training in reading the photographs or images (IIa).[303]

Limited evidence exists on the number of fields that should be viewed with a retinal camera. One systematic review considering diagnostic studies showed that single-field studies gave marginally better results than those with two or more fields (DS).[303]

Digital cameras show similar accuracy to conventional photography but have advantages in image transfer and potential for automated grading.[303] Technical failure rates are lower with digital cameras (DS).

Further evaluation of digital imaging techniques is needed to prove the usefulness of this screening method (IV).[667]

There are inconsistent results and conclusions from randomised trials regarding the use of mydriasis in retinal photography reported in a systematic review (Ia).[303]

The Health Technology Board for Scotland assessment report states that there is no clear evidence that mydriasis or the routine use of more than one image significantly alters the sensitivity or specificity of screening for the detection of sight-threatening retinopathy.[303] The review concludes that there is little difference between the accuracy and failure rates of modern cameras when used with or without mydriasis; but the analysis of failure after non-mydriatic photography may have favoured no difference to outcome. Comparable screening accuracy is achieved with digital cameras, with or without mydriasis, but direct comparisons suggest that mydriasis may occasionally result in a successful image when non-mydriatic imaging fails (DS).

A large diagnostic study of screening services in both hospital and district settings found screening tests by trained retinal screeners to have a high sensitivity and very high specificity to detect sight-threatening diabetic retinopathy as assessed by slit lamp examination (DS).[569]

NICE type 2 diabetes guidelines suggest that mydriatic 45° retinal photography is the most effective test when screening for diabetic retinopathy (NICE).[528,545]

If more than one image per eye is required for screening then mydriasis is essential because of constriction of the pupil caused by the first photographic flash (IV).

Tropicamide (0.5%–1%), administered by a trained professional is a safe and appropriate way to perform mydriasis (NICE).[667]

The use of pilocarpine to reduce mydriasis is potentially harmful (IV).[303]

Blurred vision and sensitivity to light are complications of the instillation of eye drops for mydriasis. Other related side effects such as glaucoma and allergic reactions are rare (IV).[479]

Table 112: Mydriasis with tropicamide

Mydriasis with tropicamide:
• reduces the failure rate (inadequately interpretable photographs) in around 5% of eyes of people with diabetes (in particular in the second eye and in older people), and thus, the need for recall for a further examination when tropicamide will be necessary
• allows follow-up ophthalmoscopy to be optimised reducing false-negative referrals to ophthalmologists
• carries no detectable risk to the eye except in the post-surgical period
• is briefly uncomfortable (stings)
• paralyses accommodation (near vision) and pupil constriction for 30–60 minutes (low dose), but in some people for much longer, giving problems with glare and bright light sufficient to impair vision to unsafe levels for some tasks (for example driving).

No studies reported whether differences found in sensitivities of healthcare professionals undertaking tests were statistically significant. Comparable sensitivity is achieved by GPs and optometrists using a direct ophthalmoscope through dilated pupils. Optometrists using slit lamp biomicroscopy only achieved moderate sensitivity (62% sensitivity at 95% specificity). The greatest sensitivity was found in comparative studies used in a systematic review with trained graders using mydriatic and non-mydriatic photography (DS).[303]

Initial data indicates that high-resolution automated grading systems compared to conventional grading can identify the absence of microaneurysms on digital images with a high sensitivity (Ia).[303]

A systematic review included a descriptive study evaluating a system for referring photo- graphs to the next level of expertise.[277] Referral when the grader identified any potential sign of retinopathy, with the more experienced professionals involved in the second and third levels, helped maintain effective analysis of images (IV).

Diabetes UK consensus is that an effective screening system should achieve a technical failure rate of less than 5% (IV).[716,717]

A systematic review reported inconsistent findings from controlled studies of the impact of disease condition and progression of disease on test failure rates (IIa).[303]

Lower technical failure rates are achievable with digital photography compared to conventional slide photography. Failure rates for ophthalmoscopy do not differ greatly from photography in controlled studies reported within a systematic review (IIa).[303]

There is a lack of discrete evidence about the role and usefulness of visual acuity testing. The NICE type 2 diabetes guideline retinopathy working-group supported the consensus guidelines from the Royal College of Ophthalmologists on the usefulness of visual acuity testing as part of the overall eye care approach (NICE).[528,545]

Diagnosis of macular oedema rests on the use of stereoscopic, slit lamp, indirect ophthalmoscopy in expert hands. Due to the difficulty of differentiating non-significant and clinically significant macular oedema, the use of visual acuity testing is recommended for screening in routine practice. Reduced visual acuity is an indication for specialist referral (NICE).[528,545]

16.1.2.3 Consideration

The group felt that earlier judgements (for example NICE Inherited type 2 diabetes guideline) that digital photography best met the needs of appropriate sensitivity/selectivity, feasibility and opportunities for quality assurance were clearly endorsed by the evidence review and personal experience of Group members. Mydriasis was noted to be of particular importance in particular groups of people in whom some form of ophthalmoscopy was commonly required to complete a quality examination after photography, and appears safe if inconvenient to some people. It was strongly endorsed. Patient preference studies have suggested that mydriasis may reduce attendance for retinopathy screening because of its temporary effect on vision, but there is no recorded clinical evidence to suggest this. Visual acuity testing, while ill-evidenced, was noted to be fast and non-invasive (though requiring trained staff to test), and provided a useful function in helping detect unsuspected macular oedema, a critical but treatable condition.

The current guideline recommendations can be found at

https://www.nice.org.uk/guidance/ng17

16.1.3 Referral

16.1.3.1 Rationale

The issues of surveillance programmes, screening technologies and non-blood glucose/non-blood pressure therapies for prevention are considered in the immediately prior and following sections of this guideline. This section considers the issue of how quickly a person with diabetes should be seen by an ophthalmologist once potentially sight-threatening retinopathy is detected.

16.1.3.2 Evidence statements

The SIGN guidelines showed from controlled trials that poor outcomes and severe visual loss are associated with a delay in treatment of over two years from diagnosis of sight-threatening diabetic retinopathy.[667] This figure was one year for vitrectomy (IIa).

16.1.3.3 Consideration

The group felt it inappropriate to derive and recommend new referral guidelines without detailed review of the ophthalmological literature, particularly as such guidelines were already published by the Royal College of Ophthalmologists and the National Screening Committee diabetic retinopathy screening group (www.nscretinopathy.org.uk). In the area of assessment of macular oedema it was noted that retinal screening recommendations using digital photography (see Section 9, 'Screening tests for retinopathy') could not inform the referral process suggested by the RCO guideline; thus use of unexplained change in visual acuity was substituted, reflecting current practice.

16.1.3.4 Recommendations

The current guideline recommendations can be found at

https://www.nice.org.uk/guidance/ng17

16.1.4 Non-surgical treatment of diabetic retinopathy

16.1.4.1 Rationale

The means and systems of detection of diabetic retinopathy in sufficient time to allow successful laser therapy are considered in the previous three sections. However, laser therapy is a destructive salvage therapy, and prevention by good blood glucose and good blood pressure control are not as yet absolutely successful. Accordingly it is important to consider whether other approaches can delay the development of retinopathy in people with type 1 diabetes.

16.1.4.2 Evidence statements

There is a lack of robust evidence for non-surgical, non-laser treatment of diabetic retinopathy. In general, trials in this area have limitations in their methodology.

The SIGN guideline addressed the absence of good evidence for use of ACE inhibitors in diabetic eye disease.[667] One multicentre RCT examined therein is methodologically limited. Trials with ACE inhibitor therapy are ongoing but at present there is inconclusive evidence in this area (Ia).

There is limited evidence from trials with the antiplatelet agents ticlopidine[237,237,723] and dipyridamole[562] that measures for deterioration of retinopathy were significantly lower in patients treated with antiplatelet agents compared to placebo, although potential methodological limitations would prevent this evidence forming the basis of a clinical recommendation. Ticlopidine has a high incidence of side effects (Ib).

One three-year study showed a sevenfold reduction in the number of definite annual microaneurysms compared to placebo in insulin-treated patients, and an inverse relationship between progression of microaneurysms and hypo-aggregability level in patients treated with ticlopidine.[517] The trial in this treatment area is of moderate size (Ib).

A recent randomised controlled trial showed high dose vitamin E significantly reduced mean circulation time and increased retinal blood flow in diabetic patients.[108,109] No differences were seen in retinopathy level between the placebo and vitamin E groups (Ib).

16.1.4.3 Consideration

Issues of blood glucose control, blood pressure control or smoking are covered in chapters 7 and 8. Outside these indications the evidence was not felt to be strong enough to justify any recommendation. As this is in line with current practice, no negative recommendations were felt to be needed.

16.2 Diabetic kidney disease: kidney damage [2004]

16.2.1 Rationale

Kidney damage in type 1 diabetes is the largest cause of renal failure in the working age group. Primary prevention by good blood glucose and good blood pressure control is considered elsewhere in this guideline while this section deals with the early detection of diabetic nephropathy.

16.2.2 Evidence statements

Predictors of nephropathy

One seven-year longitudinal study showed the ability to predict progression to diabetic nephropathy by the presence of microalbuminuria may not be as reliable as previous studies have assumed.[708,709] Approximately 19% to 24% of patients with microalbuminuria develop diabetic nephropathy. Systolic blood pressure, glycated haemoglobin and triglycerides were significantly higher in people with type 1 diabetes who progressed to diabetic nephropathy, than for those who did not (III).

Five year follow-up of microalbuminuric patients with type 1 diabetes showed 19% progressed to diabetic nephropathy and 33% regressed to normoalbuminuria.[28] Progressors had significantly higher HbA1c and mean blood pressure and incidence of proliferative retinopathy compared to non-progressors (III).

Another seven-year prospective study in 148 normotensive people with diabetes showed that baseline albumin excretion rate (AER) is the predominant predictor for the development of microalbuminuria in type 1 diabetes.[483] Raised mean arterial blood pressure and HbA1c also were significantly related to progression to microalbuminuria (III).

A cohort study of two years follow-up showed in sex-specific analysis that HbA1c, age and baseline AER were particularly important predictors of progression to nephropathy in men, whereas duration of diabetes and triglycerides were particularly important in women.[143] Low- density lipoprotein (LDL) cholesterol was particularly important in people with shorter duration of diabetes and triglycerides in those with a longer diabetes duration (IIa).

A case-controlled study with 10-year follow-up showed that baseline glomerular filtration rate (GFR), although not a predictor of end-point AER or microalbuminuria, was a significant predictor of end-of-study blood pressure level.[792] Levels of AER and blood pressure were the main risk factors for renal outcome. A further five-year prospective study showed that in patients with microalbuminuria decline in GFR was independently correlated to onset of diabetic nephropathy and baseline systolic blood pressure (IIa).[484]

Screening and diagnosis

The SIGN diabetes guidelines include one comparative study showing that measurements of albumin loss and serum creatinine are the best screening tests for diabetic nephropathy (III).[667]

Urine albumin concentration compared to urine albumin:creatinine ratio in a screening accuracy test showed specificity and sensitivity for microalbuminuria of 77% and 82% and 77% and 92% and for macroalbuminuria levels of 84% and 90%, and 88% and 90%.[23] No statistically significant difference was seen when comparing the performance of these two measures in detecting nephropathy (DS).

Both albumin concentration and albumin:creatinine ratio measured on a first-pass morning urine sample and compared against timed collection of urinary albumin excretion rate, showed high sensitivity and specificity for normal and elevated albuminuria.[132] Combining the two tests together in the same urine sample revealed the highest sensitivity (98%) and specificity (100%) (DS).

A comparative study reported in the SIGN guidelines reports that first-pass morning urine samples best reflect a timed collection and provide adequate assessment of urinary albumin loss (III).[667]

One test accuracy study comparing 24-hour urine collection with spot-urine samples showed both samples were accurate for the screening and diagnosis of diabetic nephropathy.[799] Urinary protein better correlates with the reference standard (urinary AER) in macro- albuminuric (0.95) and microalbuminuric (0.80) samples, than in normoalbuminuric samples (0.61) (DS).

A 10-year follow-up study showed the predication of microalbuminuria is most effective in a four-hour morning urine collection with a greater specificity than 24-hour collection (positive predictive value 91% vs 79%), and is similar to the overnight collection, but with a greater sensitivity (DS).[204,205]

One screening test study showed significant intraindividual variation of urinary albumin excretion between samples taken in triplicate for seven days.[499] Mean coefficient of variation was 49%. Urinary albumin excretion more than 1.0 mg/mmol on the first specimen had a sensitivity of 97% and specificity of 82% for detection of those with a three sample mean more than 2.5 mg/mmol (DS).

A microalbumin analyser was shown in one screening test accuracy study to have sensitivity, specificity, negative predictive and positive predictive values of 92%, 100%, 93% and 100% respectively, suggesting a high reproducibility and reliability for microalbuminuria detection.[140,141] Another accuracy study showed a different device to have sensitivity, specificity and negative and positive predictive value of 100%, 97%, 100% and 96% respectively (DS).[678]

A semi-quantitative diagnostic test reported sensitivity of 86% and specificity of 67% to estimate albumin excretion rate as a screening tool for microalbuminuria.[765] This was consider- ably lower than the reference standard of albumin concentration (sensitivity 75% and specificity 94%) using the Micral test, which itself is not an effective screening tool for microalbuminuria. A further three studies of similar design, predominantly comparing Micral test with urinary albumin excretion rates returned varying results in terms of accuracy.[15,16,20,21,278] However, all suggested a lower sensitivity of Micral test for the detection of albuminuria (DS).

One correlation study reporting on self-testing with the Micral test found that 80% of patients classified themselves correctly.[584] Using at least two positive test results increased the specificity and sensitivity to 81% and 92% with a positive predictive value 71% leading to 90% of all patients classifying themselves correctly (III).

One correlation study showed that the dipstick testing method was insensitive or not adequately specific to detect abnormal overnight albumin excretion rate.[416,417] This study had potential internal validity limitations and should not be used as the basis for a positive clinical recommendation (III).

One diagnostic study of a Clinitek microalbumin test method performed in 302 people with diabetes demonstrated sensitivity and specificity of 79% and 81% and negative and positive predictive values of 46% and 95% for determining microalbuminuria (DS).[442]

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16.2.3 Health economic evidence

The health economic literature relating to the method of surveillance for emerging kidney damage produced four papers.[222,222,440,456,457,575,575] Three of these papers concentrated on the costs of testing, and largely ignored later outcomes. The fourth of these papers presents a cost-utility analysis of laboratory testing vs double dipstick testing plus laboratory assays where either result is positive.[440] However, this paper employs a non-standard QALY measure and this limits the robustness of the conclusions.

Five studies consider ACE inhibitor use for those found to have proteinuria following screening.[134,134,255,255,315,315,622,622,748,748] One paper was excluded as it was predicated on a significantly different healthcare system than that of the UK.[134] The remaining four papers argued that ACE inhibitor treatment will be cost-saving in those found to exhibit proteinuria.

The cost-effectiveness of ACE inhibitor treatment of those with microalbuminuria[83,395,395,566,568,682,682] is also analysed in four papers based outside of the UK, of which two consider benefits from arterial disease in addition to the benefits of delaying or preventing nephropathy.[566,568,682,682] Two papers suggest ACE inhibitor treatment will be cost-effective on both base case and sensitivity analysis.[83,682,682] One cost-utility study (interpretation of which is limited by possible typographic errors in the calculations) considers nephropathy benefits only and suggests ACE inhibitor treatment is cost-effective on their base case analysis but not in sensitivity testing.[395] A final paper considers both nephropathy and arterial benefits and finds a high cost per life year saved.[566,568]

16.2.4 Consideration

The issue of blood glucose control and its role in the development of microvascular complications is considered elsewhere in this guideline.

While there was no formal evidence on frequency of testing in the individual without previous evidence of nephropathy, organisational issues and the slow time course of progression of nephropathy suggested yearly surveillance in concert with eye and foot surveillance. For perceived reasons of convenience and adherence, spot urine specimens were considered more useful than timed collections, and, because of the effects of activity on albumin excretion rate, first-pass specimens on rising (‘early morning urine’) the most desirable. As urine concentration varies considerably between and within individuals, the general recom- mendation to measure an albumin:creatinine ratio was accepted, but if this was not organisationally practical a specific and sensitive concentration test could be used. Once positive, confirmation is recommended given the variability of albumin excretion rate from day to day. It was not felt that confirmation required a further clinic visit if one was already scheduled at three to four month intervals, unless there was evidence of renal impairment or non-diabetic renal disease. It seems sensible to measure serum creatinine annually at the same time. There is a need to consider the possibility of renal disease unrelated to diabetes.

Effectiveness and cost-effectiveness evidence suggests that ACE inhibitors should be used as first-line therapy in people with type 1 diabetes once albumin excretion rate is detectably abnormal. Discussion of side effects noted the more serious of these (hyperkalaemia and acute renal impairment) related mostly to people with type 2 diabetes. No direct evidence for angiotensin 2 receptor antagonists in type 1 diabetes had been found, but as the microvascular complications of diabetes seem independent of aetiology of diabetes, the Group felt that evidence from type 2 diabetes could be extrapolated. However, being more expensive, these should be reserved as

second-line therapy. Combination therapy seems likely to be effective but no recommendation is appropriate until more evidence on benefit and risk in this area is available.

While it was not found that a low protein diet was sufficiently well supported to be recommended for people with evidence of established diabetic nephropathy, it was felt that formal advice on a non-high protein diet should be given. In the absence of useful evidence, the group were unable to set an arbitrary referral cut-off based on one biochemical measure, but agreed to leave this to local collaborative arrangements between specialists.

16.2.5 Recommendations

The current guideline recommendations can be found at

https://www.nice.org.uk/guidance/ng17

16.3 Chronic painful diabetic neuropathy [2004]

2. **For guidance on managing chronic painful diabetic neuropathy in adults with type 1 diabetes, see the NICE guideline on neuropathic pain – pharmacological management. [new 2015]**

16.4 Autonomic neuropathy [2004]

Treatments for two aspects of autonomic neuropathy – gastroparesis and erectile dysfunction – have been re-reviewed and revised in 2015. Sections relating to these two topics have been removed from this reprise of the 2004 guideline. The updated evidence for gastroparesis and erectile dysfunction can be found in sections 16.1 and 16.5.7.

16.4.1 Rationale

Autonomic neuropathy is a late complication of diabetes that presents in diverse ways and affects a variety of organ symptoms including the skin (sweating), blood vessels (orthostatic hypotension), gastrointestinal tract (gastroparesis, diarrhoea), heart (cardiac arrest), bladder and sexual function. It may blunt the symptoms of hypoglycaemia. Considerable morbidity occurs as a result of many of these problems.

16.4.2 Evidence statements

Progression of autonomic neuropathy

A long-term follow-up study measured the progression of symptoms of autonomic neuropathy in 76 people with type 1 diabetes and over nine years.[454,455] This study found that of all the symptoms of autonomic neuropathy only gastroparesis was found to have increased in prevalence from baseline. At nine years after entering the study the only other symptoms reported were diarrhoea, impotence, loss of vaginal lubrication, hypoglycaemia unawareness and postural hypotension, and these were reported in not more than 9% of the study sample. There was a tendency for many symptoms such as hypoglycaemia unawareness to recover with time (III).

Symptoms of autonomic neuropathy

Two descriptive reviews were located that suggested possible symptoms due to autonomic neuropathy across diabetes populations. One review suggested impotence, unexplained diarrhoea, faecal incontinence, unexplained urinary symptoms (increased period between micturition, muted sensation of bladder fullness, frequency, urinary incontinence, unexplained bladder dilation),

postural dizziness or faintness, gustatory sweating, dry feet, unexplained bloating, early satiety, fullness, nausea, vomiting, unexplained dysphagia and unexplained ankle oedema.[638,639] The authors suggested that tests for autonomic neuropathy may help in defining neuropathic aetiology. Another review found that autonomic symptoms can be vague and may present insidiously, and that nerve damage can be found in people without symptoms being manifest.[215] It is suggested that a mixed presentation is usual with a combination of postural hypotension, nocturnal diarrhoea, gastric problems, bladder symptoms, abnormal sweating, impotence or a failure to recognise that hypoglycaemia is likely. In addition people with severe symptoms may also have advanced retinopathy, nephropathy and somatic neuropathy (IV).

Aldose reductase inhibitors

Three randomised controlled trials have investigated the effect of ponalrestat on autonomic nerve function in mixed diabetes cohorts. Two small and short-term studies found no benefit of ponalrestat over placebo in terms of heart rate variability[263,264] or standard tests of autonomic function,[216] although a vibration perception measure or peripheral neuropathy did show a significant improvement with the intervention drug after 16 weeks of therapy.[263,264] However the potential methodological limitations of this study would not recommend it for the basis for recommendations (Ib).

A larger multicentre trial also testing the effect of 600 mg of ponalrestat compared to placebo found heart rate response to standing was significantly greater on the intervention drug while HbA1c remained constant throughout the period, and with no effect on frequency of adverse events, although only a third of the study population displayed abnormal autonomic neuropathy from tests, with the sample being drawn from people with diabetes and peripheral neuropathy (Ib).[706]

A long-term study found that there was a significant increase in indices of postural index and heart rate variability after two years of treatment with tolrestat compared with placebo, with changes in autonomic function not being influenced by changes in HbA1c level.[190,191] This study was conducted in people with diabetes who displayed abnormalities in two or more standard autonomic function tests and used a dose of 200 mg/day tolrestat (Ib).

ACE inhibitors

Two small studies with medium-term follow-up investigated the potential of the angiotensin converting enzyme inhibitor quinapril to improve the heart rate variability of people with diabetic autonomic neuropathy. One study found total heart power (by 24-hour ECG) to be improved with quinapril compared to placebo as was high frequency power at six months.[412] In addition there was a significant increase in the level of heart rate variability at both three and six months. A similar study for 12 months found quinapril to have beneficial effects on all heart rate frequency domains, and the low frequency to high frequency power ratio to be lower (improved) with quinapril than placebo, and this held for analysis of morning, evening, or night-time comparisons.[54] The study also found quinapril to reduce heart rate to 12 months although no effect was seen on blood pressure. No complications of diabetic autonomic neuropathy or hospitalisations were reported (Ib).

No studies were identified that determined the effects of quinapril on symptoms of autonomic neuropathy.

Indirect cholinergic agent cisapride

A small crossover trial of 20 mg cisapride compared to placebo in a mixed diabetes population found no increase in antral or duodenal motility with the intervention drug; but antral-duodenal coordination was significantly improved when fasting, and at other meals (Ib).[766]

Erythromycin

Three small crossover trials of erythromycin compared to placebo in people with Type 1 diabetes and documented gastroparesis found short-term improvement in emptying of solids and mixed results with liquids with oral[180,645] or intravenous[368] administration, without side effects. However no improvements in symptoms scores were reported and larger scale and longer trials will be required to prove efficacy (Ib).

16.4.3 Health economic evidence

No health economic papers were found regarding the diagnosis of either autonomic neuropathy or gastroparesis. One paper was identified in the cost-effectiveness of management for painful neuropathy.[420] However, as a review of other evidence, specific cost-effectiveness data was limited to recommending intensive treatment to reduce complications.

16.4.4 Consideration

The group noted that the manifestations of autonomic neuropathy often occurred independently of each other, with very significant overlap into many other super-specialties of medicine (for example dermatology, gastroenterology, urology). Accordingly, the topic addressed a wider range of diagnostic and management issues than could be tackled in a diabetes guideline. Nevertheless the importance of alertness to, and detection of, these conditions was clearly relevant to the practice of the diabetes team. Of specific relevance is gastroparesis because of the effect of this condition on blood glucose control, but the group recognised that the diagnosis of this condition was not easy or reliable, and the treatments available only partially and erratically successful.

16.4.5 Recommendations

The current guideline recommendations can be found at

https://www.nice.org.uk/guidance/ng17

16.5 Gastroparesis [2015]

This section was updated in 2015.

16.5.1 Introduction

Gastroparesis is the term used to describe delayed gastric emptying in the absence of mechanical obstruction.[577]It may occur as part of the manifestation of autonomic neuropathy in people with diabetes: dysfunction of the vagus nerve and intrinsic enteric autonomic nerves are involved in its pathogenesis. Patients can present with bloating and early satiety and, in more advanced disease, post-prandial vomiting, inability to eat, weight loss and malnutrition may occur (2). Diagnosis is usually made by studying gastric emptying for solids and liquids with scintigraphy studies, although improvements in emptying may not correlate directly with symptoms (3). Symptoms of gastroparesis may, however, be exacerbated by high blood glucose concentrations at the time of eating, as hyperglycaemia causes a physiological delay in gastric emptying even in health (4). Gaining control of the blood glucose during the investigation and treatment of autonomic neuropathic gastroparesis is therefore important, in addition to other treatments aimed at improving gastric emptying (5).

Impaired extrinsic and intrinsic innervation may occur elsewhere in the gastrointestinal tract in association with gastroparesis. Constipation is common but profuse and watery diarrhoea, typically occurring at night, and alternating with constipation, has also been described.[546]

Management of gastroparesis should include nutritional assessment and support, and attempts at symptomatic relief and optimisation of glycaemic control (6). In severe cases, the stomach may need to be bypassed with feeding via jejunostomy. Therapies to enhance gastric emptying include medications, electrical stimulation and surgery

The GDG asked this question:

- In adults with type 1 diabetes, what is the most effective treatment for gastroparesis?

16.5.2 Review question: In adults with type 1 diabetes, what is the most effective treatment for gastroparesis?

For full details see review protocol in Appendix C.

Table 113: PICO characteristics of review question

Population	• Adults with type 1 diabetes and Gastroparesis • Adults with type 1 diabetes or type 2 diabetes (in the same study) and gastroparesis
Intervention/s	• Prokinetic agents/gastroprokinetic agents (for example, erythromycin) • 5-Hydoxytryptamine antagonists (for example, ondansetron) • Anti-emetics • Botulinum toxin • Electrical stimulation interventions • Intensive insulin treatment/glucose control • Dietary changes • Enteral feeding • Acupuncture • Aldose reductase inhibitors (including epalrestat) • Histamine-2 receptor antagonists • Centrally acting antidepressants • Surgical interventions (including gastrectomy)
Comparison/s	• Placebo • Standard care • Each other (within class and between-class comparisons) • Continuous agent versus other agents • Rotation of medications
Outcomes	• Hospital admissions • Severe hypoglycaemia • Vomiting - including frequency • Weight loss • Quality of Life:SF-36 • HbA1c • Symptom control - as defined by the study
Study design	RCTs, prospective observational studies

16.5.3 Clinical evidence

We searched for RCTs and prospective observational studies assessing the most effective treatment for Gastroparesis in adults with type 1 diabetes. Due to lack of data specifically in a type 1 diabetes population, and because gastroparesis and its treatment is not dependent upon/not affected by the type of diabetes, we extended the inclusion criteria to include studies that involved a mixed

population of type 1 diabetes and type 1 diabetes, regardless of the percentage of type 1 diabetes that was present.

We also included two of the three relevant studies from the old 2004 NICE guideline on type 1 diabetes in adults that met our inclusion criteria.[368,645]. The third study[180] was excluded as it did not report our pre-specified outcomes and had only a 3hr treatment time.

Overall, eighteen studies have been included in this review.[13,14,94,238,241,349,368,429,490,490,491,554,555,573,618,618,645,676,684,692,692,729,730,746] Evidence from these are summarised in the GRADE tables and narrative evidence statements. See also the study selection flow chart in Appendix D, forest plots in Appendix J, study evidence tables in Appendix G and exclusion list in Appendix K.

The 18 included studies consisted of fourteen RCTs[13,14,94,238,241,368,490,490,491,554,555,573,618,618,645,684,692,692]and five observationalstudies[349,429,676,729,730,746]. Four of the RCTs [13,94,368,491] also included observational data (the follow-up period consisted of all participants being put on the treatment arm for a period of time). One of the RCTs (Janssens 1990)[368] was only used for observational data, as the RCT part of the study consisted of only 1 day of treatment, and thus did not meet our inclusion criteria.

All non-comparative observational studies were not able to be combined in a meta-analysis or GRADE profile, and were graded as Low quality (due to their study design). However, a summary of the quality and limitations of these studies can be found in Appendix G. Where data was not suitable for GRADE, a narrative report is given (see 16.1.1.1 and 16.1.1.2).

Outcomes reported include:

- Quality of Life
- Vomiting
- Adverse events
- Scores for upper GI symptoms
- HbA1c (%)
- Weight change

Included studies did not report on the following outcomes:

- Severe hypoglycaemia

There is National Institute for Health and Care Excellence (NICE) interventional procedure guidance (IPG489; issue date May2014) on gastroelectrical stimulation for the treatment of gastroparesis Gastric Electrical Stimulation for Gastroparesis. This guidance was not specific to diabeticgastroparesis, and so we have only incorporated into our reviewany relevant references from the IPG that specificallylooked at electrical stimulationin diabetic gastroparesis populations.

Table 114: Summary of studies included in the review

Study	Intervention/comparison	Population	Follow-up	Outcomes	Comments
RCTs					
Gastric electrical stimulation					
ABELL 2003[13]	GES system (implanted) System on vs. off	n=33 gastroparesis n=17 diabetes Cross-over RCT	1 month treatment (each cross-over period)	Total symptom score Vomiting frequency	Data reported for the diabetic subgroup
ABELL 2011[13,14]	GES system (implanted) System on vs. off	n=58 gastroparesis n=13 diabetes Cross-over RCT	72 hours treatment (each cross-over period)	Vomiting score	Data reported for the diabetic subgroup
FROKJAER 2008[241]	GES system (implanted) System on vs. off	n=7 diabetes with gastroparesis n=6 type 1 diabetes Cross-over RCT	1 month treatment (each cross-over period)	Vomiting episodes	
MCCALLUM 2010B[490,491]	GES system (implanted) System on vs. off	n=45 diabetes with gastroparesis Cross-over RCT	3 months treatment (each cross-over period)	Vomiting episodes	
Botox (BoNT/A)					
FRIEDENBERG 2008[238]	BOTOX (BoNT/A) 200U BoNT/A (5 ml volume) injection vs. placebo saline injection	n=32 gastroparesis n=18 diabetes RCT	1 injection; 1 month follow-up.	Symptom severity score (GCSI)	Data reported for the diabetic subgroup
Erythromycin					
SAMSOM 1997[645,646]	Erythromycin (250 g orally, 3 times a day, 30 minutes pre-meal) vs. placebo tablet	n=12 with type 1 diabetes Cross-over RCT	2 weeks treatment (each cross-over period)	Symptom severity score	
Metoclopramide					
MCCALLUM 1983[490]	Metoclopramide (10 mg tablets) four times daily vs. placebo	n=44 with diabetes (95% type 1	3 weeks treatment	Vomiting severity score	

Study	Intervention/comparison	Population	Follow-up	Outcomes	Comments
		diabetes) RCT		Adverse events	
RICCI 1985[618]	Metoclopramide (10 mg tablets) four times daily vs. placebo	n=13 with type 1 diabetes Cross-over RCT	3 weeks treatment (each cross-over period)	Symptom score – frequency Adverse events	
Domperidone, and domperidone vs. metoclopramide					
BRAUN 1989[94]	Domperidone (10 or 20-mg tablets) four times daily vs. placebo	n=13 diabetes (95% type 1 diabetes) Cross-over RCT	1 month RCT treatment (each cross-over period)	Symptom frequency score Symptom intensity score Vomiting	Run-in phase – all given domperidone treatment Only patients who improved n domperidone in the run-in phase entered the subsequent RCT phase of the study. RCT followed by observational period – all given domperidone for up to 2 years (mean 467 days)
PATTERSON 1999 [572,573]	Domperidone (two 10 mg tablets) four times daily vs. metoclopramide + placebo tablet (one 10 mg tablet + one placebo tablet) four times daily	n=95 with type 1 diabetes RCT	4 weeks treatment	Vomiting Symptom severity score	
SILVERS 1998[684]	Domperidone (two 10-mg tablets) four times daily vs. placebo (two identical dummy tablets) four times daily	n=208 with type 1 diabetes n=105 Domperidone; n=103 placebo RCT	4 weeks	QoL (physical and mental component) Vomiting Adverse events	Patients receiving cisapride or metoclopramide were required to undergo a washout period of 1 week before enrolment.
Small particle diet					
OLAUSSEN 2014[554,555]	Small particle diet (foods of small particle size or able to process to	n=56 with type 1 diabetes	20 weeks	HbA1c QoL (physical and	

Study	Intervention/comparison	Population	Follow-up	Outcomes	Comments
	small size) vs. normal diabetes diet (foods recommended for people with diabetes, any particle size, low GI)	n=28 small particle size; n=28 usual diet RCT		mental component) Vomiting severity Weight change	
Observational studies					
Gastric electrical stimulation					
ABELL 2003[13]	GES system (implanted) System on vs. off	n=33 gastroparesis n=17 diabetes Observational data within an RCT	6 months follow-up (all had GES turned ON)	Total symptom score Vomiting frequency SF-36.	Cross-over RCT but gives observational data at 6 and 12 months – all had GES system turned ON
MCCALLUM 2010B[490,491]	GES system (implanted) System on vs. off	n=45 diabetes with gastroparesis Observational data within an RCT	12 months follow-up (all had GES turned ON)	Vomiting episodes Symptom severity score	Cross-over RCT but gives observational data at 12 months – all had GES system turned ON
TIMRATANA 2013[729,730]	GES system (implanted; laparoscopic)	n=110 gastroparesis n=55 diabetes Prospective case-series	27 months follow-up (mean)	HbA1c Nausea Vomiting Bloating Pain Adverse events	
VANDERVOORT 2005[746]	Electrical stimulation Stimulator (Itrel 3, Model 7425, Medtronic Kerkrade, the Netherlands)and two unipolar intramuscular electrodes	n=17 with type 1 diabetes with Gastroparesis refractory to conventional medical therapy. Prospective case-series	12 months	Weekly vomiting frequency Weekly nausea frequency HbA1c (%)	Prior to entry, upper GI ENDOSCOPY was performed to exclude mechanical causes of gastric outlet obstruction.
Domperidone					

Study	Intervention/comparison	Population	Follow-up	Outcomes	Comments
BRAUN 1989[94]	Domperidone (10 or 20 mg tablets) four times daily	n=13 diabetes (95% type 1 diabetes) Observational data within an RCT	12 weeks and median 467 days treatment	Symptom frequency score Symptom intensity score	Cross-over RCT but gives observational data after run-in (12 weeks all had domperidone treatment) Also gives observational data after the RCT (extension of median 467 days, all had domperidone treatment).
HOROWITZ 1985[349]	Domperidone (two 10 mg tablets) three times daily	n=12 with type 1 diabetes and autonomic neuropathy Prospective case-series	Median 38 days	Hypoglycaemia episodes HbA1c Vomiting Symptom severity score	Patients had autonomic neuropathy and other complications of diabetes.
Other interventions					
JANSSENS 1990[368]	Erythromycin (200 mg IV infusion for 15 minutes post-meal) vs. placebo infusion	n=10 with type 1 diabetes Observational data within an RCT	4 weeks follow-up (all on erythromycin treatment)	HbA1c	Cross-over RCT but gives observational data at 4 weeks – all had erythromycin treatment
LACY 2004[429]	Botulinum toxin A Injection of the pylorus with 200 units during upper endoscopy. Patient was observed for 1-2 h in the recovery area and then discharged home.	n=8 with type 1 diabetes Control group consisted of age and sex-matched control subjects without diabetes and without any complaints. Observational study (case-control)	12 weeks	Mean symptom score SF-36 questionnaire scores HbA1c (%)	Patients underwent esophagogastroduodenoscopy (before intervention) to rule out mechanical obstruction.
SHARMA 2011[676]	CSII pump therapy (previously on MDI)	n=26 type 1 diabetes with	1 year	HbA1c (%) Weight change	

Study	Intervention/comparison	Population	Follow-up	Outcomes	Comments
		gastroparesis Prospective case-series		Hospital admissions	

Table 115: Clinical evidence summary table: Metoclopramide versus placebo (less than 6 months)

Outcomes	Number of studies	Imprecision	GRADE rating	Absolute difference Metoclopramide	Control event rate (per 1000 patients) Placebo
Symptom score (max 100 = worse)	1 study (n=13)	Serious imprecision	LOW	MD 18.8 lower (46.18 lower to 8.58 higher)	45.3 final value in control group
Symptoms - felt better, no. of patients	1 study (n=10)	Serious imprecision	VERY LOW	RR 15.0 (0.97 – 231.8)	0
No vomiting, no. of patients	1 study (n=10)	Serious imprecision	VERY LOW	RR 13.0 (0.83 – 203.8)	0
Vomiting, no. of patients improving by score ≥2	1 study (n=44)	Very serious imprecision	VERY LOW	100 more per 1000 (from 245 fewer to 915 more)	500
Weight loss, no. of patients	1 study (n=10)	Very serious imprecision	VERY LOW	300 fewer per 1000 (from 498 fewer to 276 more)	600
Adverse events, no. of patients	2 studies (n=60)	Serious imprecision	LOW	295 fewer per 1000 (from 79 fewer to 738 fewer)	719

Table 116: Clinical evidence summary table: Domperidone versus placebo (less than 6 months)

Outcomes	Number of studies	Imprecision	GRADE rating	Absolute difference Domperidone	Control event rate (per 1000 patients) Placebo
Quality of Life (QoL) SF36 (36 items across 8 domains that can be reduced to 2 indexes) – Physical component	1 study (n=203)	No serious imprecision	MODERATE	MD 2.42 higher (2.21 to 2.63 higher)	-1.77 final value in control group
Quality of Life (QoL) SF36 (36 items across 8 domains that can be reduced	1 study (n=203)	No serious imprecision	MODERATE	MD 0.12 lower (0.40 lower to 0.16 higher)	-0.96 final valuein control group

Outcomes	Number of studies	Imprecision	GRADE rating	Absolute difference Domperidone	Control event rate (per 1000 patients) Placebo
to 2 indexes) – Mental component					
Vomiting	1 study (n=208)	Very serious	VERY LOW	44 fewer per 1000 (from 49 fewer to 29 more)	49
Adverse events	1 study (n=208)	No serious imprecision	Moderate	574 fewer per 1000 (from 631 fewer to 372 more)	631

Table 117: Clinical evidence summary table: Domperidone versus metoclopramide (less than 6 months)

Outcomes	Number of studies	Imprecision	GRADE rating	Absolute difference Domperidone	Control event rate (per 1000 patients) Metoclopramide
Symptom severity score (TSS) – max score 12	1 study (n=93)	No serious imprecision	MODERATE	MD 0.38 lower (0.58 to 0.18 lower)	5.09 final value in control group

Table 118: Clinical evidence summary table: Erythromycin versus placebo (less than 6 months)

Outcomes	Number of studies	Imprecision	GRADE rating	Absolute difference ERYTHROMYCIN	Control event rate (per 1000 patients) PLACEBO
Symptom severity score (max. 3.0)	1 study (n=12)	Serious	LOW	MD 0.28 lower (0.9 lower to 0.34 higher)	1.81 final value in control group
Individual symptoms severity scores (max. 3.0)	1 study (n=12)	Serious	LOW	NS improvement in any individual symptom score.	-

Table 119: Clinical evidence summary table: Botox versus placebo (less than 6 months)

Outcomes	Number of studies	Imprecision	GRADE rating	Absolute difference Botox	Control event rate (per 1000 patients) Placebo
GCSI score reduction (maximum 45)	1 study (n=32)	Very serious	VERY LOW	MD 2.3 lower (11.62 lower to 7.02 higher)	13.7

Table 120: Clinical evidence summary table: Electrical stimulation: ON versus OFF (less than 6 months)

Outcomes	Number of studies	Imprecision	GRADE rating	Absolute difference ON	Control event rate (per 1000 patients) OFF
Total symptom severity score (TSS) - 6 symptoms (Max 24)	1 study (n=17)	Not serious	LOW	MD 1.9 lower (2.98 to 0.82 lower)	13.2 final value in control group
Total symptom severity score (TSS) - 7 symptoms (Max 28)	1 study (n=45)	Serious	LOW	MD 1.08 higher (1.65 lower to 3.81 higher)	9.81 final value in control group
Total symptom frequency score (TSS) - 7 symptoms (Max 28)	1 study (n=45)	No serious	MODERATE	MD 0.61 higher (2.4 lower to 3.62 higher)	11.89 final value in control group
Vomiting severity score (Max 4)	1 study (n=45)	Serious	LOW	MD 0.42 higher (0.1 lower to 0.94 higher)	1.64 final value in control group
Vomiting frequency (episodes/day)	1 study (n=7)	Very serious	VERY LOW	MD 0.8 higher (0.21 lower to 1.81 higher)	0.33 final value in control group
Vomiting frequency score (Max 4)	1 study (n=45)	No serious	MODERATE	MD 0.28 higher (0.32 lower to 0.88 higher)	2.03 final value in control group
Weekly vomiting frequency; episodes/week	1 study (n=17)	Serious	VERY LOW	Median 6.0 (IQR 3.0-14.8)	Median 12.8 (5.5-24.2)
Weekly vomiting frequency; episodes/week	1 study (n=45)	Serious	LOW	Median 3.8 (IQR 0.75-14.0)	Median 4.3 (0.4-15.1)
Vomiting score	1 study (n=17)	No serious	LOW	-0.31 units/day (-0.64, 0.02) with stimulation (p=0.069)	

Table 121: Clinical evidence summary table: Small particle size diet versus usual diabetic diet (less than 6 months)

Outcomes	Number of studies	Imprecision	GRADE rating	Absolute difference Small particle diet	Control event rate (per 1000 patients) Placebo
HbA1c, %	1 study (n=56)	Serious	VERY LOW	MD 0.4 lower (0.9 lower to 0.1 higher)	7.8%
SF-36 – PCS	1 study (n=56)	Serious	VERY LOW	MD 4.70 higher (1.53 lower to 10.93 higher)	35.5
SF-36 - MCS	1 study (n=56)	Serious	VERY LOW	MD 2.30 higher (5.56 lower to 10.16 higher)	41.5
Vomiting severity	1 study	Serious	VERY LOW	MD 0.56 lower (1.01 to 0.11 lower)	Not reported

Outcomes	Number of studies	Imprecision	GRADE rating	Absolute difference Small particle diet	Control event rate (per 1000 patients) Placebo
	(n=56)				
Weight change, kg	1 study (n=56)	No serious	LOW	MD 0.012 lower (1.6 lower to 1.6 higher)	78.5

16.5.4 Economic evidence

Published literature

No relevant economic evaluations were identified.

One economic evaluation relating to this review question was identified but was excluded due to a combination of limited applicability and methodological limitations.[293] This is summarised in Appendix L, with reasons for exclusion given.

See also the economic article selection flow chart in Appendix E.

Unit costs

Relevant unit costs are provided below to aid consideration of cost effectiveness.

Table 122: Staff costs

Group	Cost
Dietitian (band 5)	£34
GP appointment	£43
Consultant: medical	£157

Source: PSSRU 2012[159]

Table 123: Pharmacological treatments

Dose	Administration	Unit cost (per individual dose)	Annual cost
Metoclopramide[a]			
10 mg 3 times a day	Tablet (10 mg)	£0.03	£36
10 mg 3 times a day.	Oral solution (150 ml, 5 mg/5 ml)	£1.52	£1,662
10 mg 3 times a day	Injection (2-ml amp, 5 mg/ml)	£0.26	£285
Erythromycin[b]			
250 mg 3 times a day	Tablet (250 mg)	£0.07	£72
250 mg 3 times a day	Capsules (250 mg)	£0.84	£916
250 mg 3 times a day	Oral solution (100 ml, 250 mg/5 ml)	£0.20	£215
Domperidone			
10 mg 3 times a day	Tablet (10 mg)	£0.04	£42
20 mg 4 times a day	Tablet (10 mg)	£0.04	£113
10 mg 3 times a day	Oral solution (200 ml, 1 mg/ml)	£0.63	£686
20 mg 4 times a day	Oral solution (200 ml, 1 mg/ml)	£0.63	£1,829

Source: All doses and costs from MIMS Dec 2013 [9]
(a) MHRA warning
(b) Off license use

Table 124: Cost of hospital stay

HRG[a]	HRG codes[b,c]	National Average Unit Cost	Lower Quartile Unit Cost	Upper Quartile Unit Cost
Non-malignant stomach or duodenum disorders (elective inpatient)	FZ43A, FZ43B, FZ43C[d]	£1,872	£1,024	£2,201
Non-malignant stomach or duodenum disorders (non- elective inpatient)	FZ43A, FZ43B, FZ43C[e]	£1,023	£782	£1,169

(a) Gastroparesis is coded under this HRG but unable to work out the percentage of these finished consultant episodes which are accredited to gastroparesis.
(b) NHS Reference Costs[177]
(c) HRG codes for all levels of complications have been included and a weighted average calculated
(d) Total activity – 2,021 finished consultant episodes
(e) Total activity – 31,762 FCE's

Table 125: Cost of enteral tube feeding and parenteral nutrition

Feeding Method	Total Cost	Eligible patients	Annual cost per patient
Enteral tube	£112,396,000	93,186	£1,206
Parenteral nutrition	£25,719,000	18,100	£1,421

(a) NICE CG32: Nutrition support in adults: oral nutrition support, enteral tube feeding and parenteral nutrition- Costing Report[530]

Table 126: Cost of electrical stimulation – Medtronic Enterra System

Component	Ex. VAT	Inc. VAT
Neurostimulator[a]	£4,700[a]	£5,640
Electrode leads (x2)[a]	£2,600[a]	£3,120
Laparoscopic surgery[b]	-	£5,000[b]
Total cost[c]	-	£13,760[c,d]

(a) Personal communication with Medtronic
(b) Estimated cost[350]
(c) Likely to underestimate the total cost as this does not include follow-up cost, device replacement or any adverse events.
(d) The device has a limited lifespan dictated principally by battery life, officially estimated at 5 to 10 years, although in practice 7 to 12 years is the norm. When the device has expired it will require surgery to be removed or replaced.

16.5.5 Evidence statements

Clinical

Evidence from RCT data

Metoclopramide versus placebo

Low and very low quality evidence from small studies showed a clinical benefit of metoclopramide over placebo at less than 6 months for symptom score, the number of patients who felt better, the number who had no vomiting, the number who lost weight, and the number who experienced adverse events. However, there was no clinical difference between metoclopramide and placebo for the number of patients improving vomiting by a score more than or equal to 2.

Domperidone versus placebo

Moderate and very low quality evidence from a single study showed a clinical benefit of domperidone over placebo at less than 6 months (4 weeks) for the physical component of the SF-36 QoL measure, reduction in vomiting, and reduction in adverse events. However there was no clinical

difference between domperidone and placebo at less than 6 months (4 weeks) for the mental component of the SF-36 questionnaire scores.

Domperidone versus metoclopramide

Moderate quality evidence from a single study showed no clinically significant benefitof domperidone and metoclopramide at less than 6 months (4 weeks) for total symptom severity score.

Erythromycin versus placebo

Low quality evidence from a small single study showed no clinical difference between erythromycin and placebo at less than 6 months (2 weeks) for both individual and total symptom severity scores.

Botox versus placebo

Very low quality evidence from a small single study showed no clinical difference between Botox and placebo at less than 6 months (1 month) for reduction in GCSI score.

Electrical stimulation ON versus OFF

Moderate, low, and very low quality evidence from small studies showed a clinical benefit of electrical stimulation compared with no stimulation at less than 6 months for weekly vomiting frequency (episodes/week). However the evidence also showed clinical harm of electrical stimulation in terms of vomiting severity score, and vomiting frequency (episodes/day). There was no clinical difference for total symptom severity scores, vomiting frequency score, vomiting score, or for weekly vomiting frequency (episodes/week – a different study to the one that showed clinical benefit).

Small particle diet versus normal diabetic diet

Low and very low quality evidence from a single study showed a clinical benefit of small particle diet compared with usual diabetic diet at less than 6 months (20 weeks) for HbA1c, vomiting severity, and for QoL (SF-36 physical component). There was no clinical difference for QoL (SF-36 mental component), and for weight change.

Evidence from observational data - narrative summary

The following studies have been summarised as a narrative because they were not suitable study designs for meta-analysis or GRADE. All observational study data is graded as Low quality.

Botulinum toxin A during upper endoscopy

One case-control study (n=8; n=16, including controls) LACY 2004[429] found that compared with baseline, there was a reduction in symptom score at 12 weeks, but there were no differences in HbA1c or SF-36.

Electrical stimulation

One study (n=17), reporting observational follow-up data from an RCT (ABELL 2003)[13] found that compared with baseline, after treatment with electrical stimulation there were improvements in weekly vomiting frequency, total symptom severity score, and SF-36 physical function at both 6 months and 12 months. However, SF-36 mental component was worse.

One study (n=45), reporting observational follow-up data from an RCT (MCCALLUM 2010B)[490,491] found that compared with baseline, after treatment with electrical stimulation there were

improvements in symptom scores (both frequency and severity), SF-36, and in-hospital days at 4.5 months. However, there was no impact on HbA1c, weekly hypoglycaemic episodes or BMI.

One study, a case-series (n=17), (VANDERVOORT 2005)[746] found that compared with baseline, after treatment with electrical stimulation there were improvements in HbA1c, and weekly nausea and vomiting at 6 months and 12 months.

One study, a case-series (n=55), TIMRATANA 2013 [729,730] found that compared with baseline, after a mean of 27 months treatment with laparoscopic electrical stimulation there were improvements in nausea, vomiting, and pain. However there was no difference for bloating, and there were 5 adverse events (post-surgical complications).

Erythromycin

One study (n=10), found accelerated gastric emptying after a single intravenous administration of erythromycin given in an RCT design, each subject receiving active or placebo in random order, and also reported observational follow-up data with all subjects continuing on oral erythromycin (JANSSENS 1990)[368]which had intermediate effect on gastric emptying, anecdotal evidence of subjective improvement and an HbA1c at 4 weeks of 7.6 (5.1-10.0%) versus baseline 8.5 (5.3-11.6)% (non-diabetic range 3.6-6.4%), for which there was no statistical analysis. .

CSII pump therapy

One study (n=26), a case-series (SHARMA 2011)[676], found that compared with baseline, after treatment with CSII pump therapy there were improvements in BMI (which was increased at 6 months) and HbA1c and frequency of hospital admissions due to gastroparesis measured one year into therapy.

Domperidone

One study (n=13), reporting observational follow-up data from an RCT (n=1989)[94] found that compared with baseline, after treatment with domperidone, there were improvements in the intensity and severity of all individual symptoms at 12 weeks, as well as the total symptom scores (TSS) at 12 weeks and median of 467 days.

One study (n=12), a case-series (HOROWITZ 1985)[349], found that compared with baseline, after treatment with domperidone, there were improvements in the severity of symptoms at median 38 days.

Economic

No relevant economic evaluations were identified.

16.5.6 Recommendations and link to evidence

The current guideline recommendations can be found at

https://www.nice.org.uk/guidance/ng17

Research recommendation	Further research and RCTs are required for further assessment of interventions for gastroparesis, including the use of dopamine antagonists and patient selection, and clinical and cost effectiveness of gastric electrical stimulation interventions.
Relative values of different outcomes	The available RCT evidence and evidence from prospective observational studies was sought for the following interventions used in the management of gastroparesis: • Dopamine antagonists (for example, metoclopramide, domperidone) • Prokinetic agents/gastroprokinetic agents (for example, erythromycin)

	• 5-Hydoxytryptamine antagonists (for example, ondansetron) • Anti-emetics • Botulinum toxin • Electrical stimulation interventions • Intensive insulin treatment/glucose control • Dietary changes • Enteral feeding • Acupuncture • Aldose reductase inhibitors (including epalrestat) • Histamine-2 receptor antagonists • Centrally acting antidepressants • Surgical interventions (including gastrectomy) The evidence was reviewed to look at the impact of each intervention on the symptoms and clinical outcomes experienced by individuals with gastroparesis, including: • Nausea and vomiting – the most common symptoms reported by individuals with gastroparesis as a consequence of gastric stasis, and the greatest contributor to reduced quality of life. • Quality of life – this has been reported to be significantly reduced in individuals with gastroparesis • Hypoglycaemia - Hypoglycaemia is a regular occurrence in many people with type 1 diabetes and gastroparesis. The action of administered insulin at mealtimes can be faster than the rate of absorption of carbohydrate from the digestive tract due to reduced gastric motility. Particular focus was given to the incidence of severe hypoglycaemia (hypoglycaemia event requiring help from a 3rd party for correction), an event which has been recognised as having a significant impact on quality of life in patients with type 1 diabetes. • Glycaemic control -. Increased lability of blood glucose levels has been described in individuals with gastroparesis, as both postprandial hypo- and hyper-glycaemia can occur as insulin absorption fails to match glucose absorption from the meal. This can be a disincentive for people to take insulin. • Weight loss – this can occur in patients with gastroparesis as a consequence of early satiety and vomiting and subsequent food avoidance. Furthermore, absorption of nutrients from the digestive tract might be less when gut motility is reduced. • Hospital admissions – gastroparesis is associated with increased risk of hypoglycaemia and episodes of intractable vomiting, which may increase the risk of ketoacidosis, all ofwhich can result in admission to hospital. • Adverse events – if any treatment causes adverse events, its benefits must be weighed against the frequency and severity of such adverse events.
Trade-off between clinical benefits and harms	**Dopamine antagonists** Three very old and very small RCTs, each reporting different outcomes, about the use of metoclopramide in the management of gastroparesis[490,618,685,692] showed that it reduced physical symptoms and vomiting, and more patients experienced weight gain. The number of patients with adverse events was also lower with metoclopramide. One RCT using domperidone in the management of gastroparesis[684] showed that it reduced physical symptoms and vomiting, but had no effect on the mental symptoms associated with gastroparesis. No adverse events were reported in this trial.

	A randomised controlled trial comparing domperidone use to metoclopramide showed that metoclopramide was more likely to induce central nervous system side-effects. [572,573] **Promotility agents** Erythromycin increases gastric motility but a significant reduction in symptom severity scores was not achieved in trials[645]. An observational study reported an improvement in glycaemic control following a single intravenous infusion of erythromycin use (HbA1c 8.0% at baseline reducing to 7.6% at four weeks)[368]. The GDG did not consider the association between the treatment and the improvement to be necessarily causal **Botulinum toxins** An observational study reported that Botox significantly reduced gastroparesis symptoms[429] but this study was in only eight patients. No significant impact on quality of life was achieved and glycaemic control was not significantly different from baseline. A subsequent RCT showed that Botox treatment was less effective than placebo in reducing gastroparesis cardinal symptom index (GCSI) scores[238]. **Gastric electrical stimulation interventions** Four observational studies [746,13,729,747] reported a favourable outcome for electrical stimulation interventions for gastroparesis (reduction in weekly vomiting frequency and reduction in symptom severity scores), with one of the trials also reporting a significant improvement in glycaemic control.[746] However, subsequent RCTs investigating electrical stimulation interventions randomised to 'on' or 'off' reported variable outcomes: symptom severity scores improved in one study[13,14] but other studies reported no benefit[241,491] and suggested it could cause a harmful increase in the frequency of vomiting. **Small particle diet** One RCT comparing the effect of a small particle diet vs. a normal diabetic diet (any particle size) in the management of gastroparesis[555] showed that it reduced HbA1c and vomiting severity, and improved the physical component of SF-36. However, there was no difference on the mental component of Sf-36 or on weight loss. **Intensive insulin treatment with CSII** An observational study for the use of continuous subcutaneous insulin infusions (CSII) in individuals with gastroparesis showed that extended insulin bolus regimens could be used with meals to improve clinical outcomes[676]. The study reported that glycaemic control improved significantly (HbA1c 9.8% at baseline versus 8.0% at one year), a weight gain of 2.9 kg was achieved at 6 months, and hospital admission frequency for management of gastroparesis was reduced from 8.5 median inpatient bed days/patient/year down to 0 days at one year follow-up. No RCT evidence or evidence from prospective observational studies was found for other interventions used in the management of gastroparesis by the GDG, including enteral/parenteral feeding and gastrectomy.
Economic considerations	The primary treatment goals for gastroparesis related to diabetes are to improve gastric emptying, improve quality of life and to regain control of blood glucose levels. No cost effectiveness analysis was available about the impact of interventions on these outcomes for the management of gastroparesis in adults with type 1 diabetes. The annual unit costs of some of the interventions were presented to the GDG for consideration when making recommendations.

	Given the relatively low cost and the availability of dopamine antagonists (metoclopramide £36 per year for 10 mg three times a day; domperidone £42 per year for 10 mg three times a day), these medications were considered to be a cost-effective treatment for the management of gastroparesis symptoms, especially if their use might reduce the frequency of non-elective inpatient hospital stays for treatment of gastroparesis (national average £1,023 per stay). Electrical stimulation interventions were costed at £13,760 per system implant. The evidence of clinical benefit was not consistent across studies, and the intervention was considered unlikely to be cost-effective.
Quality of evidence	As the number and size of the trials investigating interventions for gastroparesis in adults with type 1 diabetes are small, the GDG reviewed additional evidence from trials that were undertaken in mixed populations of type 1 and type 2 diabetes patients, although the GDG did not consider evidence taken from studies looking at populations only with type 2 diabetes. The available RCT evidence was GRADE assessed for quality: • The GRADE quality of the evidence for metoclopramide versus placebo ranged from Low to Very low, with a serious/very serious risk of bias. • The GRADE quality of the evidence for domperidone versus metoclopramide was Moderate, with a serious risk of bias. • The GRADE quality of the evidence for domperidone versus placebo ranged from Moderate to Very low, with a serious risk of bias. • The GRADE quality of the evidence for erythromycin versus placebo was low, with a serious risk of bias. • The clinical evidence profile for the botulinum toxins was of Very low quality but with no serious risk of bias. • The quality of evidence from electrical stimulation studies ranged from High to Very low but there was a serious risk of bias for many of the measured outcomes.
Other considerations	The European Medicines Agency (EMA) and Medicines and Healthcare products Regulatory Agency (MHRA) guidance has stated that domperidone, metoclopramide and ondansetron should not be used for more than 5 days due to an increased risk of cardiovascular disease and the risk of developing tardive dyskinesia, outweighing the benefits of symptom relief. The exception to this in the UK is their use following radiotherapy and chemotherapy. These recommendations are not based on clinical study data but made following a review of completed adverse drug event reports. Whilst acknowledging the importance of MHRA advice, the GDG considered that the risks had to be weighed carefully against the risks and distress caused by uncontrolled chronic causes of vomiting, such as diabetic gastroparesis. They also noted that there is a paucity of proven treatments for gastroparesis. The GDG noted that all the RCTs for metoclopramide were small n=10 to n=44 patients). The single RCT on domperidone was larger and no adverse events were reported in this study in individuals with gastroparesis[684]. The GDG also noted that in a randomised controlled trial comparing domperidone use to metoclopramide[573], domperidone was less likely to induce central nervous system side-effects. The GDG therefore concluded that domperidone should be preferred to metoclopramide for the management of gastroparesis symptoms.

16.5.7 Research recommendations

32. In adults with type 1 diabetes, clinical and cost effective treatments for diabetic gastroparesis are needed, together with further evidence for the clinical and cost effectiveness of existing treatments such as dopamine antagonists, insulin pump therapy, and gastric electrical stimulation.

16.6 Acute painful neuropathy of rapid glycaemic control [2015]

This section was updated in 2015.

16.6.1 Introduction

Sudden insulinisation after a prolonged period of severe insulin deficiency can cause short- and medium-term complications. These are associated with the use of insulin itself and the sudden reduction of chronic hyperglycaemia. They include salt and water retention with weight gain, weight gain due to retention of calories previously lost in glycosuria, deterioration of existing retinopathy (attributed at least in part to a fall in the hyperperfusion of the insulin deficient, hyperglycaemic state) and a very distressing painful acute-onset neuropathy. The neuropathy has been described as “insulin induced neuritis”; “insulin induced neuropathy” and, as here, the more descriptive “acute painful neuropathy of rapid glycaemic control”, a term which acknowledged the probable role of the sudden change in ambient glucose. This neuropathy is distinct from other forms of diabetic neuropathy, management of which is described in NICE clinical guideline 173, Neuropathic pain – pharmacological management. Its onset is usually sudden and it is self-limiting. However, the duration of symptoms may be very long and the pain can be very severe. It classically affects the limbs, particularly the lower limbs, and it can be associated with more generalised allodynia (the skin is painful when touched).

Acute painful neuropathy of rapid glycaemic control is not common but it can be very distressing. Because of its aetiology, it may occur when an adult with type 1 diabetes has been able to engage with self-care after a prolonged period of self-neglect, with a negative impact on the person’s motivation for on-going self-care, which may also need to be addressed.

The aim of treatment is to reduce the pain felt to tolerable levels, so that the pain does not interfere with daily function, while continuing the insulin treatment regimen. The pain is often resistant to simple analgesia. The GDG therefore addressed the question: In adults with type 1 diabetes, what is the most effective treatment for acute painful neuropathy of rapid glycaemic control/insulin-induced neuropathy?

16.6.2 Updated review question: In adults with type 1 diabetes, what is the most effective treatment for acute painful neuropathy of rapid glycaemic control?

For full details see review protocol in Appendix C.

Table 127: PICO characteristics of review question

Population	Adults with type 1 diabetes and insulin-induced neuropathy
Intervention/s	• Analgesia, for example, Duloxetine, tramadol • Anti-epileptics, antidepressants - tricyclic antidepressants (SNRIs and duloxetine), anti-convulsants (gabapentin, pregabalin), pump therapy • Lidocaine/lignocaine (anaesthetics) • Capsaicin • Insulin pump
Comparison/s	• Anything • None
Outcomes	Outcomes • Pain scores (continuous) • Retinopathy – incidence (dichotomous) • Low-level (micro) albuminuria - incidence (dichotomous) • Resolution of symptoms (continuous) • Improvement in pain scores (dichotomous)

Study design	RCTs, observational studies, case-series

16.6.3 Clinical evidence

One study was included in the review[261]. Evidence from this study is summarised in Table 2. This study was a non-comparative observational study (case-series), and therefore were not able to be combined in a meta-analysis or GRADE profile, and was graded as Low quality (due to the study design). However, a summary of the quality and limitations of this study can be found in Appendix G. The study details and the full results have been summarised in the tables below. See also the study selection flow chart in Appendix D, study evidence tables in Appendix G and exclusion list in Appendix K.

A number of RCTs were identified in the literature search. However, these were conducted in a mixed population of type 1 diabetes and type 2 diabetes patients who had chronic diabetic neuropathy and/or did not refer not acute painful neuropathy of rapid glycaemic control. These studies were therefore excluded from the review.

The included study was a prospective case-series of n=16 diabetic patients (n=9, type 1 diabetes) reporting acute onset of insulin-induced neuropathy associated with improved glycaemic control. All patients had historically poor glycaemic control either due to anorexia and/or treatment non-adherence. The patients in the study were on different combinations of treatments and there was no direct comparison of the intervention and comparators listed in the protocol. The results from this study have been reported narratively in Table 114.

Data were available for the following outcomes:

- Improved pain scores: reported as duration of treatment for a 50% reduction in pain
- Pain Scores: reported at baseline (after intensive glycaemic control) and at follow-up
- Resolution of symptoms reported as:
  - Neuropathy impairment scores in the lower limb (NIS-LL) at baseline and 18 months
  - Autonomic symptom scores at baseline and 18 months
  - % of patients with abnormal autonomic function at baseline and 18 months
- Deterioration of other complications associated with sudden onset of diabetes control such as:
  - Retinopathy[d]: reported as no. of patients at baseline and after 6 months of intensive glycaemic control
  - Low-level (micro) albuminuria: reported as no. of patients at baseline and after 1 year of intensive glycaemic control

All outcomes (except for the following) were reported from a mixed population of type 1 diabetes and type 2 diabetes patients and are, therefore, not an exact match (that is, considered indirect) to the protocol population. Results from these have been included in this review due to the scarcity of evidence. Type 1 diabetes subgroup data were only reported in the following outcomes:

- Resolution of symptoms reported as:
  - Neuropathy impairment scores in the lower limb (NIS-LL) at baseline and 18 months
  - Autonomic symptom scores at baseline and 18 months

d Retinopathy and microalbuminuria outcomes are complications alongside acute painful neuropathy of rapid glycaemic control and not outcomes for the interventions used for the treatment of the neuropathy itself.

Table 128: Summary of studies included in the review

Study	Intervention/comparison	Population	Outcomes	Results
GIBBONS 2010[261] Prospective case-series	Various medications (alone or in combination): Anti-epileptics + TCA + Tramadol n=2 Anti-epileptics + TCA n=1 Anti-epileptics + SNRI n=1 Anti-epileptics + SNRI + tramadol n=2 Anti-epileptics + tramadol n=1 Anti-epileptics + SNRI + methadone n=1 SNRI + tramadol n=1	n=16 (n=9 type 1 diabetes) Acute painful neuropathy after rapid and sustained glycaemic control Setting: US 7/9 patients had a remote history of diabetic anorexia and other 2 subjects had historically poor BG control due to treatment non-compliance	**Improved pain scores**[a] Duration of treatment for a 50% reduction in pain	At 15 months (range 12-28)
			Pain scores[a] Pain, 0-10 Likert scale, 0=no pain; 10=worst pain imaginable)	Baseline, mean (SD) = 10 (0) • At Follow-up: 7-9
			Resolution of symptoms[b] Neuropathy impairment score in lower limb (NIS-LL; muscle strength graded as normal, zero, to max score of 64 if paraplegic, reflexes graded zero to 8 and sensation graded 0 to 16)	• Baseline: 5.1(1.4) • At 1 year: 5.3 (1.3) Reported NS
			Resolution of symptoms[b] Autonomic symptoms (11 point Likert scale; (0=no symptoms; 10=severe symptoms), baseline vs. 18 months	**SS improvement reported in the following scores:** orthostatic lightheadedness, orthostatic dizziness, pre-syncope, syncope, orthostatic symptoms worse with standing, nausea, vomiting, diarrhoea, early satiety **NS difference reported in the following scores:** Orthostatic symptoms after meals, loss of appetite, urinary frequency, nocturia, hyperhidrosis, anhidrosis, erectile dysfunction.
			Resolution of symptoms[a] Autonomic dysfunction	**Abnormal HR response deep breathing** • Baseline: 69% • At 18 months: 48% **Abnormal inspiratory-expiratory ratio** • Baseline: 62% • At 18 months: 19%

Study	Intervention/comparison	Population	Outcomes	Results
				Valsalva ratio • Baseline: 56% • At 18 months: 43% **Orthostatic hypotension** • Baseline: 69% • At 18 months: 31%
			Retinopathy[a,c] Retinopathy, no. of patients	• Baseline: 7/16 • At 6 months of sustained BG control:16/16
			Low-level (micro) albuminuria[a,c] Low-level (micro) albuminuria, number of patients	• Baseline: 8/16 • At 1 year 13/16

(a) Data from mixed population of type 1 diabetes and type 2 diabetes
(b) Data from type 1 diabetes subgroup analysis
(c) Retinopathy and Low-level (micro) albuminuria outcomes are complications alongside insulin-induced neuritis due to intensive glycaemic control and not outcomes for the interventions used for the treatment of insulin induced neuritis

16.6.4 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow diagram in Appendix E.

Unit costs

Relevant unit costs are as follows. These have been taken from NICE CG173: Neuropathic pain – pharmacological management.

Table 129: Daily dosages and cost of recommended drugs – CG173 [526]

Drug	Daily dosage[a]	Cost per electronic drug tariff[b]	Cost per day	Annual cost[d]
Amitriptyline	50 mg[c] once daily	50-mg tablets – £0.99 for 28 40-mg tablets - 4 x 10-mg - £0.87 for 28	£0.03 £0.12	£10.95 £43.80
Gabapentin	1800 mg (600 mg three times daily)	600-mg capsules – £11.50 for 100 300-mg capsules – £3.54 for 100 400-mg capsules x 4 + 2 x 100-mg capsules - £4.53 and £2.56 for 100 respectively	£0.35 £0.21 £0.23	£127.75 £76.65 £83.95
Duloxetine	60 mg once daily	60-mg capsules – £27.72 for 28	£0.99	£361.35
Pregabalin	300 mg (150 mg twice daily)	150-mg capsules – £64.40 for 56	£2.30	£839.50
Tramadol	400 mg (100 mg four times daily)	50-mg capsules – £3.73 for 100	£0.30	£109.50
Capsaicin cream (0.075%)	4 g (1 g four times daily)	45-g tube – £14.58	£1.32	£481.80
Carbamazepine	800 mg (200 mg four times daily)	200-mg tablets – £5.78 for 28	£0.80	£292.00

(a) The Guideline Development Group (GDG) provided estimates of the most common doses for each drug. The GDG pharmacist checked and confirmed drug prices and formulations (table F15 of Appendix F of the full guideline CG173).
(b) The drug costs are taken from the NHS Electronic Drug Tariff[540]
(c) The mean daily dose for amitriptyline is 37.5 mg. This has been rounded up to 50 mg for the purpose of calculating the cost per dose, as this is the nearest whole-tablet dosage.
(d) The GDG advised that the administration costs of the drugs would be equal in a primary care setting, so these have excluded from the costs above.

16.6.5 Evidence statements

Clinical [2015]

Low quality evidence from a very small case-series (n=16) showed that compared with baseline, treatment for acute insulin induced neuritis using anti-epileptics alone or in combination with other medications, resulted in a 50% reduction in pain, occurring at a median of 15 months treatment, and an improvement in and resolution of some symptoms of the neuropathy. However, treatment of the neuropathy did not seem to have any beneficial effect on other complications of rapid glycaemic control in people with a long history of poor control, such as the further development of retinopathy

or of low-level (micro) albuminuria. All outcomes were reported at either 6 months, 1 year, or 18 months

Economic [2015]

No relevant economic evaluations were identified.

16.6.6 Recommendations and link to evidence

Relative values of different outcomes	To determine the optimum treatment for acute painful neuropathy of rapid glycaemic control in individuals with type 1 diabetes, the GDG reviewed whether the following UK licensed interventions had any influence on clinical outcome for the condition: • Antidepressant therapies, including tricyclic antidepressants and duloxetine • Anti-epileptic treatments, including gabapentin, pregabalin • Analgesia, including opiates • Topical therapies, including topical anaesthetics (lignocaine), capsaicin cream • Intensive insulin therapy, including use of insulin pump The impact of treatment interventions on acute painful neuropathy of rapid glycaemic control was assessed by the following clinical parameters: Pain score: reported at baseline (after intensive glycaemic control) and at follow-up • Improvement in pain scores: reported as duration of treatment for a 50 % reduction in perceived pain versus pre-intervention pain scores • Time to resolution of symptoms: reported as neuropathy impairment scores in the lower limb at baseline and at 18 months post-treatment.
Trade-off between clinical benefits and harms	The GDG recognised that acute painful neuropathy of rapid glycaemic control has a natural history of being a self-limiting condition. Although it is a result of rapid glycaemic control, the available evidence does not suggest that glycaemic control needs to be relaxed for resolution of the condition or symptomatic relief. The GDG therefore wanted clinicians to be confident in reassuring individuals diagnosed with the condition that they could expect their symptoms to improve with time, and not to relax glycaemic control in individuals diagnosed with the condition with all the potential deleterious effects that might follow from allowing higher blood glucose levels. Only one study specific to acute painful neuropathy of rapid glycaemic control was included in the evidence review[261]. The study assessed the impact of treatment interventions in 16 adults with diabetes (9 with type 1 diabetes) reporting acute onset of the painful neuropathy of rapid glycaemic control. All patients in the study had historically poor glycaemic control as a consequence of anorexia and/or treatment non-adherence before study entry. Treatments used in the study included tricyclic antidepressants (amitriptyline, nortriptyline or desipramine), anti-epileptics (gabapentin, pregabalin, lamotrigine or topirmate), and the analgesics tramadol and methadone. No more than two patients used the same combination of treatments in each intervention group, and therefore direct comparison of interventions was not possible. The available evidence did not indicate that any pharmaceutical intervention had an advantage over any other in the management of acute painful neuropathy of rapid glycaemic control. A 50 % reduction in pain was achieved at a median of 15 (range 12-28) months following treatment initiation. Treatment of neuropathy did not seem to have any beneficial effect on other complications of rapid glycaemic control in people with a long history of poor control, such as the further development of retinopathy or of low-level (micro) albuminuria. Clinical experience acquired by members of the GDG reflected that there was often a

	propensity for individuals diagnosed with painful neuropathies to be treated with opioid therapies, and that this might put a treated individual at risk of dependence. There was no evidence in the available literature to suggest that opioid therapies were any more effective than other therapeutic interventions in providing symptomatic relief. Given that acute painful neuropathy of rapid glycaemic control is normally a self-limiting condition, members of the GDG were keen to stress in their recommendations that alternative interventions be selected in preference to opioid therapies in the management of the condition. No evidence about the use of topical anaesthetics, capsaicin cream or insulin pump therapy was found in the literature review about the management of acute painful neuropathy of rapid glycaemic control.
Economic considerations	No economic evaluations about management of acute painful neuropathy of rapid glycaemic control were identified by the GDG. In order to make an assessment of the cost-effectiveness of the pharmaceutical interventions available for the management of neuropathic pain, the GDG referred to the relevant unit costs provided in NICE Care Guideline 173: 'Neuropathic pain – pharmacological management'[526]. As a result of the severity of the pain reported by individuals with acute painful neuropathy of rapid glycaemic control, the GDG recognised that a combination of medications might be used more readily in individuals with this conditions than that used for the management of chronic painful neuropathy. The GDG recognised that acute painful neuropathy of rapid glycaemic control is reported to be associated with a pain that is much more intense than that of chronic painful peripheral neuropathy experienced by individuals with long-term diabetes. Therefore, the GDG recognised that any reduction in subjective pain in individuals was likely to produce a substantial improvement in quality of life. Given the cost of the treatment interventions available, all were likely to be of cost-benefit in the management of the condition.
Quality of evidence	Randomised controlled trial evidence about the management of chronic painful peripheral neuropathy in populations of adults with type 1 and type 2 diabetes was identified by the GDG but excluded from the review as they did not specifically address the management of acute painful neuropathy of rapid glycaemic control. Only one study specific to acute painful neuropathy of rapid glycaemic control was included in the evidence review[261]. This study was a case series design and therefore could not be GRADE rated.
Other considerations	The term "acute painful neuropathy of rapid glycaemic control" was preferred by the GCG over "insulin-induced neuropathy" or "insulin induced neuritis" to establish the link between a rapid fall in glycated haemoglobin and to avoid the implication that the condition is driven by insulin itself, for which there is no evidence. Expert opinion from the GDG recognised that acute painful neuropathy of rapid glycaemic control is an uncommon condition and that the natural history of the condition is that it is likely to resolve spontaneously, even when treatment is not administered. However, all members of the GDG acknowledged that individuals developing the condition subjectively reported pain that was of a high intensity, and that clinical interventions aimed at reducing the intensity of the pain were warranted. This guidance specifically addresses the management of acute painful neuropathy of rapid glycaemic control only, and not the management of chronic painful peripheral neuropathy experienced by a proportion of adults with long-standing type 1 diabetes. Nonetheless, the range of drugs available for treating the two conditions is the same, and the GDG therefore took note of NICE Guidance 173[526], in addition to the more limited evidence available on acute painful neuropathy, in developing their

	recommendations. Although the SSRI-related antidepressant duloxetine was not included in the case series of Gibbons (2010)[261], the GDG included it here because of evidence of benefit in other forms of painful neuropathy as recommended in NCG 173.

The current guideline recommendations can be found at

https://www.nice.org.uk/guidance/ng17

16.6.7 Research recommendations [2015]

33. What is the clinical and cost-effectiveness of constructing a national database and centralising supervision of the management of adults with type 1 diabetes who have painful neuropathy of rapid glycaemic control?

16.7 Diabetes foot problems [2004]

For guidance on diabetic footcare, please see the NICE clinical guideline on diabetic foot problems (add link to diabetic foot care guideline when published).

The recommendations and text from the 2004 guideline pertaining to foot care can be found in Appendix S.

3. For guidance on preventing and managing foot problems in adults with type 1 diabetes, see the NICE guideline on diabetic foot problems. [new 2015]

16.8 Erectile dysfunction [2015]

16.8.1 Introduction [2015]

Erectile dysfunction in men with diabetes is common, and to a greater extent than in the matched general population. While psycho-sexual causes are no less common in men with type 1 diabetes than men without, the man with diabetes may also experience impaired sexual function as a result of diabetic autonomic neuropathy and/or vascular disease, either of which can impair the ability to achieve an erection. It is therefore appropriate to include an assessment of erectile function in reviewing the man with type 1 diabetes. There are treatments now available to help men with erectile dysfunction achieve erection sufficient to allow intercourse.

The assessment of fertility and hypogonadism in men is beyond the scope of the present review.

The GDG addressed only this question:

- What pharmacological treatment should be used to manage erectile dysfunction in men with type 1 diabetes?

16.8.2 New review question [2015]: What pharmacological treatment should be used to manage erectile dysfunction in men with type 1 diabetes?

16.8.3 Clinical evidence [2015]

The pharmacological management of erectile dysfunction was originally covered as part of the 2004 guidance. Updated searches were carried out by the NICE 2015 GDG, developing guidance for type 2 diabetes, who looked at both type 1 diabetes and type 2 diabetes populations as part of their review. The evidence that was found assessed the impact of treatments in mixed populations of people with

type 1 diabetes or type 2 diabetes; two of the assessed studies reported outcomes exclusively in adults with type 1 diabetes type 1 diabetes (Stuckey 2003, Ziegler 2006). The type 1 diabetes GDG subsequently interpreted the evidence independently and produced their own recommendations for the management of erectile dysfunction in adults with type 1 diabetes.

Details of the evidence used for this review can be found in the NICE 2015 clinical guideline for type 2 diabetes (due for publication August 2015). However, forest plots pertaining to the two studies that performed a subgroup analysis in people with type 1 diabetes, can be found in Appendix J.

16.8.4 Economic evidence [2015]:

The economic literature review for this question was also conducted by the type 2 diabetes guideline GDG (as per clinical evidence) on behalf of type 1 diabetes in adults.

16.8.5 Evidence statements [2015]

Please see the 2015 NICE type 2 diabetes guideline (add hyperlink when published)

16.8.6 Recommendations and links to evidence [2015]

The current guideline recommendations can be found at

https://www.nice.org.uk/guidance/ng17

Relative values of different outcomes	The review question addressed whether pharmacological treatment should be used in the management of erectile dysfunction in adults with type 1 diabetes. A literature review was undertaken to assess the evidence for the following pharmacological interventions • Phosphodiesterase-5 inhibitors (PDEIs) • Testosterone therapy • Alprostadil The main outcomes for this review question were erectile function, quality of life and adverse events. Erectile function was assessed using four main measures: • Erectile function domain of the international index of erectile function (IIEF) questionnaire • Question 2 from the sexual encounter profile (SEP-2) relating to success in penetration • Question 3 from the sexual encounter profile (SEP-3) relating to success in intercourse • Global efficacy question (GEQ) relating to whether treatment has improved erections Adverse events assessed included headache, flushing, upper respiratory tract infection, dyspepsia, abnormal vision.
Trade-off between clinical benefits and harms	Pair-wise comparisons showed that erectile function was significantly improved with use of PDEIs compared with placebo. Subsequent review of the available evidence comparing PDEIs showed no significant difference in outcome achieved for measures of erectile function using sildenafil, vardenafil or tadalafil. One study[88] reported a significantly improved quality of life score with sildenafil use compared with placebo. The use of PDEIs was associated with a significantly increased risk of developing adverse events when compared with placebo. Adverse events included headaches, flushing, upper respiratory tract infections, dyspepsia, abnormal vision and priapism. The GDG considered these to be relatively mild side-effects compared with the

	benefits in erectile function gained. The available evidence did not suggest that the use of a particular PDEI might have an improved side effect profile compared with other PDEIs. It is noted that all trials will have excluded men with known contraindications, listed by the British National Formulary as concomitant use of nitrates, where vasodilation or sexual activity is inadvisable, men with a history of non-arteritic anterior ischaemic optic neuropathy; to which manufacturers have added systolic blood pressure below 90 mmHg, recent stroke, unstable angina, and myocardial infarction. One open-label trial of oral testosterone supplementation therapy (120 mg oral testosterone undecanoate per day) compared with no treatment[90]reported significantly improved erectile function, blood glucose control and lower body weight. Subgroup analyses by baseline HbA1c levels for all assessed studies showed that there were no differences in erectile function between the different levels of baseline HbA1c.
Economic considerations	Literature searches were undertaken for cost utility analyses of the pharmacological management of erectile dysfunction in adults with diabetes. No cost utility analyses about the use of testosterone therapies in individuals with diabetes were available for review. Three cost utility analyses about the use of PDEIs were recognised as suitable for further assessment[52,690,701] but none of the studies were specific to diabetes populations. However, the GDG accepted that it was possible to extrapolate findings from these studies to populations with diabetes. One of the three studies stated that no difference in clinical effectiveness of treatment interventions by risk factor (including diabetes) had been identified in the cost utility analysis.[52] Of the three cost utility analyses, one compared sildenafil to no treatment[690], one compared sildenafil to injection therapies[701] and the third study assessed the cost-effectiveness of varying doses of vardenafil[52]. All three studies reported that sildenafil[690,701] and vardenafil[52] were cost-effective in comparison to placebo or alternative treatments, with incremental cost-effectiveness ratios likely to remain below conventional thresholds in the majority of cases. Sildenafil treatment was cost-effective compared with no treatment at $50,000 per QALY threshold[690]; sildenafil was cost-effective compared with usual care at $20,000 per QALY threshold[701]; and provision of extra doses of vardenafil was cost-effective compared with less monthly doses at $50,000 per QALY threshold. It was noted that all three cost utility analyses contained assumptions that were conservative or biased towards the alternative treatment but under sensitivity analysis, the treatment option remained likely to be cost-effective. The GDG recognised that individuals with diabetes might require higher doses of PDEIs but the available evidence reviewed indicated that available treatments were still likely to increase utility by an extent that would offset reasonable costs. Sildenafil is now off patent, and the estimated annual cost of treatment is £75/year. By comparison, tadalafil currently has an estimated annual cost of treatment of £715/year. The reviewed evidence did not indicate a significant difference in adverse event profiles for different PDEIs, and therefore the GDG recommended that the PDEI with the lowest acquisition cost be selected by prescribers for the management of erectile dysfunction in adults with type 1 diabetes.
Quality of evidence	Only randomised controlled trials (RCTs) were included for the evidence review. Nine RCTs originally included in the literature review for the development of CG 66[89,110,270,362,615,642,643,705,801]and four newly identified RCTs[91,181,300,383] were reviewed for this guideline development. Twelve of the studies reported on outcomes on the use of PDEIs, with ten placebo controlled trials (five sildenafil trials, two tadalafil trials and three vardenafil trials), one head-to-head comparison trial (tadalafil versus verdenafil)[383] and one study

	examining on-demand versus three times a week dosing regimens with tadalafil[110]. One study assessed the use of testosterone therapy in the management of erectile dysfunction[91]. No studies assessing the use of alprostadil were available in the evidence review. The GRADE quality of the available evidence for PDEIs assessing erectile function varied from Very low to Low; GRADE assessment of quality of life measures was Moderate; and GRADE assessment of adverse events was Very low to Moderate. Only one study was available for the evidence of testosterone therapy use in adults with diabetes and erectile dysfunction, and GRADE quality of this study was Very low. Given the paucity and low quality of the evidence available for testosterone therapy in the treatment of erectile dysfunction in adults with diabetes, the GDG was not able to make any recommendations about its use for erectile dysfunction in individuals with diabetes at the present time.
Other considerations	The GDG considered that men starting treatment should be advised to discuss management options for erectile dysfunction with their partners and the men and their clinicians should enable partners to participate in management decision-making. However, the duty of care is to the patient first and foremost and at the present time the onus is not with the clinician to ensure that these conversations take place between patient and partner before treatment being started for erectile dysfunction in adults with type 1 diabetes.

16.9 Thyroid disease –frequency of monitoring [2015]

16.9.1 Introduction

Thyroid disease is common in the general population, and the prevalence increases with age. The assessment of thyroid function by modern assays is both reliable and inexpensive. People with type 1 diabetes have a higher prevalence of thyroid disorders compared with the non-diabetic population in both cross-sectional and longitudinal studies. This is because patients with one organ-specific autoimmune disease are at increased risk of developing other autoimmune disorders. Thyroid disorders are more common in females and up to 30% of female with type 1 diabetes may have some thyroid disease (1). Transient thyroid dysfunction is common in the postpartum period and the rate of postpartum thyroiditis in those with diabetes is three times that in normal women (2).

The presence of thyroid dysfunction may affect diabetes control. Hyperthyroidism is typically associated with worsening glycaemic control and increased insulin requirements. There is underlying increased hepatic gluconeogenesis, rapid gastrointestinal glucose absorption, and probably increased insulin resistance. Treatment of the hyperthyroidism may increase the risk of hypoglycaemia in adults with type 1 diabetes, as insulin requirements fall. Though wide-ranging changes in carbohydrate metabolism are seen in hypothyroidism, clinical manifestation of these abnormalities is seldom conspicuous. However, the reduced rate of insulin degradation may lower the exogenous insulin requirement, increasing the risk of hypoglycaemia.

Thyroid dysfunction cannot be diagnosed solely on clinical manifestations.. The highly sensitive immunoassay for serum thyroid stimulating hormone or TSH, with a detection limit of less than 0.1 mU/litre, is commonly used to test for thyroid dysfunction and allows both hypothyroidism and hyperthyroidism to be diagnosed. Subclinical thyroid dysfunction may be diagnosed by an abnormal TSH, when serum T3 and T4 are near-normal and, by definition, the patients are asymptomatic. Given the potential for hypo- or hyperthyroidism to affect glucose control and the increased risk for autoimmune thyroid disease in people with type 1 diabetes, it is appropriate to screen for thyroid

dysfunction in the adult type 1 diabetic population, as well as testing when there is a clinical indication of it.In addition to testing for biochemical evidence of thyroid dysfunction, tests are also available to detect the presence of autoimmune thyroid disease, including antibodies against thyroid antigens such as anti-TPO.

The GDG therefore addressed these questions:

- How should adults with type 1 diabetes be monitored for thyroid disease, and, in the absence of symptoms of thyroid disease, how frequently?
- In addition, the GDG examined the performance of the different tests available for screening adults with type 1 diabetes for thyroid disease.

16.9.2 New review question: How should adults with type 1 diabetes be monitored for thyroid disease, and, in the absence of symptoms of thyroid disease, how frequently?

For full details see review protocol in Appendix C.

Table 130: PICO characteristics of review question

Population	Adults with type 1 diabetes • Adult defined as aged >18 years
Intervention/s	Thyroid disease monitoring Thyroid function tests Thyroid autoantibodies/antibodies (for example, peroxidase)
Comparison/s	• As for intervention but at a different frequency • Standard care/no monitoring • No comparison (non-comparative studies)
Outcomes	• Detection of thyroid disease • Incidence of thyroid disease • Frequency of treatment
Study design	RCTs, observational studies, prognostic studies, prevalence studies

16.9.3 Clinical evidence

For this review on thyroid disease monitoring in adults with type 1 diabetes we searched for RCTs, observational studies, prognostic studies or prevalence studies that reported information on any of the following three topics:

- which tests should be used to monitor thyroid disease in a type 1 diabetes population?
- the prevalence of thyroid disease in a type 1 diabetes population
- the frequency of monitoring thyroid disease in a type 1 diabetes population

For topic one (which tests to use) and topic two (prevalence of thyroid disease) we found 22 relevant studies[26,73,79,115,161,195,226,273,296,374,382,423,469,563,577,595,609,739,759,762,774]. These studies included 7 cohort studies (retrospective or prospective, and prevalence in studies)[195,296,374,563,577,609,774], three cross-sectional studies (also prevalence information included in one study)[563,595,762] and 12 case studies (also prevalence information included in these studies)[26,73,115,161,226,273,382,423,469,739,759,789,791].No studies were found directly addressing the remaining topic, the frequency of monitoring for thyroid disease in people with type 1 diabetes.

It was decided that studies with population size less than 20 were excluded from the review.

All studies were observational studies, and therefore were not able to be combined in a meta-analysis or GRADE profile, and were graded as Low quality (due to their study design). However, a

summary of the quality and limitations of these studies can be found in Appendix G. The study details and the full results have been summarised in tables below.

Table 131: Summary of studies included in the review for thyroid disease and type 1 diabetes

Study	Intervention/ comparison	Population	Follow-up	Results
ALLEN 2008 [25,26]	Retrospective Case series Evaluation of antiTPO and thyroid receptor antibody	n=328 (n=180 adult onset, n=148 childhood onset) type 1 diabetes	5 years	TPO: Prevalence of positive TPO antibodies in childhood onset=11.8% (11/93) Prevalence of positive TPO antibodies was: 11.5% (13/113) in adult onset TRAB Prevalence of positive TRAB antibodies in childhood onset=1.9% (1/54) Prevalence of positive TRAB antibodies in adult onset=9.1%(5/55)
BIANCHI 1995[73]	Case control (cross-sectional) study Prevalence of thyroid nodules by ultrasound and also measurement of anti-thyroid antibodies	n=45 adults with type 1 diabetes without overt thyroid disease n=45 control group (matched for sex and age, residing in the same geographical area, admitted to department for functional gastrointestinal tract or kidney disorders, and who did not have diseases known to influence thyroid function or size	No follow-up reported	Cases vs. controls: Increased thyroid volume Prevalence of antimicrosome and antithyroglobulin antibodies=33% and 16% vs. 0% and 2%
CARDOSO 1995[115]	Case-controlstudy Prevalence of thyroid autoantibodies Thyroid function and prevalence of thyroid autoantibodies in an African diabetic population	n=40 type 1 diabetes n=60 type 2 diabetes n=100 control group	No follow-up reported	Cases vs. control: Prevalence of serum thyroid autoantibodies=46% type 1 diabetes (13/28) vs. 1.43% controls (1/70) T3 serum concentration in type 1 diabetes within normal range, lower than control group T4 serum concentration in type 1 diabetes within normal range ,lower than control group TSH concentration in type 1 diabetes within normal, higher than control group

Study	Intervention/ comparison	Population	Follow-up	Results
DAGDELEN 2009[161]	Case control study Prevalence of positive thyroid antibodies and clinical presentation of glutamate decarboxylase antibody, coeliac disease and thyroid disease	n=65 type 1 diabetes n=124 first degree relatives n=65 control group	No follow-up reported	Cases vs. controls: Prevalence of positive TPO antibodies= 24.6% (16/65) type 1 diabetes vs. 4.6% (3/65) controls Prevalence of positive TSH antibodies 1.5% (1/65) type 1 diabetes vs. 0% (0) in controls
DUFAITRE 2006[195]	Cohort study (prospective) Prevalence of clinical and subclinical autoimmune diseases According to treatment type Continuous intraperitoneal insulin infusion vs. continuous subcutaneous insulin infusion using an external pump	Adults with type 1 diabetes+ CIPII n=154 Adults with type 1 diabetes+ CSII n=121	1 year after inclusion	Clinical disease in treatment groups: CIPII group=8.4% (13/154) Hashimoto's thyroiditis and 1.3% (2/154) Graves' disease CSII group=7.5% (9/121) Hashimoto's thyroiditis and 2.5% (3/121) Graves' disease Subclinical disease in treatment groups: TPO >60 ml/U in CIPII group= 25/9% (36/139) vs. CSII=30.6% (33/108) Incidence of autoimmune disease according treatment mode: 7.2% (5/69) developed TPO positivity in CIPII group vs. 7.3% (3/41) in CSII group at T=1 Prevalence and incidence regardless of treatment: Whole group prevalence of thyroid disease=9.8% (clinical disease) and 28% (subclinical disease) Combined total prevalence of clinical and subclinical autoimmune disease=31% Combined total incidence of clinical and subclinical autoimmune disease=7.3% No new cases after T=0

Study	Intervention/ comparison	Population	Follow-up	Results
				Prevalence of autoimmune disease is not correlated with age, duration of diabetes or duration of external or implanted pump treatment Prevalence of thyroid autoimmune disease=41.1% in females and 20.5% in males
FIALKOW 1975[226]	Case series Prevalence thyroid autoantibodies Evaluation of insulin status	n=52 type 1 diabetes (n=1 Graves' disease) n=1 Surgery or goitre or both) n=48 type 2 diabetes (n=1 hypothyroidism)	Duration=2 years	Prevalence of clinical disease: Prevalence of thyroid antibodies type 1 diabetes =35% (18/52) Prevalence of type 1 diabetes and Graves' disease= 1.9% (1/52), type 1 diabetes and Hashimoto's thyroiditis=1.9% (1/52) 20-39 year subgroup: 60% (18/30) patients tested positive for thyroid antibodies: 23% (7/30)= TPO+ (low titre) 4/30= TPO+ (high titre), 5/30=TGab+ (low titre), 2/30=TGab+ (high titre) 40-59 year subgroup: 27% (6/22) patients tested positive for thyroid antibodies: 27% (2/22)= TPO+ (low titre) 27% (2/22)= TPO+ (high titre), 27%(2/22)=TGab+ (low titre), 27 %(0/22)=TGab+ (high titre) Frequencies of antibodies to thyroglobulin and to thyroid cytoplasm were equally elevated in type 1 diabetes Presence of antibodies was not correlated significantly with duration of disease or of insulin therapy
GOMEZ 2003[273,274]	Case control Prevalence Measurement of thyroid volume by ultrasonography	n=65 adults with newly diagnosed type 1 diabetes n=65 healthy matched controls	Recruited over4 years	Basal TSH levels in type 1 diabetes males and females vs. control group: Type 1 diabetes males =1.6%±1.14 vs. control group=1.5%±0.78 (95%CI -0.56 to 0.41; P=0.76) Type 1 diabetes females=1.69%±1.08 vs. control group=1.59%±0.96 (P=0.48)

Study	Intervention/ comparison	Population	Follow-up	Results
HANUKOGLU 2003[296]	Cohort study Prevalence Prevalence rates of autoimmune thyroiditis diagnosed by abnormally high TPO and Tg antibodies	Probands=109 Relatives screened=100 Relatives interviewed=312 Control subjects=78	Study over 3 years	Prevalence of autoimmune thyroid disease as determined by positive TPO and/or TG antibody rates among type 1 diabetes probands was 27%, with 6% of those being hypothyroid The corresponding rates among screened first-degree relatives (positive TPO and/or TG 25%, hypothyroid Hashimoto disease 8%) did not significantly differ from the rates found in probands, but were higher than rates in control subjects The frequencies of positive TPO and TG antibodies alone and together were 18, 19, and 11%, respectively, in probands. The corresponding rates among first-degree relatives were quite similar (19, 17, and 10%, respectively) TPO titres in three control subjects were only slightly elevated (1/84, 1/118, and 1/98), in most probands and family members TPO was elevated (5-fold in 13 probands and 12 relatives and2.5-fold in 3 probands and 6 relatives) In first degree relatives who were screened, medical history revealed pre-existing Hashimoto thyroiditis in five and Graves disease in one The frequency of

Study	Intervention/ comparison	Population	Follow-up	Results
				pre-existing autoimmune thyroiditis detected by interview only, was low (1%) Probands with Hashimoto thyroiditis did not have more relatives with positive antibodies than probands with normal antibody titres. Among 50 probands whose relatives were screened, 12 probands with thyroiditis had 8 relatives with positive antibodies and 13 relatives with normal antibody titres. Among 13 probands without thyroiditis, the corresponding numbers were 16 (positive) and 17 (normal) relatives
JIN 2011[374]	Cohort study (prospective) Prevalence Evaluation of genetic and immunological factors involved in the development of thyroid autoimmunity	n=190 type 1 diabetes n=135 LADA	4 years	Prevalence of thyroid antibodies at start type 1 diabetes: TGab =23.7% TPOab =24.7% Prevalence of thyroid antibodies at 4 years follow-up type 1 diabetes: TGab=24.5% TPOab =25.5%. Prevalence of thyroid antibodies at start in LADA: TGab=16.3% TPOab =18.5% Prevalence of thyroid antibodies at 4 years follow-up in LADA: TGab=17.7% TPOab=20.0%
JUNIK 2006[382]	Case control study Intervention: ultrasound, TSH, T4, free T3, Free T4	n=30 type 1 diabetes n=98 type 2 diabetes n=50 matched controls treated in department at same time for diseases other than diabetes mellitus and thyroid disorders	No follow-up	Ultrasound and thyroid volume (type 1 diabetes vs. control group): type 1 diabetes = 20% relative increase in thyroid volume vs. control group Thyroid volume exceeded reference range for 13% (4/30) type 1 diabetes vs. 3% (1/38) control group Hormone measurement (type 1 diabetes vs. control group): 7% (2/30) type 1 diabetes = subclinical hyperthyroidism vs. 3% (1/38) control group 3% (1/30) type 1 diabetes =subclinical hypothyroidism vs. 5% (2/38) control group TSH levels =0.97 (range 0.61-1.58)

Study	Intervention/ comparison	Population	Follow-up	Results
				mIU/litre type 1 diabetes vs. 1.66 (range 0.76-2.09) mIU/litre control group
KUCERA 2003[423]	Case-control study Prevalence of thyroid autoantibodies	n=153: n=68 type 1 diabetes n=85 type 2 diabetes n= 62 controls selected randomly from a common population of older people and from a senior's home with no signs of severe metabolic disease, matched by age and sex	No Follow-up reported	Prevalence of thyroid autoantibodies: 8.82% (6/68) type 1 diabetes =positive thyroglobulin antibodies vs. 3.5% (3/85) type 2 diabetes 22.1% (15/68) type 1 diabetes =positive TG antibodies vs. 9.4% (8/85) type 2 diabetes Prevalence of positive thyroglobulin and TPO antibodies=higher in type 1 diabetes group vs. type 2 diabetes group
LUPI 2013[469]	Case control study Assessment of antiTPO, antiTG type 1 diabetes with Hashimoto's thyroiditis or Graves' disease	n=111 adults with type 1 diabetes n=110 type 2 diabetes n=214 controls	No follow-up reported	Clinical disease in type 1 diabetes: Hashimoto's disease =31% (35/111) Grave's disease=6% (7/111)
PALMA 201[563]3	Cohort study (cross-sectional) Prevalence of thyroid dysfunction by testing for anti-TPO, FT4 and TSH	n=386: n=82 type 1 diabetes n=304 type 2 diabetes	Follow-up not reported	Prevalence thyroid antibodies in type 1 diabetes: Anti-TPO positivity=14.6% (12/82) vs. 9.9% (30/304) type 2 diabetes Subclinical hypothyroidism without previous thyroid disease =13% Incidence of new subclinical hypothyroidism without prior thyroid disease =13% (9/70) Thyroid hormones in type 1 diabetes: TSH and FT4 levels = normal range in type 1 diabetes with prior thyroid disease was 50% (6/12)
PERROS 1995[577]	Cohort study (prospective) Assessment of prevalence and incidence of thyroid	n=1310: n=406 adults with type 1 diabetes n=904 type 2 diabetes	Blood tests at year 1 after recruitment, and then retested after 12 months	Prevalence of thyroid disease: Overall 13% (176/1310) of study population had previous or present thyroid disease Prevalence of thyroid disease in type 1 diabetes males was 12.4%

Study	Intervention/ comparison	Population	Follow-up	Results
	dysfunction			and type 1 diabetes females was 31.4%, prevalence peak at 60-70 years of age Annual incidence of new thyroid disease: New thyroid disease =6.7% (89/1310) Annual risk of thyroid disease =12.3% in type 1 diabetes females Thyroid antibodies: 64% study population =positive thyroid antibodies 80% hypothyroid cases=positive thyroid antibodies 44.4% hyperthyroid cases=positive thyroid antibodies 90.9% sub clinical hypothyroid cases=positive thyroid antibodies Clinical management influence in 4% (49/1310) of the study population
PRAZNY 1999[595]	Cross-sectional study Evaluation of thyroid and islet autoantibodies	n=55 type 1 diabetes	No follow-up	Thyroid autoantibodies: 18% (10/55) patients had positive anti-TPO antibodies
RATTARASARN 2000[609]	Cohort study Clinical significance of thyroid autoantibodies Prediction of thyroid dysfunction in Thai patient group	n=50 type 1 diabetes n=29 non-diabetic patients with hyperthyroid Graves' disease or Hashimoto's thyroiditis as control group	Up to 3 years	Thyroid autoantibodies: 18% (9/50)=TGab positivity 30% (15/50)=TPOab positivity 16% (8/50)= positive for both antibodies 2/16 type 1 diabetes with positive TGab or TPOab had hyperthyroidism before diabetes onset 2 patients newly diagnosed hyperthyroidism (1 patient with clinical hypothyroidism and elevation of serum TSH; 1 patient with mild elevation of serum TSH without hypothyroidism) In 8 patients with TGab or TPO

Study	Intervention/ comparison	Population	Follow-up	Results
				positivity and without thyroid dysfunction (2 patients developed hypothyroidism during follow-up 19±8 months; serum TSH increased from 10.0 to 20.75 mU/litre after 20 months in 1 patient and 4.64 to 33.87 mU/litre after 35 months in another patient) 21 patients tested for thyroid antibodies remained negative for thyroid dysfunction during 16.4±6.3 months follow-up 3/14 type 1 diabetes patients without previous a previous history of thyroid diseases had a significantly higher frequency of thyroid dysfunction at the start of the study and tended to have a higher risk of developing thyroid dysfunction up to approximately 3 years of follow-up Antibody positivity was higher in females than males
UMPIERREZ 2003[739]	Case series (prospective) Evaluation of thyroid status and presence of TPO antibodies	n=58 type 1 diabetes	18 years (TSH, thyroxine and triiodothyronine measured every year TPO antibodies measured at 4 year intervals)	Prevalence of clinical disease and thyroid antibodies: 18/58 patients had hypothyroidism Hypothyroidism was more common in females (41%) than males (19%) and in patients with positive TPO antibodies Type 1 diabetes with TPO positive antibodies were 18 times more likely to develop hypothyroidism Presence of TPO antibodies was associated with an increased risk of hypothyroidism Most patients with positive TPO antibodies at the beginning of the study remained positive throughout the study One patient who was negative for TPO antibodies developed low TPO titres after 12 years follow-up No differences in TSH values on diagnosis of hypothyroidism between patients with positive or negative antibodies
VONDRA 2004[759]	Case series (prospective)	n=109 adults with type 1 diabetes Subgroup1:	12 years	Clinical disease, thyroid antibodies, and thyroid hormones: Cumulative incidence of positivity

Study	Intervention/ comparison	Population	Follow-up	Results
	Subgroups of patients were compared over 12 years thyroid autoantibodies	positive for both thyroid autoantibodies Subgroup 2: Positive antiTPO antibody only Subgroup 3: thyroid autoimmunitynot present)		of thyroid antibodies during 12 follow-up was 51% Hypoechogenic thyroid was detected in 59% of group 1 compared with 25% of group 2 TSH levels above 4.5 mIU/litre were found in 30% of group 1 compared with 7% of group 2 At 4 years of follow-up, subclinical hypothyroidism was found in 100% of group 1 compared with 11% of group 2 Cumulative incidence peaked in group 1 during 4-12 years of follow-up of antiTPO and antiTgI positivity (25%) compared with 9-12 years antiTPO positivity (26%) in group 2
WALTER 2007[762]	Cross-sectional study Prevalence of autoimmune disease in type 1 diabetes	n=124 type 1 diabetes	No follow-up reported	Prevalence of thyroid disease: 31% (38/124) of type 1 diabetes patients had thyroid disease The detection rate for new cases as 5.8% (true prevalence 35%) Thyroid disease was more common in women than men (33/77 vs. 10/47)
WHITEHEAD 2010[774]	Cohort study. Prevalence Screening for hypothyroidism	n=400 type 1 diabetes n=400 type 2 diabetes	Type 1 diabetes (median range) 9.5 years	Prevalence ofclinical hypothyroidism: Prevalence of autoimmune hypothyroidism (including subclinical hypothyroidism) in type 1 diabetes was 10.8% (43/400) Prevalence of hypothyroidism requiring thyroxine treatment in type 1 diabetes was 6.8%, and increased with age, particularly after 50 years age Dose of treatment: Average dose of thyroxine replacementin type 1 diabetes patients requiring thyroxine treatment was 134ug (SD 62) Routine thyroid hormone testing done at annual review detected hypothyroidism requiring thyroxine treatment in 1.8% of patients with type 1 diabetes.
YAMAGUCHI 199[788,789]	Case control Investigation of islet cell antibodies	n= 316 patients with autoimmune disease Group I: type 1	Study duration=6 years	Prevalence of thyroid autoantibodies: 87.5% (18/21) type 1 diabetes patients were positive for anti-

Study	Intervention/ comparison	Population	Follow-up	Results
	and insulin dependent diabetes in patients with autoimmune disease Prevalence of insulin dependent diabetes in Japan	diabetes +Graves' disease Group II: type 1 diabetes +Hashimoto's thyroiditis Group III: type 1 diabetes only Group IV: healthy control group		thyroidal autoantibodies
YASMIN 2006[791]	Case control study	n=163: n=51 type 1 diabetes n=61 type 1 diabetes n=51 controls	Followed for 1 year from recruitment	Thyroid antibodies: 39% had normal anti-TPO levels, 21% had mild level of anti-TPO, 20% had moderate levels of anti-TPO 20% had high levels of anti-TPO. Levels of anti-TPO and TSH in type 1 diabetes were higher than in the control group Thyroid hormones: Levels of FT4 were lower in the type 1 diabetes compared with the control group

Table 132: Summary table showing the prevalence results from all the studies.

Study	Frequency of monitoring	Thyroid auto anti-body positive	Hashimoto's disease	Graves' disease	Sub-clinical/clinical hypothyroidism	Sub-clinical/ clinical hyperthyroidism	TPO antibody positive	Tg antibody positive	TSH positive	FT4/T4 positive	T3/ FT3 positive	TRAB (receptor antibody) positive
ALLEN 2008 (childhood onset and adult onset type 1 diabetes)							11.5% (adult onset) 11.8% (child onset)					9.1% (adult onset) 1.9%(child onset)
BIANCHI 1995 (type 1 diabetes with no previous thyroid disorder)							33%	16%	8.8% =below detection threshold (Ab negative)	8.8% high FT4	8.8% high FT3	
CARDOSO 1995 (adult onset of type 1 diabetes)		46.6%										
DAGDELEN 2009 (adult onset of type 1 diabetes)							24.6%		1.5%			

Study	Frequency of monitoring	Thyroid auto anti-body positive	Hashimoto's disease	Graves' disease	Sub-clinical/clinical hypothyroidism	Sub-clinical/ clinical hyperthyroidism	TPO antibody positive	Tg antibody positive	TSH positive	FT4/T4 positive	T3/ FT3 positive	TRAB (receptor antibody) positive
DUFAITRE 2006 (unclear onset of type 1 diabetes)	Monitored at 1 year after inclusion, No new cases of autoimmune disease recorded at 1 year FU		8.4% (CIPII patients 7.4% (CSII patients)	1.3% (CIPII patients) 2.4%(CSII patients)	Subclinical disease (all patients): 28%		25.9% (CIPII patients) 30.6% (CSII patients)					
FIALKOW1975 (unclear duration of type 1 diabetes)		35% 40-59 years: 9%		1.9%			20-30 years: positive and low titre= 23.3%; positive and high titre= 13%	20-30 years: positive and low titre= 16.6%; positive and high titre= 6%				
GOMEZ 2003 (newly diagnosed type 1 diabetes)									Basal level: 1.6% (men); 1.7% (women)			
HANUKOGLU 2003 (type 1 diabetes	.	Probands =27% First-		0			Probands=18% First-degree relatives=19%	Probands =19% First				

Study	Frequency of monitoring	Thyroid auto anti-body positive	Hashimoto's disease	Graves' disease	Sub-clinical/clinical hypothyroidism	Sub-clinical/ clinical hyperthyroid ism	TPO antibody positive	Tg antibody positive	TSH positive	FT4/T4 positive	T3/ FT3 posit ive	TRAB (recep tor antibo dy) positiv e
diagnosed before 18 years age)		degree relatives= 25%						degree relatives= 17%				
JIN 2011 (late onset of type 1 diabetes)	TPO At 4 years =25.5% Tg At 4 years =24.5%	Baseline= 27.4% 95% patients Ab positive at baseline were also positive during FU			9.5%		Baseline= 24.7%	Baseline= 23.7%				
JUNIK 2006 (unclear onset and duration of type 1 diabetes)					Subclinical: 3%	Subclinical: 7%	Normal range					
KUCERA 2003 (late onset of type 1 diabetes)							22.1%	8.8%				
LUPI 2013 (unclear			31.5%	6.3%								

Study	Frequency of monitoring	Thyroid auto anti-body positive	Hashimoto's disease	Graves' disease	Sub-clinical/clinical hypothyroidism	Sub-clinical/ clinical hyperthyroidism	TPO antibody positive	Tg antibody positive	TSH positive	FT4/T4 positive	T3/ FT3 positive	TRAB (receptor antibody) positive
onset of type 1 diabetes)												
PALMA 2003 (Adult onset of type 1 diabetes)					Subclinical without dysfunction: 13%		14.6%					
PERROS 1995 (Adult onset of type 1 diabetes)	Annual incidence of new thyroid disease=6.7 %				5.9% (men); 14.5% (women)-hypothyroidism Sub-clinical: 5.4% (men); 9.5% (women)	1.1% (men); 6.4% (women)-hyperthyroidism Sub-clinical: 0% (men) 0.9% (women)						
PRAZNY 1999 (Adult onset of type 1 diabetes)							14% (men); 21% (women) 11% positive for both TPO and TgAb	Higher in women				
RATTARASARAN 2000 (Childhood and adult	At 19 months FU: TGab or TPO	16%					30%	18%				

Study	Frequency of monitoring	Thyroid auto anti-body positive	Hashimoto's disease	Graves' disease	Sub-clinical/clinical hypothyroidism	Sub-clinical/ clinical hyperthyroidism	TPO antibody positive	Tg antibody positive	TSH positive	FT4/T4 positive	T3/ FT3 positive	TRAB (receptor antibody) positive
onset of type 1 diabetes)	without obvious thyroid disease=25 % At 20 months FU: 13% elevated TSH 25% were at higher risk of developing thyroid dysfunction at 3 years FU											
UMPIEREZ 2003 (Adult onset of type 1 diabetes)	Patients TPO+17.9xlikely to develop hypothyroidism vs. TPO- patients.				Average: 31% 19% (men); 44% (women)							
VONDRA 2004	Annual new cases of						26% (group 1 TPO positive only)					

Study	Frequency of monitoring	Thyroid auto anti-body positive	Hashimoto's disease	Graves' disease	Sub-clinical/clinical hypothyroidism	Sub-clinical/ clinical hyperthyroid ism	TPO antibody positive	Tg antibody positive	TSH positive	FT4/T4 positive	T3/ FT3 posit ive	TRAB (recep tor antibo dy) positiv e
(Newly diagnosed type 1 diabetes)	TPO+ during FU = 26% (at year 9); 0% (at years 10, 11, and 12) Cumulative incidence of positive TPO and Tg=25% in the study and at FU						25% (group 2 TPO+Tg positive)					
WALTER 2007 (Adult onset of type 1 diabetes)		Autoimm une thyroid disease=3 1% More common in women (43%) vs. men (21%)										
WHITEHEA D 2010 (Adult	Annual thyroid hormone testing to				10.8% Subclinical: 4% Hypothyroidismdu	1% Hypothyroidi sm requiring						

Study	Frequency of monitoring	Thyroid auto anti-body positive	Hashimoto's disease	Graves' disease	Sub-clinical/clinical hypothyroidism	Sub-clinical/ clinical hyperthyroidism	TPO antibody positive	Tg antibody positive	TSH positive	FT4/T4 positive	T3/ FT3 positive	TRAB (receptor antibody) positive
onset of type 1 diabetes)	detect hypothyroidism for thyroxine treatment= 1.8%				e to surgery: 2%	Thyroxine treatment: increased with age after 50 years						
YAMAGUCHI 1991 (Adult onset of type 1 diabetes)		87.5%										
YASMIN 2006 (childhood and adult onset of type 1 diabetes)							61% Higher in women			84%		
MEDIAN % (RANGE)		33% (16 - 88)	8.4% (7.4 – 31.5)	2.2% (1.3–6.3)	SUBCLINICAL (all): 4% (3-13) SUBCLINICAL (men): 5.4% (5.4) SUBCLINICAL (women): 9.5% (9.5) CLINICAL (all): 10.8% (6-31)	SUBCLINICAL (all): 7% (7) SUBCLINICAL (men): 0% (0) SUBCLINICAL (women): 0.9% (0.9) CLINICAL (all):	25.9% (11.5 – 61) Higher in women; similar for child and adult onset	16% (6-23.7) Higher in women	1.6% (1.5 – 1.7) Similar in men and women	46% (8.8 – 84)	8.8% (8.8)	5.5% (1.9 - 9.1) Lower in child onset

Study	Frequency of monitoring	Thyroid auto anti-body positive	Hashimoto's disease	Graves' disease	Sub-clinical/clinical hypothyroidism	Sub-clinical/ clinical hyperthyroidism	TPO antibody positive	Tg antibody positive	TSH positive	FT4/T4 positive	T3/ FT3 positive	TRAB (receptor antibody) positive
					CLINICAL (men): 12.5% (5.9-19) CLINICAL (women):29.3% (14.5-44) Higher in women	1% (1) CLINICAL (men): 1.1% (1.1) CLINICAL (women):6.4 % (6.4) Higher in women						

Percentages are the prevalence of people with type 1 diabetes who had the marker or disease of interest.

16.9.4 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix E.

16.9.5 Evidence statements

Clinical

16.9.5.1 Prevalence of thyroid antibodies ([25,26,73,115,161,195,226,296,595,609,739,759,788,789,791])

- Low quality evidence from 7 studies reported prevalence of multiple thyroid autoantibodies in type 1 diabetes patients and ranged from 1.43% to 87.5%.[73,115], [226], [577], [609], [788,789]
- Low quality evidence from 6 studies reported prevalence of antiTPO positivity of 11.5%, 14.6%, 18%, 22.1%, 24.6%, and 30% in type 1 diabetes patients [25,26], [161], [563], [609], [595], [423] and one study reported 21% type 1 diabetes with mild levels of ant-TPO antibody, 20% type 1 diabetes patients with moderate levels of anti-TPO antibody, and 20% type 1 diabetes patients with high levels of anti-TPO antibody.[791]
- Low quality evidence from one study reported prevalence of autoimmune thyroiditis determined by high TPO and/or Tg titres was 27 and 25% for probands and relatives respectively. [296]
- Low quality evidence from one study reported 23% type 1 diabetes patients (20-39 years) with low and 13% with high levels of anti-TPO antibody.[226]In the older subgroup (40-59 years) with type 1 diabetes, 27% had low and 27% had high levels of anti-TPO antibody. This study also showed an increase in anti-TPO antibodies in type 1 diabetes patients over 4 years from 24.7% to 25.5%.
- Low quality evidence showed that the presence of TPO antibodies was associated with an increased risk of hypothyroidism; type 1 diabetes patients with TPO positive antibodies were 18 times more likely to develop hypothyroidism. Most patients with positive TPO antibodies at the beginning of the study remained positive throughout the study.[739],
- Low quality evidence from one study showed that the prevalence of anti-TPO antibody positivity was higher in females than males.[609]
- Low quality evidence from two studies reported prevalence of thyroglobulin antibody positivity of 8.8% and 18%.[423], [595]
- Low quality evidence from one study reported 17% type 1 diabetes patients (20-39 years) to have low levels of thyroglobulin antibody positivity and 6.6% type 1 diabetes patients to have high levels of thyroglobulin antibody positivity compared with higher levels in 40-59 years subgroup of type 1 diabetes patients (27% low levels and 27% high levels of thyroglobulin antibody positivity).[226]
- Low quality evidence from one study reported a prevalence of 23.7% of thyroglobulin antibody positivity at the start of the study which increased to 24.5% prevalence after 4 years.[374]

16.9.5.2 Prevalence of thyroid hormones [115], [161], [273,274], [382], [563], [759],[791]

- Low quality evidence from one study reported prevalence of positive TSH to be higher in patients with type 1 diabetes compared with the control group.[161]
- Low quality evidence from one study reported FT4 and TSH concentrations to be lower in type 1 diabetes compared with control group

- Low quality evidence from two studies reported FT4 and TSH levels to be within the normal range in 50% patients.[563] with type 1 diabetes and also in type 1 diabetes patients with previous thyroid disease [577]
- Low quality evidence from one study reported T3 and T4 concentrations to be within normal range, but lower than in the control group, and TSH concentration was within normal range but higher than in the control group.[115]
- Low quality evidence from one study reported TSH levels above 4.5mU/litre in 30% of patients who were positive for both thyroid antibodies compared with 7% of patients who were positive for TPO antibody only.[759]
- Low quality evidence from one study reported TSH levels to be lower in type 1 diabetes patients (0.97 (range 0.61-1.58) mlU/litre) compared with control group (1.66 (range 0.76-2.09) mlU/litre). [382]
- Low quality evidence from one study showed that basal levels of TSH were higher in females compared with males (1.6%±1.14 versus 1.69%±1.08) and higher in type 1 diabetes patients compared with the control group (type 1 diabetes males =1.6%±1.14 versus control group=1.5%±0.78; type 1 diabetes females=1.69%±1.08 versus control group=1.59%±0.96).[273,274]

16.9.5.3 Prevalence of thyroid disease [195], [226], [469], [577], [739], [759], [762], [774]

- Low quality evidence from one study reported 31% type 1 diabetes patients to have thyroid disease. [762]
- Low quality evidence from two studies reported overall prevalence of previous or present thyroid disease was 13% [577] and 9.8% [195].The combined total prevalence of clinical and subclinical disease was 31%. [195]
- Low quality evidence from one study reported hypo-echogenic thyroid in 59% type 1 diabetes patients positive for both thyroid antibodies.At 4 years follow-up, 100% of people with type 1 diabetes who were positive for both TPO and Thyroglobulin antibodies had subclinical hypothyroidism compared with 11% of those with type 1 diabetes positive for TPO antibody only.[759]
- Low quality evidence from two studies reported prevalence of 10.8% and 31% for hypothyroidism (including subclinical hypothyroidism) in patients with type 1 diabetes.[774], [739]
- Low quality evidence from three studies reported that prevalence of thyroid disease was higher in females (43%, 41%, and 31.4%) than males (21%, 19%, and 12.4%).[762], [577], [774]
- Low quality evidence showed that the prevalence of Hashimoto's thyroiditis (two studies) was 31% and 1.9%, and Graves' disease 6% and 1.9% in type 1 diabetes patients.[469], [226].In another study the prevalence of Hashimoto's thyroiditis was 8.4% and 7.5%, and 1.4% and 2.5% for Graves' disease intype 1 diabetes patients treated different insulin treatments.[195]
- Low quality evidence from one study reported that prevalence of autoimmune disease was not correlated with age, duration of diabetes or duration of treatment. [195]

16.9.5.4 Tests for monitoring thyroid disease[739,774]

T4, T3, TSH tests

The tests used in the included studies were T4, T3, TSH, with TSH and T4 measured more frequently

- Low quality evidence from one study, that measured TSH, T3, T4 every year, and TPO antibody every 4 years, over an 18 year period. Presence of TPO antibodies was associated with an increased risk of hypothyroidism.Most patients with positive TPO antibodies at the beginning of the study remained positive throughout the study.One patient who was negative for TPO

antibodies developed low TPO titres after 12 years follow-up.No differences in TSH values on diagnosis of hypothyroidism between patients with positive or negative antibodies. [739]

- Low quality evidence fromone study found that routine thyroid hormone testing done at annual review detected hypothyroidism requiring thyroxine treatment in 1.8% of patients with type 1 diabetes.[774]

16.9.5.5 Antibody tests [26,195,226,374,577,609,759,791]

Tests for thyroid disease studies included anti-TPO and anti-thyroglobulin positivity.

- Low quality evidence from one study that measured anti-TPO positivity in type 1 diabetes patients over 4 years and resulted in mild increase in the number of patients that were positive either anti-TPO or anti-TG antibodies.[374]
- Low quality evidence from one study that measured anti-TPO antibody in type 1 diabetes patients over 5 years and reported positive antibodies in 13 patients.[25,26]
- Low quality evidence from one study that measured anti-TPO antibody over one year and reported that anti-TPO positivity developed in 7.2% after one year.[195]
- Low quality evidence from one study that measured anti-TPO and anti-TG antibodies over two years reported that frequencies of antibodies to thyroglobulin and TPO were equally elevated. [226]
- Low quality evidence from one study that measured thyroid antibodies over one year and reported an annual risk of thyroid disease of 12.3% in females with type 1 diabetes.The annual incidence of new thyroid disease was 6.7%.Clinical management was influenced in 4% of the study group. [577]
- Low quality evidence fromone study in patients with TGab or TPO positivity and without thyroid dysfunction, found that 2 patients developed hypothyroidism during follow-up 19±8 months; serum TSH increased from 10.0 to 20.75 mU/litre after 20 months in 1 patient and 4.64 to 33.87 mU/litre after 35 months in another patient.21 patients tested for thyroid antibodies remained negative for thyroid dysfunction during 16.4±6.3 months follow-up. Subjects with positive antibodies had a higher risk of developing thyroid dysfunction up to approximately 3 years of follow-up.[609]
- One study measured thyroid antibodies over 12 years and reported cumulative incidence of positivity of thyroid antibodies during 12 follow-up of 51%. Hypoechogenic thyroid was detected in 59% type 1 diabetes patients positive for both antibodies compared with 25% type 1 diabetes patients who were positive for one antibody.TSH levels above 4.5 mlU/litre were found in 30% type 1 diabetes patients positive for both antibodies compared with 7% type 1 diabetes patients who were positive for one antibody.At 4 years of follow-up, subclinical hypothyroidism was found in 100% o type 1 diabetes patients positive for both antibodies compared with 11% type 1 diabetes patients who were positive for one antibody.Cumulative incidence of concomitant positivity of both antibodies (anti-Tgl and antiTPO) in type 1 diabetes patients, peaked at 25% in year 8 of follow-up and did not change during the remaining 4 years of the 12 years total follow-up time. In patients with type 1 diabetes who were only positive for antibody (anti-TPO), the cumulative incidence of positivity varied over the follow-up period and peaked at 26% at year 9, and did not change and did not change during the remaining 3 years of the 12 years total follow-up time.[759]
- One study measured thyroid autoantibodies for one year after recruitment and reported 39% with normal anti-TPO levels, 21% with low levels of anti-TPO, 20% with moderate levels of anti-TPO, 20% with high levels of anti-TPO.Measurement of T4 was lower, and TSH and TPO were higherin subjects with type 1 diabetes compared with a control group without diabetes.[791]

Economic

No relevant economic evaluations were identified.

16.9.6 Recommendations and link to evidence

The current guideline recommendations can be found at

https://www.nice.org.uk/guidance/ng17

Relative values of different outcomes	The GDG agreed that the purpose of this question was to look at the detection of asymptomatic thyroid disease. This is because adults with autoimmune type 1 diabetes are at increased risk for primary auto-immune thyroid disease and the detection of subclinical disease will allow appropriate treatment to start without delay. Secondary causes of thyroid disease are much less common and not specific to adults with type 1 diabetes. Their routine detection may be more complex, especially if thyroid function monitoring is by measurement of TSH alone, and this does not fall within the remit of routine diabetes management. Among primary thyroid diseases, hypothyroidism is more common than hyperthyroidism, but the screening tests are the same for both and both were considered Ideally this question would be informed by RCTs evaluating different screening strategies for thyroid disease against one another and against no screening. No such RCTs were found. The GDG therefore looked for cohort studies, case-control studies or observational studies which provided data about the incidence of thyroid disease in people with type-1 diabetes. Data on frequency of testing were also sought, but no study was found that directly addressed this. The marker of thyroid disease used was different between studies. Some looked at clinical thyroid disease, some at thyroid antibodies (presence of thyroid antibodies is an established risk factor for development of thyroid disease), some at abnormal thyroid function tests (TSH +/- thyroid hormones) and some at combinations of these. The GDG agreed that it was appropriate to consider detection before thyroid disease is clinically apparent, because sub-clinical disease has a very high rate of conversion to clinical disease which can be avoided with appropriate treatment. The data of particular interest were therefore: Rate of development of thyroid auto-antibodies (thyroid Ab) over time in people with type 1 diabetes Rate of development of abnormal thyroid function tests (TFT) over time in people with type 1 diabetes The relationship between these two, that is, how reliably does the development of thyroid Ab predict the development of abnormal TFT, and what is the associated time-scale. This is relevant to the issue of whether both thyroid Ab and TFT need to be measured.
Trade-off between clinical benefits and harms	The studies confirmed the expected high prevalence of thyroid dysfunction in people with type 1 diabetes. Many of the studies reported at one time point only. Among the studies which reported thyroid Ab and/or TFT results at more than one time point, it was noted that: Perros[577]re-measured TFT at 12 months in 1,310 adult diabetic patients (the largest cohort in the available evidence) including 406 with type 1 diabetes. The incidence of new thyroid disease (clinical plus sub-clinical) at 12 months was 6.7% Jin[374]found a positive TPO antibody test in 24.7% of 190 patients with type 1 diabetes. At re-test 4 years later this had risen only slightly to 25.5%, and virtually all of the positive results were in those who had been positive at first test (95% remained Ab positive). Less than 1% of the antibody negative subjects became positive. Vondra[759] followed 109 subjects with type 1 diabetes for 12 years. Those with

	thyroid Ab had a substantially greater risk of developing sub-clinical or clinical thyroid disease (All patients with repeated positivity of both thyroid autoantibodies – T-Ab and anti-TgL – developed subclinical hypothyroidism within 4 years after the first detection of T-Ab, whereas this figure was only 11% in patients with isolated antiTPO positivity). Umpierrez[739] in a smaller study over 4 years also showed that those with type 1 diabetes who have thyroid Ab are much more likely to develop thyroid disease (OR 17.91) As already noted, there is value in picking up thyroid dysfunction because symptomatic deterioration can be avoided, in the case of hypothyroidism using simple replacement therapy which is generally extremely well tolerated. The GDG considered there to be very little risk in screening people with type 1 diabetes. A blood test is required, but as this can bepart of the annual metabolic screen; there is no need for an additional blood test
Economic considerations	There were no economic studies of screening for, or early detection of, thyroid disease in type 1 diabetes. The cost of the most commonly tested thyroid Ab (TPO antibody) is approximately £7.50. The cost of a TSH measurement is approximately £3.50. The GDG recognised that thyroid screening blood testscould be carried out as part of the annual metabolic screening and therefore do not incur additional phlebotomy costs, so only the cost of the assay need be considered. . Carrying out the test would improve the detection and treatment of thyroid disease, reducing its symptoms and complications. Therefore testing for thyroid disease is likely to have a positive effect on quality of life and it is likely to justify its cost.
Quality of evidence	There were no RCTs, and the GDG had to develop their recommendations by inference from the available cohort and cross-sectional studies. There were differences between studies in the characteristics of the subjects in terms of age (and whether or not both children and adults were included); duration of diabetes (this information was generally not available); and country of origin. The antibody tests under consideration also differed between studies. Antibodies against thyroid antigens can logically be used to predict risk of hypothyroidism (in hyperthyroidism anti-TSH receptor antibodies are used to diagnose autoimmune hyperthyroidism once the diagnosis has been established). In screening for hypothyroidism the most commonly used antibodies were anti-peroxidase (TPO) and anti-thyroglobulin antibodies. Expert opinion within the GDG was that TPO antibodies are better predictors of the subsequent development of hypothyroidism. Most of the available studies measured thyroid Ab and/or TFT at only one time point. Moreover, all but one of studies reporting repeat measurement made only one further measurement within the study, and this additional measurement was not made at a similar time point in all studies. Only the study by Vondra and colleagues[759] in 109 people with type 1 diabetes reported thyroid measurements at multiple time-points.
Other considerations	The GDG agreed that monitoring for thyroid disease in people with type 1 diabetes was worthwhile given the marked increase in risk in this population. There was debate about the optimum strategy. The evidence suggests that the risk of sub-clinical or clinical thyroid disease is much greater in those who are thyroid Ab

	positive, and that routine measurement of TFT in antibody-negative people is less obviously beneficial. One study[759] suggested the rate of TPO positivity rises after diagnosis of type 1 diabetes but plateaus at 10 -12 years.A further study[739] showed TPO negativity stable after 12 years diabetes duration.One strategy would therefore be to measure for the presence of thyroid antibodies annually for the first 10-12 years after diagnosis of type 1 diabetes. In those who develop antibodies, annual TFT measurement should be performed. In those without antibodies TFT may not be necessary. An alternative strategy is to measure TSH (which the GDG considered was the only TFT required in monitoring for primary thyroid disease) annually; this takes into account the very low cost of a TSH measurement. In this strategy annual TSH measurement is offered to all people with type 1 diabetes, irrespective of antibody status which therefore does not need to be measured routinely at all. The majority view was that annual TFT for all was preferable because it is much simpler and therefore more likely to be successfully implemented.

16.10 Psychological problems [2004]

16.10.1 Rationale

The management demands of insulin therapy, the risks of late complications of diabetes, and the problems of hypoglycaemia and social discrimination, can place significant emotional stress on people with type 1 diabetes. This might precipitate or exacerbate psychological difficulties present for other reasons. Additionally, the stresses might in themselves be expected to interfere with a person's ability to self-manage their diabetes.

16.10.2 Evidence statements

Depressed mood and glycaemic control

A small cohort study examining depressed mood as a factor in glycaemic control in type 1 diabetes found a strong positive correlation between mood and glycaemic control.[749] As the depression scores for this sample were mainly in the normal range, the results of this study indicate that mood, rather than clinical depression per se, is associated with significant differences in glycaemic control (IIa).

A medium-sized cohort study316 examined depression and its effect on reporting diabetes symptoms in type 1 diabetes. The study found that seven of nine symptoms attributed to diabetes (hyperglycaemic symptoms, hypoglycaemic symptoms and non-specific symptoms of poor control) were associated with depression whereas only one of nine symptoms attributed to diabetes was related to HbA1 (IIa).

A meta-analysis of cross-sectional studies examined whether depression is associated with glycaemic control.[470,471] A weak correlation was found between depression and glycaemic control. However, the study has certain potential issues with the methodology used. No systematic quality appraisal has been given for those studies included in the meta-analysis. Effect size estimates may be unstable due to the small number of studies and the small sample sizes of some studies (III).

Injection anxiety and glycaemic control

One medium-sized cohort study examined 'fear of blood and injury' and its association with glycaemic control in type 1 diabetes.[70,71] The study shows that Type I diabetes adults with poorer glycaemic control perform fewer blood glucose measurements per day. The relationship between poor glycaemic control and fewer blood glucose measurements is mediated by fear of blood and injury (IIa).

Another medium-sized cohort study examined injection anxiety in type 1 and type 2 diabetes.[797] The study found a significant negative correlation between injection anxiety and the number of insulin injections. However, no significant difference was found in the degree of glycaemic control between diabetes patients with high vs low anxiety scores. The results of this study are not analysed separately for people with type 1 and type 2 diabetes (III).

One meta-analysis320 examined whether or not anxiety is associated with poor glycaemic control in adults with type 1 and type 2 diabetes. The studies that were limited to type 1 diabetes found a weak correlation between anxiety and glycaemic control. However, the study has some possible methodological limitations which may have introduced bias into analysis. No systematic quality appraisal has been given for those studies included in the meta-analysis. Effect size estimates may be unstable due to the small number of studies and the small sample sizes of some studies (III).

Prevalence of depression in Type I diabetes

One recent meta-analysis of prevalence studies examining the prevalence of depression in type 1 diabetes found a significantly higher prevalence of depression in type 1 diabetes (21.7%) than in non-diabetes control subjects (8.6%).[35,38] Potential methodological factors inherent to the study may limit the validity of the results derived from the meta-analysis (III).

One retrospective cross-sectional case-control study examined the prevalence of antidepressant use in type 1 diabetes compared to age- and sex-matched controls.[437] The study found a significantly higher proportion of type 1 diabetes patients (12.8%) had received a prescription for antidepressants in the past twelve months compared to controls (7.4%). The data for this study was derived from a localised computerised database of 28 GP practices so caution needs to be taken when generalising these results to other geographical areas (III).

Management of depression

A medium-sized prospective 12-month follow-up study in type 1 diabetes evaluated whether a blood glucose awareness training programme (BGAT-2) would improve mood.[147,151] No significant improvement in mood was detected in baseline scores at six and 12 months. This is attributed to baseline scores being within the normal limits. When subjects who feel within the range of mild depression were examined separately, these individuals did demonstrate a significant reduction in baseline scores at six and 12 months (IIb).

A small randomised controlled trial evaluated the efficacy of nortriptyline for depression and poor glycaemic control in a mixed (type 1 and type 2) diabetes population with poor glycaemic control.[471,474] The study found that the nortriptyline group were significantly less depressed after eight weeks than the placebo-treated patients. Of the nortriptyline-treated patients, 57% successfully remitted compared to 35.7% of the placebo-treated patients. No significant difference in response rate was found between type 1 and type 2 diabetes. Further- more, in the sample as a whole (type 1 and type 2) there was a non-significant trend towards worsened glycaemic control, both in patients who received nortriptyline and those who received placebo (Ib).

A small randomised controlled trial evaluated the antidepressant efficacy of fluoxetine in diabetic patients (mixed population type sample) with major depressive disorder.[471,472] At the conclusion of the eight-week treatment period, a significant reduction in symptoms of depression was found in the fluoxetine-treated group compared to the placebo group. However, no significant difference in the improvement of glycaemic control was found between patients who received fluoxetine and those who received placebo (Ib).

A small random two-group parallel comparison with a pre-test and nine and 15 months follow- up study compared the effects of a standard intensive treatment, patient education and distress reduction programme, with a standard treatment and patient education.[696] Outcomes examined

were psychological variables and metabolic control. At nine months follow-up, depression improved significantly in the intensive treatment group compared to the standard treatment group. No significant difference was found in metabolic control between the two groups. At 15 months follow-up, improvement in depression faded and metabolic control was worsened (Ib).

Management of anxiety in type 1 diabetes

A small double-blind randomised controlled trial in a mixed (type 1 and type 2) diabetes population examined the effects of alprazolam on glucose regulation in anxious and non- anxious patients with poor glycaemic control.[471,473] Patients treated with alprazolam had a significantly greater reduction in GHb levels than those receiving placebo, regardless of anxiety. Both alprazolam and placebo similarly improved anxiety among anxious patients. Results were not analysed separately for type 1 and type 2 diabetes (Ib).

16.10.3 Consideration

It was felt that, whether or not depression and other psychological illness was more common in people with type 1 diabetes, the literature being inconclusive, the interaction with self-management demanded professional alertness to such problems. A degree of competence in managing these problems at least matching that of an experienced general practitioner is clearly desirable.

16.10.4 Recommendations

The current guideline recommendations can be found at

https://www.nice.org.uk/guidance/ng17

See also the NICE guidelines on common mental health disorders, generalised anxiety disorder and panic disorder (with or without agoraphobia) in adults and depression in adults with a chronic health problem. [2004, amended 2015]

16.11 Eating disorders [2004]

16.11.1 Rationale

Due to the inadequacies of subcutaneous insulin therapy, dietary self-management is an inevitable consequence of the optimal self-care of type 1 diabetes. Eating disorders are not uncommon in the general population, while type 1 diabetes is most commonly diagnosed at an age (12–20) when consciousness of own body image is high. Accordingly, eating disorders are seen in people with type 1 diabetes, and will interfere with self-management.

A review of the management of eating disorders is outside the scope of this guideline. A systematic search of the literature was, however, undertaken to review the types and relevant prevalence of eating disorders, and whether any specific issues of management had been identified in the type 1 diabetes population.

16.11.2 Evidence statements

Many papers on eating disorders in diabetes include people with type 2 diabetes. Extrapolation to type 1 diabetes from such populations is not safe. Assessment of eating disorders can be by interview (specific, low prevalence) or questionnaire (non-specific, high prevalence), and may or may not include manipulation of insulin dosage (dose omission or reduction). Accordingly published prevalence and odds ratio vs matched populations vary. Furthermore there may be cultural variations depending on attitudes to obesity and peer pressure. People with diabetes often are in

continued contact with professional care teams, and the input of those teams might be expected to have influence on behavioural disorders (IV).

A follow-up study using interview methods in a clinic population found no eating disorders at all.[104] Nevertheless a proportion of young people did use insulin dose manipulation to control weight, and appeared to have worse outcomes (markers of late complications of diabetes) as a result (III).

A group in Toronto published a series of papers over the last decade, including a non-systematic review.[323,623] They note the odds ratio for eating disorders in young people compared to non-diabetic controls is around 2.0, with an excess prevalence of 2%–5%. The principal disorders described are bulimia nervosa and insulin dose manipulation, the conditions tend to be chronic even under care, and diabetes outcomes relatively poor compared to peers (III).

A review, described as a meta-analysis of prevalence studies, concurred with these figures for bulimia and dose manipulation, and could not find evidence of increased prevalence of anorexia nervosa (III).[548,549]

One small randomised controlled trial of a group psycho-education programme to improve sub-clinical disordered eating in women with type 1 diabetes found no significant differences between the intervention and control (standard care) in outcomes of metabolic control with both groups showing improvements from baseline.[27] There was also no significant difference in concordance with diabetes treatment or eating disorder symptomology at six weeks (Ib).

A position statement of the American Dietetic Association and the Dietitians of Canada found evidence that the prevalence of eating disorders among young adult women with type 1 diabetes to be about 5% to 11%.[19] It is suggested that dietetic professionals have a vital role in the management of diabetes as they have an understanding of the health issues that affect women with diabetes (IV).

16.11.3 Consideration

The group felt that the evidence on the whole suggested that eating disorders were more prevalent in people with type 1 diabetes, and particularly in young adults. Insulin dose manipulation of calorie loss accounted for much of this, and perhaps the long-term follow-up study's results were influenced by the benefits of the good long-term support offered. Experience of eating disorders in clinical practice was that in the context of insulin therapy they can have serious short- and long-term impacts, sometimes fatal.

16.11.4 Recommendations

The current guideline recommendations can be found at

https://www.nice.org.uk/guidance/ng17

16.12 Management of special situations [2004]

Adults who are newly diagnosed

16.12.1 Rationale

The time following diagnosis is one of marked stress for many adults with diabetes. However, decisions taken at this time may have a long-term impact, and to be accurate and effective would appear to need fairly complete assessment of medical and lifestyle factors. These can be expected to affect choice of therapy and monitoring requirements, educational requirements, input from

different members of the multidisciplinary team, site of care and the need for involvement of other health-related services and perhaps employers and other institutions.

16.12.2 Evidence statements

Organisation of initial assessment planning

Consensus in the ADA guidelines suggests that medical evaluation is made to classify the person presenting as a basis for a management plan and to assess complications.[29] This is echoed by Diabetes UK recommendations for management in primary care which indicate that a planned programme of diabetes care should include systems for ensuring assessment and acute management of all newly-diagnosed patients.[183,184] In addition, American guidelines from the Department of Veterans Affairs identify initial assessment as a useful tool to review systems and set priorities for care (IV).[178]

Content of the initial assessment plan

All of the guidelines reviewed are aimed at a mixed diabetic population and do not specify any specific features of initial assessment that are particular to people with type 1 diabetes. All guidance[29,30,178,183,184] suggests that assessment should look for co-morbid conditions that people with diabetes are more commonly at risk from and should consider factors that may affect the management of diabetes such as COPD, substance misuse and depression.[29,30,178] Factors that may precipitate diabetes secondary to other medical conditions should also be considered (IV).[178]

Other factors of initial assessment that can aid management planning that are widely suggested included physical examinations, laboratory tests including lipid profile, urinalysis and ECG.[29,178,183,184] Consideration for referral is advised for (IV):

- urgent hospitalisation if patient is clearly unwell,[183,184] or
- where specialist examination is required for eye exam, family planning, diabetes education, behavioural advice or foot disorders.[29]

Consistent documentation of assessment is widely recommended,[178,183,184] and initial assessment should be used for the baseline of an individualised management plan (IV).[29,183,184]

Adults who are newly diagnosed

16.12.2.1 Rationale

The time following diagnosis is one of marked stress for many adults with diabetes. However, decisions taken at this time may have a long-term impact, and to be accurate and effective would appear to need fairly complete assessment of medical and lifestyle factors. These can be expected to affect choice of therapy and monitoring requirements, educational requirements, input from different members of the multidisciplinary team, site of care and the need for involvement of other health-related services and perhaps employers and other institutions.

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Consistent documentation of assessment is widely recommended,[178,183,184] and initial assessment should be used for the baseline of an individualised management plan (IV).[29,183,184]

Benefit of initial assessment plan

No interventional studies were identified that assess the effect on outcomes of improved initial assessment planning. It may be assumed that benefits may accrue in terms of understanding and satisfaction with care, and potentially with adherence to management plans, although these cannot be quantified at this time (IV).

16.12.3 Health economic evidence

The health economic searches produced no studies giving guidance on appropriate insulin regimens for those newly diagnosed with type 1 diabetes.

16.12.4 Consideration

The group noted that this was not an area in which to expect RCT evidence of different styles of initial management planning, and endorsed in general the views expressed in other recent guidelines for people with type 1 diabetes. An overlap with the education recommendations of this guideline (see Chapter 7) was noted.

16.12.5 Recommendations

The current guideline recommendations can be found at

https://www.nice.org.uk/guidance/ng17

17 Reference list

1 Epidemiology of severe hypoglycemia in the diabetes control and complications trial. The DCCT Research Group. American Journal of Medicine. 1991; 90(4):450-459

2 Implementation of treatment protocols in the Diabetes Control and Complications Trial. Diabetes Care. 1995; 18(3):361-376

3 The relationship of glycemic exposure (HbA1c) to the risk of development and progression of retinopathy in the diabetes control and complications trial. Diabetes. 1995; 44(8):968-983

4 The absence of a glycemic threshold for the development of long-term complications: the perspective of the Diabetes Control and Complications Trial. Diabetes. 1996; 45(10):1289-1298

5 Hypoglycemia in the Diabetes Control and Complications Trial. The Diabetes Control and Complications Trial Research Group. Diabetes. 1997; 46(2):271-286

6 Assessing the benefit of support groups. New England Journal of Medicine. 2001; 345(24):1719-1726,1767-68

7 Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA. 2002; 288(23):2981-2997

8 The DAWN (Diabetes Attitudes, Wishes and Needs) study. Practical Diabetes International. 2002; 19(1):22a-24a

9 MIMS. 2013. Available from: http://www.mims.co.uk/ [Last accessed: 12 December 2013]

10 A'Campo T, Schouwenberg B, Veldman B, Tack CJ, Smits P, de Galan BE. Prevalence and risk factors of hypoglycaemia unawareness and severe hypoglycaemia in patients with type 1 diabetes. Diabetologia. 2010; 53(Suppl.1):S239

11 Abdelgadir M, Elbagir M, Eltom M, Berne C. The influence of glucose self-monitoring on glycaemic control in patients with diabetes mellitus in Sudan. Diabetes Research and Clinical Practice. 2006; 74(1):90-94

12 Abelev Z, Seth A, Patel R, Goldstein S, Bogun M, Paliou M et al. Continuous insulin infusion is associated with a reduced post-surgical length of stay, but not with the complication rate, in patients with diabetes mellitus undergoing coronary artery bypass graft. Journal of Endocrinological Investigation. 2011; 34(10):770-774

13 Abell T, Mccallum RW, Hocking M, Koch K, Abrahamsson H, Leblanc I et al. Gastric electrical stimulation for medically refractory gastroparesis. Gastroenterology. 2003; 125(2):421-428

14 Abell TL, Johnson WD, Kedar A, Runnels JM, Thompson J, Weeks ES et al. A double-masked, randomized, placebo-controlled trial of temporary endoscopic mucosal gastric electrical stimulation for gastroparesis. Gastrointestinal Endoscopy. 2011; 74(3):496

15 Adamson CL, Kumar S, Sutcliffe H, France MW, Boulton AJM. Screening strategies in the detection of microalbuminuria in insulin-dependent diabetic patients. Practical Diabetes. 1993; 10(4):142-144

16 Adamson KA, Hassanein M, Malik I, White H, Vora J. Short or intermittent use of continuous glucose monitoring (CGM) enhances glycaemic control in subjects with persistently poorly controlled diabetes. Diabetic Medicine. 2013; 30(Suppl.1):160

17 Adler AI, Stratton IM, Neil HA, Yudkin JS, Matthews DR, Cull CA et al. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. BMJ. 2000; 321(7258):412-419

18 AETMIS. Screening for diabetic retinopathy: validation of a system using telemedicine approach- primary research (project). Montreal. Agence d'Evaluation des Technologies et des Modes d'Intervention en Sante (AETMIS), 2002. Available from: http://www.aetmis.gouv.qc.ca

19 Affenito SG, Kerstetter J. Position of the American Dietetic Association and Dietitians of Canada: women's health and nutrition. Journal of the American Dietetic Association. 1999; 99(6):738-751

20 Agardh CD. A new semiquantitative rapid test for screening for microalbuminuria. Practical Diabetes. 1993; 10(4):146-147

21 Agardh CD, Agardh E, Torffvit O. The association between retinopathy, nephropathy, cardiovascular disease and long-term metabolic control in type 1 diabetes mellitus: a 5 year follow-up study of 442 adult patients in routine care. Diabetes Research and Clinical Practice. 1997; 35(2-3):113-121

22 Aggarwal S, Goel A, Jain A. Role of C- peptide in identification of patients suspected of having latent autoimmune diabetes in adults (LADA) in north Indian type 2 diabetes mellitus population. International Journal of Pharma and Bio Sciences. 2010; 1(3)

23 Ahn CW, Song YD, Kim JH, Lim SK, Choi KH, Kim KR et al. The validity of random urine specimen albumin measurement as a screening test for diabetic nephropathy. Yonsei Medical Journal. 1999; 40(1):40-45

24 Aiello LP, DCCT/EDIC Research Group. Diabetic retinopathy and other ocular findings in the diabetes control and complications trial/epidemiology of diabetes interventions and complications study. Diabetes Care. 2014; 37(1):17-23

25 Allen C, LeCaire T, Palta M, Daniels K, Meredith M, D'Alessio DJ et al. Risk factors for frequent and severe hypoglycemia in type 1 diabetes. Diabetes Care. 2001; 24(11):1878-1881

26 Allen S, Huber J, Devendra D. Prevalence of organ-specific autoantibodies in childhood- and adult-onset type 1 diabetes. Annals of the New York Academy of Sciences. 2008; 1150:260-262

27 Alloway SC, Toth EL, McCargar LJ. Effectiveness of a group psychoeducation program for the treatment of subclinical disordered eating in women with type 1 diabetes. Canadian Journal of Dietetic Practice and Research. 2001; 62(4):188-192

28 Almdal T, Norgaard K, Feldt-Rasmussen B, Deckert T. The predictive value of microalbuminuria in IDDM. A five-year follow-up study. Diabetes Care. 1994; 17(2):120-125

29 American Diabetes Association. Standards of medical care for patients with diabetes mellitus. Diabetes Care. 2003; 26(Suppl.1):S33-S50

30 American Healthways. Inpatient management guidelines for people with diabetes. Nashville, Tennessee. American Healthways., 2002

31 Amiel S, Beveridge S, Bradley C, Gianfrancesco C, Heller S, James P et al. Training in flexible, intensive insulin management to enable dietary freedom in people with type 1 diabetes: dose adjustment for normal eating (DAFNE) randomised controlled trial. BMJ. 2002; 325(7367):746-749

32 Amrouche C, Jamoussi Kamoun H, Trabelsi N, Blouza Chabchoub S. Latent autoimmune diabetes in Tunisian adults (LADA): identification of autoimmune markers. La Tunesie Medicale. 2008; 86(4):316-318

33 Andersen MK, Sterner M, Forsen T, Karajamaki A, Rolandsson O, Forsblom C et al. Type 2 diabetes susceptibility gene variants predispose to adult-onset autoimmune diabetes. Diabetologia. 2014; 57(9):1859-1868

34 Anderson JH, Jr., Brunelle RL, Koivisto VA, Pfutzner A, Trautmann ME, Vignati L et al. Reduction of postprandial hyperglycemia and frequency of hypoglycemia in IDDM patients on insulin-analog treatment. Diabetes. 1997; 46:265-270

35 Anderson JW, Zeigler JA, Deakins DA, Floore TL, Dillon DW, Wood CL et al. Metabolic effects of high-carbohydrate, high-fiber diets for insulin-dependent diabetic individuals. American Journal of Clinical Nutrition. 1991; 54(5):936-943

36 Anderson J, Brunelle RL, Trautmann ME, Vignati L, DiMarchi R, Cameron DP et al. Improved mealtime treatment of diabetes mellitus using an insulin analogue. Clinical Therapeutics. 1997; 19(1):62-72

37 Anderson RJ, de Groot M, Grigsby AB, McGill JB, Freedland KE, Clouse RE et al. Anxiety and poor glycemic control: a meta-analytic review of the literature. International Journal of Psychiatry in Medicine. 2002; 32(3):235-247

38 Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. The prevalence of comorbid depression in adults with diabetes: a meta-analysis. Diabetes Care. 2001; 24(6):1069-1078

39 Annuzzi G, Del PS, Arcari R, Bellomo DA, Benzi L, Bruttomesso D et al. Preprandial combination of lispro and NPH insulin improves overall blood glucose control in type 1 diabetic patients: a multicenter randomized crossover trial. Nutrition, Metabolism, and Cardiovascular Diseases. 2001; 11(3):168-175

40 Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ. 2002; 324(7329):71-86

41 Apelqvist J, Ragnarson-Tennvall G, Persson U, Larsson J. Diabetic foot ulcers in a multidisciplinary setting. An economic analysis of primary healing and healing with amputation. Journal of Internal Medicine. 1994; 235(5):463-471

42 Araszkiewicz A, Zozulinska DA, Trepinska MM, Wierusz-Wysocka B. Inflammatory markers as risk factors for microangiopathy in type 1 diabetic patients on functional intensive insulin therapy from the onset of the disease. Diabetes Research and Clinical Practice. 2006; 74(2 Suppl.):S34-S40

43 Araszkiewicz A, Zozulinska-Ziolkiewicz DA, Trepinska M, Wierusz-Wysocka B. Why does intensive insulin therapy implemented at the onset of type 1 diabetes not decrease prevalence of diabetic microangiopathy? Archives of Medical Research. 2008; 4(2):167-173

44 Arikan E, Sabuncu T, Ozer EM, Hatemi H. The clinical characteristics of latent autoimmune diabetes in adults and its relation with chronic complications in metabolically poor controlled Turkish patients with Type 2 diabetes mellitus. Journal of Diabetes and Its Complications. 2005; 19(5):254-258

45 Aronson R, Gibney MA, Oza K, Berube J, Kassler-Taub K, Hirsch L. Insulin pen needles: Effects of extra-thin wall needle technology on preference, confidence, and other patient ratings. Clinical Therapeutics. 2013; 35(7):923-933

46 Arora S, Probst MA, Agy C, Menchine M. Point-of-care beta-hydroxybutyrate testing for assessing diabetic ketoacidosis severity prior to treatment in the emergency department. Diabetes Research and Clinical Practice. 2011; 94(3):e86-e88

47 Arora S, Henderson SO, Long T, Menchine M. Diagnostic accuracy of point-of-care testing for diabetic ketoacidosis at emergency-department triage: {beta}-hydroxybutyrate versus the urine dipstick. Diabetes Care. 2011; 34(4):852-854

48 Arslan D, Merdin A, Tural D, Temizel M, Akin O, Gunduz S et al. The effect of autoimmunity on the development time of microvascular complications in patients with type 1 diabetes mellitus. Medical Science Monitor. 2014; 20:1176-1179

49 Asakura T, Seino H, Nunoi K, Hashimoto K, Mutou T, Yamazaki K et al. Usability of a microtapered needle (TN3305) for insulin treatment in Japanese patients with diabetes mellitus: a comparative clinical study with a standard thin wall needle. Diabetes Technology and Therapeutics. 2006; 8(4):489-494

50 Ashwell SG, Amiel SA, Bilous RW, Dashora U, Heller SR, Hepburn DA et al. Improved glycaemic control with insulin glargine plus insulin lispro: a multicentre, randomized, cross-over trial in people with Type 1 diabetes. Diabetic Medicine. 2006; 23(3):285-292

51 Ashwell SG, Gebbie J, Home PD. Twice-daily compared with once-daily insulin glargine in people with type 1 diabetes using meal-time insulin aspart. Diabetic Medicine. 2006; 23(8):879-886

52 Aspinall SL, Smith KJ, Cunningham FE, Good CB. Incremental cost-effectiveness of various monthly doses of vardenafil. Value in Health : the Journal of the International Society for Pharmacoeconomics and Outcomes Research. 2011; 14(1):97-101

53 Assal JP, Jacquemet S, Morel Y. The added value of therapy in diabetes: the education of patients for self-management of their disease. Metabolism: Clinical and Experimental. 1997; 46(12 Suppl.1):61-64

54 Athyros VG, Didangelos TP, Karamitsos DT, Papageorgiou AA, Boudoulas H, Kontopoulos AG. Long-term effect of converting enzyme inhibition on circadian sympathetic and parasympathetic modulation in patients with diabetic autonomic neuropathy. Acta Cardiologica. 1998; 53(4):201-209

55 Azzopardi J, Fenech FF, Junoussov Z, Mazovetsky A, Olchanski V. A computerized health screening and follow-up system in diabetes mellitus. Diabetic Medicine. 1995; 12(3):271-276

56 Bailey BJ, Kahn A. Apportioning illness management authority: how diabetic individuals evaluate and respond to spousal help. Qualitative Health Research. 1993; 3(1):55-73

57 Bantle JP, Neal L, Frankamp LM. Effects of the anatomical region used for insulin injections on glycemia in type I diabetes subjects. Diabetes Care. 1993; 16(12):1592-1597

58 Bao J, Gilbertson HR, Gray R, Munns D, Howard G, Petocz P et al. Improving the estimation of mealtime insulin dose in adults with type 1 diabetes: the Normal Insulin Demand for Dose Adjustment (NIDDA) study. Diabetes Care. 2011; 34(10):2146-2151

59 Barker A, Lauria A, Schloot N, Hosszufalusi N, Ludvigsson J, Mathieu C et al. Age-dependent decline of beta-cell function in type 1 diabetes after diagnosis: a multi-centre longitudinal study. Diabetes Obesity and Metabolism. 2014; 16(3):262-267

60 Bartley PC, Bogoev M, Larsen J, Philotheou A. Long-term efficacy and safety of insulin detemir compared to Neutral Protamine Hagedorn insulin in patients with Type 1 diabetes using a treat-to-target basal–bolus regimen with insulin aspart at meals: a 2-year, randomized, controlled trial. Diabetic Medicine. 2008; 25(4):442-449

61 Barton FB, Rickels MR, Alejandro R, Hering BJ, Wease S, Naziruddin B et al. Improvement in outcomes of clinical islet transplantation: 1999-2010. Diabetes Care. 2012; 35(7):1436-1445

62 Battelino T, Conget I, Olsen B, Schutz-Fuhrmann I, Hommel E, Hoogma R et al. The use and efficacy of continuous glucose monitoring in type 1 diabetes treated with insulin pump therapy: a randomised controlled trial. Diabetologia. 2012; 55(12):3155-3162

63 Bayly GR, Bartlett WA, Davies PH, Husband D, Haddon A, Game FL et al. Laboratory-based calculation of coronary heart disease risk in a hospital diabetic clinic. Diabetic Medicine. 1999; 16(8):697-701

64 Beck RW, Lawrence JM, Laffel L, Wysocki T, Xing D, Huang ES et al. Quality-of-life measures in children and adults with type 1 diabetes: Juvenile Diabetes Research Foundation Continuous Glucose Monitoring randomized trial. Diabetes Care. 2010; 33(10):2175-2177

65 Beik N, Anger KE, Forni AA, Bawa K, Szumita PM. Evaluation of an institution-wide guideline for hyperglycemic emergencies at a tertiary academic medical center. Annals of Pharmacotherapy. 2013; 47(10):1260-1265

66 Bektas F, Eray O, Sari R, Akbas H. Point of care blood ketone testing of diabetic patients in the emergency department. Endocrine Research. 2004; 30(3):395-402

67 Bell DS, Cutter G. Characteristics of severe hypoglycemia in the patient with insulin-dependent diabetes. Southern Medical Journal. 1994; 87(6):616-620

68 Bell DSH, Ovalle F. The role of C-peptide levels in screening for latent autoimmune diabetes in adults. American Journal of Therapeutics. 2004; 11(4):308-311

69 Bell PM, Walshe K. Home blood glucose monitoring. Impact on lifestyle and diabetes control. Practitioner. 1984; 228(1388):197-202

70 Berlin I, Bisserbe JC, Eiber R, Balssa N, Sachon C, Bosquet F et al. Phobic symptoms, particularly the fear of blood and injury, are associated with poor glycemic control in type I diabetic adults. Diabetes Care. 1997; 20(2):176-178

71 Berlin I, Sachon CI, Grimaldi A. Identification of factors associated with impaired hypoglycaemia awareness in patients with type 1 and type 2 diabetes mellitus. Diabetes & Metabolism. 2005; 31(3 Pt.1):246-251

72 Besser RE, Ludvigsson J, Jones AG, McDonald TJ, Shields BM, Knight BA et al. Urine C-peptide creatinine ratio is a noninvasive alternative to the mixed-meal tolerance test in children and adults with type 1 diabetes. Diabetes Care. 2011; 34(3):607-609

73 Bianchi G, Montanari P, Fabbri A, Gamberini A, Zoli M, Marchesini G. Thyroid volume in type 1 diabetes patients without overt thyroid disease. Acta Diabetologica. 1995; 32(1):49-52

74 Biermann E, Dietrich W, Rihl J, Standl E. Are there time and cost savings by using telemanagement for patients on intensified insulin therapy: a randomised, controlled trial. Computer Methods and Programs in Biomedicine. 2002; 69(2):137-146

75 Birkebaek NH, Solvig J, Hansen B, Jorgensen C, Smedegaard J, Christiansen JS. A 4-mm needle reduces the risk of intramuscular injections without increasing backflow to skin surface in lean diabetic children and adults. Diabetes Care. 2008; 31(9):e65

76 Birkeland KI, Home PD, Wendisch U, Ratner RE, Johansen T, Endahl LA et al. Insulin degludec in type 1 diabetes: a randomized controlled trial of a new-generation ultra-long-acting insulin compared with insulin glargine. Diabetes Care. 2011; 34(3):661-665

77 Bjorvig S, Johansen MA, Fossen K. An economic analysis of screening for diabetic retinopathy. Journal of Telemedicine and Telecare. 2002; 8(1):32-35

78 Bodalska-Lipinska J, Szadkowska A, Markuszewski L. Principles of diagnosis of latent autoimmune diabetes in adults (LADA). Diabetologia Doswiadczalna i Kliniczna. 2006; 6(2):69-74

79 Bode B, Hirsch IB. Sustained reduction of biochemical, clinical and severe hypoglycaemia with extended CGM use: Results of JDRF CGM six month extension study. Diabetologia. 2009; 52(S1):S235

80 Bode BW, Buse JB, Fisher M, Garg SK, Marre M, Merker L et al. Insulin degludec improves glycaemic control with lower nocturnal hypoglycaemia risk than insulin glargine in basal–bolus treatment with mealtime insulin aspart in Type 1 diabetes (BEGIN(®) Basal–bolus Type 1): 2-year results of a randomized clinical trial. Diabetic Medicine. 2013; 30(11):1293-1297

81 Boehm BO, Home PD, Behrend C, Kamp NM, Lindholm A. Premixed insulin aspart 30 vs. premixed human insulin 30/70 twice daily: a randomized trial in Type 1 and Type 2 diabetic patients. Diabetic Medicine. 2002; 19(5):393-399

82 Bolli GB, Songini M, Trovati M, Prato S, Ghirlanda G, Cordera R et al. Lower fasting blood glucose, glucose variability and nocturnal hypoglycaemia with glargine vs NPH basal insulin in subjects with type 1 diabetes. Nutrition, Metabolism, and Cardiovascular Diseases. 2009; 19(8):571-579

83 Borch-Johnsen K, Wenzel H, Viberti GC, Mogensen CE. Is screening and intervention for microalbuminuria worthwhile in patients with insulin dependent diabetes? BMJ. 1993; 306(6894):1722-1725

84 Borg H, Arnqvist HJ, Bjork E, Bolinder J, Eriksson JW, Nystrom L et al. Evaluation of the new ADA and WHO criteria for classification of diabetes mellitus in young adult people (15-34 yrs) in the Diabetes Incidence Study in Sweden (DISS). Diabetologia. 2003; 46(2):173-181

85 Bott U, Ebrahim S, Hirschberger S, Skovlund SE. Effect of the rapid-acting insulin analogue insulin aspart on quality of life and treatment satisfaction in patients with type 1 diabetes. Diabetic Medicine. 2003; 20(8):626-634

86 Bott U, Jorgens V, Grusser M, Bender R, Muhlhauser I, Berger M. Predictors of glycaemic control in type 1 diabetic patients after participation in an intensified treatment and teaching programme. Diabetic Medicine. 1994; 11(4):362-371

87 Bottazzo GF, Bosi E, Cull CA, Bonifacio E, Locatelli M, Zimmet P et al. IA-2 antibody prevalence and risk assessment of early insulin requirement in subjects presenting with type 2 diabetes (UKPDS 71). Diabetologia. 2005; 48(4):703-708

88 Boulton AJ, Selam JL, Sweeney M, Ziegler D. Sildenafil citrate for the treatment of erectile dysfunction in men with Type II diabetes mellitus. Diabetologia. 2001; 44(10):1296-1301

89 Boulton AJ, Selam JL, Sweeney M, Ziegler D. Sildenafil citrate for the treatment of erectile dysfunction in men with Type II diabetes mellitus. Diabetologia. 2001; 44(10):1296-1301

90 Boyanov MA, Boneva Z, Christov VG. Testosterone supplementation in men with type 2 diabetes, visceral obesity and partial androgen deficiency. Aging Male : the Official Journal of the International Society for the Study of the Aging Male. 2003; 6(1):1-7

91 Boyanov MA, Boneva Z, Christov VG. Testosterone supplementation in men with type 2 diabetes, visceral obesity and partial androgen deficiency. Aging Male : the Official Journal of the International Society for the Study of the Aging Male. 2003; 6(1):1-7

92 Bragd J, Adamson U, Lins PE, Wredling R, Oskarsson P. A repeated cross-sectional survey of severe hypoglycaemia in 178 Type 1 diabetes mellitus patients performed in 1984 and 1998. Diabetic Medicine. 2003; 20(3):216-219

93 Braid E, Campbell B, Curtis S, Eden G, Keast T, Hardcastle S et al. The diabetes Annual Review as an educational tool: assessment and learning integrated with care, screening, and audit. Diabetic Medicine. 1992; 9(4):389-394

94 Braun AP. Domperidone in the treatment of symptoms of delayed gastric emptying in diabetic patients. Advances in Therapy. 1989;(6):51-62

95 Brazeau AS, Mircescu H, Desjardins K, Leroux C, Strychar I, Ekoe JM et al. Carbohydrate counting accuracy and blood glucose variability in adults with type 1 diabetes. Diabetes Research and Clinical Practice. 2013; 99(1):19-23

96 Bridgford A, Davis TME. A comprehensive patient-held record for diabetes. Part one: initial development of the Diabetes Databank. Practical Diabetes International. 2001; 18(7):241-245

97 Brinchmann-Hansen O, Dahl-Jorgensen K, Sandvik L, Hanssen KF. Blood glucose concentrations and progression of diabetic retinopathy: the seven year results of the Oslo study. BMJ. 1992; 304(6818):19-22

98 Brink SJ, Miller M, Moltz KC. Education and multidisciplinary team care concepts for pediatric and adolescent diabetes mellitus. Journal of Pediatric Endocrinology & Metabolism. 2002; 15(8):1113-1130

99 Brock J, I, Vind BF, Korsholm L, Flyvbjerg A, Frystyk J, Holst JJ et al. Counter-regulatory hormone responses to spontaneous hypoglycaemia during treatment with insulin aspart or human

soluble insulin: a double-blinded randomized cross-over study. Acta Physiologica. 2011; 202(3):337-347

100 Brooks AM, Walker N, Aldibbiat A, Hughes S, Jones G, de Havilland J et al. Attainment of metabolic goals in the integrated UK Islet Transplant Program with locally isolated and transported preparations. American Journal of Transplantation. 2013; 13(12):3236-3243

101 Brunetti P, Muggeo M, Cattin L, Arcangeli A, Pozzilli P, Provenzano V et al. Incidence of severe nocturnal hypoglycemia in patients with type 1 diabetes treated with insulin lispro or regular human insulin in addition to basal insulin glargine. Nutrition, Metabolism, and Cardiovascular Diseases. 2010; 20(7):519-526

102 Brunova J, Bruna J, Koning M, Meyer M, Joubert G, Mollentze W. GAD65Ab and primary hypothyroidism in type 1 and 2 diabetic subjects. Journal of Endocrinology, Metabolism and Diabetes of South Africa. 2002; 7(1):6-8

103 Bruttomesso D, Barberio S, Fongher C, Lisato G, Silvestri B, Briani G et al. Retrospective analysis of daily glucose profile in type 1 diabetic patients with continuous subcutaneous insulin infusion (CSII). Diabetes Research and Clinical Practice. 1992; 16(3):197-202

104 Bryden KS, Neil A, Mayou RA, Peveler RC, Fairburn CG, Dunger DB. Eating habits, body weight, and insulin misuse. A longitudinal study of teenagers and young adults with type 1 diabetes. Journal of Psychosomatic Research. 1999; 22(12):1956-1960

105 Burchardt P, Zawada A, Tabaczewski P, Naskret D, Kaczmarek J, Marcinkaniec J et al. Metformin added to intensive insulin therapy reduces plasma levels of glycated but not oxidized low-density lipoprotein in young patients with type 1 diabetes and obesity in comparison with insulin alone: a pilot study. Polskie Archiwum Medycyny Wewnetrznej. 2013; 123(10):526-532

106 Burnett SD, Press M, Yudkin JS. Compiling a district diabetic register: theoretical and practical considerations. Diabetic Medicine. 1993; 10(3):199-200

107 Burnett SD, Woolf CM, Yudkin JS. Developing a district diabetic register. BMJ. 1992; 305(6854):627-630

108 Bursell SE, Clermont AC, Aiello LP, Aiello LM, Schlossman DK, Feener EP et al. High-dose vitamin E supplementation normalizes retinal blood flow and creatinine clearance in patients with type 1 diabetes. Diabetes Care. 1999; 22(8):1245-1251

109 Bursell SE, Brazionis L, Jenkins A. Telemedicine and ocular health in diabetes mellitus. Clinical and Experimental Optometry. 2012; 95(3):311-327

110 Buvat J, van AH, Schmitt H, Chan M, Kuepfer C, Varanese L. Efficacy and safety of two dosing regimens of tadalafil and patterns of sexual activity in men with diabetes mellitus and erectile dysfunction: Scheduled use vs. on-demand regimen evaluation (SURE) study in 14 European countries. Journal of Sexual Medicine. 2006; 3(3):512-520

111 Cagliero E, Levina EV, Nathan DM. Immediate feedback of HbA1c levels improves glycemic control in type 1 and insulin-treated type 2 diabetic patients. Diabetes Care. 1999; 22(11):1785-1789

112 Calle-Pascual AL, Gomez V, Leon E, Bordiu E. Foods with a low glycemic index do not improve glycemic control of both type 1 and type 2 diabetic patients after one month of therapy. Diabetes & Metabolism. 1988; 14(5):629-633

113 Cameron CG, Bennett HA. Cost-effectiveness of insulin analogues for diabetes mellitus. Canadian Medical Association Journal. 2009; 180(4):400-407

114 Canadian Agency for Drugs and Technologies in Health. An economic evaluation of insulin analogues for the treatment of patients with type 1 and type 2 diabetes mellitus in Canada. COMPUS. 2008; 2(4):1-52

115 Cardoso C, Ohwovoriole AE, KuKu SF. A study of thyroid function and prevalence of thyroid autoantibodies in an African diabetic population. Journal of Diabetes and Its Complications. 1995; 9(1):37-41

116 Castleden HAJ, Shields B, Bingley PJ, Williams AJK, Sampson M, Walker M et al. GAD antibodies in probands and their relatives in a cohort clinically selected for Type 2 diabetes. Diabetic Medicine. 2006; 23(8):834-838

117 Cavan DA, Hamilton P, Everett J, Kerr D. Reducing hospital inpatient length of stay for patients with diabetes. Diabetic Medicine. 2001; 18(2):162-164

118 Cerna M, Novota P, Kolostova K, Cejkova P, Zdarsky E, Novakova D et al. HLA in Czech adult patients with autoimmune diabetes mellitus: comparison with Czech children with type 1 diabetes and patients with type 2 diabetes. European Journal of Immunogenetics. 2003; 30(6):401-407

119 Chan JCN, Gagliardino JJ, Baik SH, Chantelot JM, Ferreira SRG, Hancu N et al. Multifaceted determinants for achieving glycemic control: the International Diabetes Management Practice Study (IDMPS). Diabetes Care. 2009; 32(2):227-233

120 Chan WB, Chow CC, Yeung VTF, Chan JCN, So WY, Cockram CS. Effect of insulin lispro on glycaemic control in Chinese diabetic patients receiving twice-daily regimens of insulin. Chinese Medical Journal. 2004; 117(9):1404-1407

121 Chatterjee S, Jarvis-Kay J, Rengarajan T, Lawrence IG, McNally PG, Davies MJ. Glargine versus NPH insulin: efficacy in comparison with insulin aspart in a basal–bolus regimen in type 1 diabetes--the glargine and aspart study (GLASS) a randomised cross-over study. Diabetes Research and Clinical Practice. 2007; 77(2):215-222

122 Chen JW, Lauritzen T, Bojesen A, Christiansen JS. Multiple mealtime administration of biphasic insulin aspart 30 versus traditional basal–bolus human insulin treatment in patients with type 1 diabetes. Diabetes Obesity and Metabolism. 2006; 8(6):682-689

123 Chiarelli F, Verrotti A, Di Ricco L, LaPorte RE. Information superhighway, Internet and diabetes. Diabetes, Nutrition and Metabolism - Clinical and Experimental. 1998; 11(4):219-224

124 Chico A, Vidal-Rios P, Subira M, Novials A. The continuous glucose monitoring system is useful for detecting unrecognized hypoglycemias in patients with type 1 and type 2 diabetes but is not better than frequent capillary glucose measurements for improving metabolic control. Diabetes Care. 2003; 26(4):1153-1157

125 Choudhary P, Davies C, Emery CJ, Heller SR. Do high fasting glucose levels suggest nocturnal hypoglycaemia? The Somogyi effect-more fiction than fact? Diabetic Medicine. 2013; 30(8):914-917

126 Choudhary P, Geddes J, Freeman JV, Emery CJ, Heller SR, Frier BM. Frequency of biochemical hypoglycaemia in adults with Type 1 diabetes with and without impaired awareness of hypoglycaemia: no identifiable differences using continuous glucose monitoring. Diabetic Medicine. 2010; 27(6):666-672

127 Choudhary P, Parrott NR, Birtles L, Rutter MK. Islet cell transplantation: current status in the UK. Practical Diabetes. 2012; 29(7):280-285

128 Choudhary P, Ramasamy S, Green L, Gallen G, Pender S, Brackenridge A et al. Real-time continuous glucose monitoring significantly reduces severe hypoglycemia in hypoglycemia-unaware patients with type 1 diabetes. Diabetes Care. 2013; 36(12):4160-4162

129 Chowta MN, Adhikari PM, Chowta NK, Shenoy AK, D'Souza S. Serum C peptide level and renal function in diabetes mellitus. Indian Journal of Nephrology. 2010; 20(1):25-28

130 Christiansen CL, Schurizek BA, Malling B, Knudsen L, Alberti KG, Hermansen K. Insulin treatment of the insulin-dependent diabetic patient undergoing minor surgery. Continuous intravenous infusion compared with subcutaneous administration. Anaesthesia. 1988; 43(7):533-537

131 Christiansen M, Bailey T, Watkins E, Liljenquist D, Price D, Nakamura K et al. A new-generation continuous glucose monitoring system: improved accuracy and reliability compared with a previous-generation system. Diabetes Technology and Therapeutics. 2013; 15(10):881-888

132 Ciavarella A, Silletti A, Forlani G, Morotti L, Borgnino LC, D'Apote M et al. A screening test for microalbuminuria in type 1 (insulin-dependent) diabetes. Diabetes Research and Clinical Practice. 1989; 7(4):307-312

133 Ciofetta M, Lalli C, Del Sindaco P, Torlone E, Pampanelli S, Mauro L et al. Contribution of postprandial versus interprandial blood glucose to HbA1c in type 1 diabetes on physiologic intensive therapy with lispro insulin at mealtime. Diabetes Care. 1999; 22(5):795-800

134 Clark WF, Churchill DN, Forwell L, Macdonald G, Foster S. To pay or not to pay? A decision and cost-utility analysis of angiotensin-converting-enzyme inhibitor therapy for diabetic nephropathy. Canadian Medical Association Journal. 2000; 162(2):195-198

135 Clarke WL, Cox DJ, Gonder-Frederick LA, Julian D, Schlundt D, Polonsky W. Reduced awareness of hypoglycemia in adults with IDDM. A prospective study of hypoglycemic frequency and associated symptoms. Diabetes Care. 1995; 18(4):517-522

136 Clinical Immunology Service. Laboratory handbook and price list; a brief guide for clinical and laboratory staff. Birmingham. University of Birmingham, School of Immunity & Infection, College of Medical and Dental Sciences, 2010. Available from: www.uhb.nhs.uk/pdf/laboratoryhandbookuob.pdf

137 Close N, Alejandro R, Hering B, Appel M. Second annual analysis of the collaborative islet transplant registry. Transplantation Proceedings. 2007; 39(1):179-182

138 Collaborative Islet Transplant Registry Coordinating Registry. Collaborative Islet Transplant Registry seventh annual report. Collaborative Islet Transplant Registry, 2011. Available from: https://web.emmes.com/study/isl//reports/01062012_7thAnnualReport.pdf

139 Collier A, Steedman DJ, Patrick AW, Nimmo GR, Matthews DM, Macintyre CCA et al. Comparison of intravenous glucagon and dextrose in treatment of severe hypoglycemia in an accident and emergency department. Diabetes Care. 1987; 10(6):712-715

140 Collins AC, Vincent J, Newall RG, Mitchell KM, Viberti GC. An aid to the early detection and management of diabetic nephropathy: assessment of a new point of care microalbuminuria system in the diabetic clinic. Diabetic Medicine. 2001; 18(11):928-932

141 Collins JE, Heward JM, Nithiyananthan R, Nejentsev S, Todd JA, Franklyn JA et al. Lack of association of the vitamin D receptor gene with Graves' disease in UK Caucasians. Clinical Endocrinology. 2004; 60(5):618-624

142 Connell CM, Davis WK, Gallant MP, Sharpe PA. Impact of social support, social cognitive variables, and perceived threat on depression among adults with diabetes. Health Psychology. 1994; 13(3):263-273

143 Coonrod BA, Ellis D, Becker DJ, Bunker CH, Kelsey SF, Lloyd CE et al. Predictors of microalbuminuria in individuals with IDDM. Pittsburgh Epidemiology of Diabetes Complications Study. Diabetes Care. 1993; 16(10):1376-1383

144 Cooper JG, Mathieu C, Hollander P, Miranda-Palma B, Franek E, Bain S et al. Insulin degludec allows for flexible daily dosing in type 1 diabetes, providing equal glycaemic control with less nocturnal hypoglycaemia than insulin glargine over 52 weeks. Diabetologia. 2012; 55(Suppl.1):S374

145 Corney SM, Dukatz T, Rosenblatt S, Harrison B, Murray R, Sakharova A et al. Comparison of insulin pump therapy (continuous subcutaneous insulin infusion) to alternative methods for perioperative glycemic management in patients with planned postoperative admissions. Journal of Diabetes Science and Technology. 2012; 6(5):1003-1015

146 Cox D, Gonder-Frederick L, Polonsky W, Schlundt D, Julian D, Clarke W. A multicenter evaluation of blood glucose awareness training-II. Diabetes Care. 1995; 18(4):523-528

147 Cox DJ, Gonder-Frederick L, Polonsky W, Schlundt D, Kovatchev B, Clarke W. Blood glucose awareness training (BGAT-2): long-term benefits. Diabetes Care. 2001; 24(4):637-642

148 Cox DJ, Kovatchev BP, Julian DM, Gonder-Frederick LA, Polonsky WH, Schlundt DG et al. Frequency of severe hypoglycemia in insulin-dependent diabetes mellitus can be predicted from self-monitoring blood glucose data. Journal of Clinical Endocrinology and Metabolism. 1994; 79(6):1659-1662

149 Cox DJ, Gonder-Frederick L, Ritterband L, Clarke W, Kovatchev BP. Prediction of severe hypoglycemia. Diabetes Care. 2007; 30(6):1370-1373

150 Cox DJ, Kovatchev B, Koev D, Koeva L, Dachev S, Tcharaktchiev D et al. Hypoglycemia anticipation, awareness and treatment training (HAATT) reduces occurrence of severe hypoglycemia among adults with type 1 diabetes mellitus. International Journal of Behavioral Medicine. 2004; 11(4):212-218

151 Cox R, Beaven DW, Helm AM. Home monitoring of blood glucose: a retrospective assessment in 38 insulin-requiring diabetics. New Zealand Medical Journal. 1980; 92(667):193-196

152 Cranston I, Lomas J, Maran A, Macdonald I, Amiel SA. Restoration of hypoglycaemia awareness in patients with long-duration insulin-dependent diabetes. Lancet. 1994; 344(8918):283-287

153 Crijns H, Casparie AF, Hendrikse F. Continuous computer simulation analysis of the cost-effectiveness of screening and treating diabetic retinopathy. International Journal of Technology Assessment in Health Care. 1999; 15(1):198-206

154 Cryer PE. Severe hypoglycemia predicts mortality in diabetes. Diabetes Care. 2012; 35(9):1814-1816

155 Cucinotta D, Mannino D, Lasco A, Di Cesare E, Musolino C, Alessi R. Premixed insulin at ratio 3/7 and regular + isophane insulins at mixing ratios from 2/8 to 4/6 achieve the same metabolic control. Diabetes & Metabolism. 1991; 17(1):49-54

156 Cummings DM, Morrissey S, Barondes MJ, Rogers L, Gustke S. Screening for diabetic retinopathy in rural areas: the potential of telemedicine. Journal of Rural Health. 2001; 17(1):25-31

157 Currie CJ, Morgan CL, Poole CD, Sharplin P, Lammert M, McEwan P. Multivariate models of health-related utility and the fear of hypoglycaemia in people with diabetes. Current Medical Research and Opinion. 2006; 22(8):1523-1534

158 Curtis L. Unit costs of health and social care 2011. Canterbury: Personal Social Services Research Unit, University of Kent; 2012. Available from: http://www.pssru.ac.uk/project-pages/unit-costs/2011/

159 Curtis L. Unit costs of health and social care 2012. Canterbury: Personal Social Services Research Unit, University of Kent; 2012. Available from: http://www.pssru.ac.uk/project-pages/unit-costs/2012/

160 Czyzewska K, Czerniawska E, Szadkowska A. Prevalence of hypoglycemia unawareness in patients with type 1 diabetes. Pediatric Diabetes. 2012; 13(S17):77

161 Dagdelen S, Hascelik G, Bayraktar M. Simultaneous triple organ specific autoantibody profiling in adult patients with type 1 diabetes mellitus and their first-degree relatives. International Journal of Clinical Practice. 2009; 63(3):449-456

162 Dagogo-Jack SE, Craft S, Cryer PE. Hypoglycemia-associated autonomic failure in insulin-dependent diabetes mellitus. Recent antecedent hypoglycemia reduces autonomic responses to, symptoms of, and defense against subsequent hypoglycemia. Journal of Clinical Investigation. 1993; 91(3):819-828

163 Dahl-Jorgensen K, Brinchmann-Hansen O, Hanssen KF. Rapid tightening of blood glucose control leads to transient deterioration of retinopathy in insulin dependent diabetes mellitus: The Oslo study. BMJ. 1985; 290(6471):811-815

164 Dargis V, Pantelejeva O, Jonushaite A, Vileikyte L, Boulton AJ. Benefits of a multidisciplinary approach in the management of recurrent diabetic foot ulceration in Lithuania: a prospective study. Diabetes Care. 1999; 22(9):1428-1431

165 Davey P, Grainger D, MacMillan J, Rajan N, Aristides M, Dobson M. Economic evaluation of insulin lispro versus neutral (regular) insulin therapy using a willingness-to-pay approach. Pharmacoeconomics. 1998; 13(3):347-358

166 Davies H, Brophy S, Fielding A, Bingley P, Chandler M, Hilldrup I et al. Latent autoimmune diabetes in adults (LADA) in South Wales: incidence and characterization. Diabetic Medicine. 2008; 25(11):1354-1357

167 Davies M, Dixon S, Currie CJ, Davis RE, Peters JR. Evaluation of a hospital diabetes specialist nursing service: a randomized controlled trial. Diabetic Medicine. 2001; 18(4):301-307

168 Davis RE, McCann VJ, Stanton KG. Type 1 diabetes and latent pernicious anaemia. Medical Journal of Australia. 1992; 156(3):160-162

169 Davis TME, Bridgford A. A comprehensive patient-held record for diabetes. Part two: Large-scale assessment of the diabetes databank by patients and health care workers. Practical Diabetes International. 2001; 18(9):311-314

170 Davis TME, Holman RR, Eaton PM, Turner RC. A regular meal and insulin infusion regimen: Its use in the treatment of acute-onset ketotic diabetes and in stabilization of poorly controlled established diabetic subjects. Diabetes Care. 1982; 5(5):492-496

171 Davis TME, Mehta Z, Mackay IR, Cull CA, Bruce DG, Fida S et al. Autoantibodies to the islet cell antigen SOX-13 are associated with duration but not type of diabetes. Diabetic Medicine. 2003; 20(3):198-204

172 Day JL, Metcalfe J, Johnson P. Benefits provided by an integrated education and clinical diabetes centre: a follow-up study. Diabetic Medicine. 1992; 9(9):855-859

173 de Weerdt I, Visser AP, Kok GJ, de Weerdt O, van der Veen EA. Randomized controlled multicentre evaluation of an education programme for insulin-treated diabetic patients: effects on metabolic control, quality of life, and costs of therapy. Diabetic Medicine. 1991; 8(4):338-345

174 de Zoysa N, Rogers H, Stadler M, Gianfrancesco C, Beveridge S, Britneff E et al. A psychoeducational program to restore hypoglycemia awareness: The DAFNE-HART pilot study. Diabetes Care. 2014; 37(3):863-866

175 Deiss D, Bolinder J, Riveline JP, Battelino T, Bosi E, Tubiana-Rufi N et al. Improved glycemic control in poorly controlled patients with type 1 diabetes using real-time continuous glucose monitoring. Diabetes Care. 2006; 29(12):2730-2732

176 Delahanty L, Simkins SW, Camelon K. Expanded role of the dietitian in the Diabetes Control and Complications Trial: implications for clinical practice. The DCCT Research Group. Journal of the American Dietetic Association. 1993; 93(7):758-64, 767

177 Department of Health. NHS reference costs 2011-12. 2012. Available from: https://www.gov.uk/government/publications/nhs-reference-costs-financial-year-2011-to-2012 [Last accessed: 7 October 2014]

178 Department of Veterans Affairs. The management of diabetes mellitus in the primary care setting. Washington (DC). Department of Veterans Affairs, 1999

179 Desai M, Cull CA, Horton VA, Christie MR, Bonifacio E, Lampasona V et al. GAD autoantibodies and epitope reactivities persist after diagnosis in latent autoimmune diabetes in adults but do not predict disease progression: UKPDS 77. Diabetologia. 2007; 50(10):2052-2060

180 Desautels SG, Hutson WR, Christian PE, Moore JG, Datz FL. Gastric emptying response to variable oral erythromycin dosing in diabetic gastroparesis. Digestive Diseases and Sciences. 1995; 40(1):141-146

181 Deyoung L, Chung E, Kovac JR, Romano W, Brock GB. Daily use of sildenafil improves endothelial function in men with type 2 diabetes. Journal of Andrology. 2012; 33(2):176-180

182 Dhatariya K, Levy N, Kilvert A, Watson B, Cousins D, Flanagan D et al. NHS Diabetes guideline for the perioperative management of the adult patient with diabetes. Diabetic Medicine. 2012; 29(4):420-433

183 Diabetes UK. Recommendations for the management of diabetes in primary care, 2000. Available from: http://www.diabetes.org.uk/infocentre/carerec/primary.htm

184 Diabetes UK. Carbs count: an introduction to carbohydrate counting and insulin dose adjustment, 2011. Available from: https://shop.diabetes.org.uk/usr/downloads/A%20Carbs-Count-2012-reducedsize.pdf

185 Diabetes UK. Evidence-based nutrition guidelines for the prevention and management of diabetes. London. Diabetes UK, 2011. Available from: http://www.diabetes.org.uk/Documents/Reports/Nutritional_guidelines200911.pdf

186 Diabetes UK and Care Interventions Team. Needs of the recently diagnosed. Listening project. Report and recommendations. Diabetes UK, 2001

187 Diamante E. Renal involvement in type 1 (IDDM) diabetes in Spain. Diabetes Research and Clinical Practice. 1997; 38(2):129-137

188 Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, and Ades AE. NICE DSU Technical Support Document 4: Inconsistency in Networks of Evidence Based on Randomised Controlled Trials, 2011. Available from: http://www.nicedsu.org.uk

189 Dias VM, Pandini JA, Nunes RR, Sperandei SL, Portella ES, Cobas RA et al. Effect of the carbohydrate counting method on glycemic control in patients with type 1 diabetes. Diabetology and Metabolic Syndrome. 2010; 2:54

190 Didangelos T, Anastasiou E, Vasilopoulos C, Zoupas C, Manes C, Tsatsoulis A et al. Improvement of metabolic control after three months of RT-CGM in type 1 diabetics with CSII. Diabetes Multicenter Observational Study (DIAMOND). Diabetes Technology and Therapeutics. 2014; 16(S1):A14-A15

191 Didangelos TP, Karamitsos DT, Athyros VG, Kourtoglou GI. Effect of aldose reductase inhibition on cardiovascular reflex tests in patients with definite diabetic autonomic neuropathy over a period of 2 years. Journal of Diabetes & Its Complications. 1998; 12(4):201-207

192 Dinneen SF, O'Hara MC, Byrne M, Smith D, Courtney CH, McGurk C et al. Group follow-up compared to individual clinic visits after structured education for type 1 diabetes: a cluster randomised controlled trial. Diabetes Research and Clinical Practice. 2013; 100(1):29-38

193 Dranitsaris G, Longo CJ, Grossman LD. The economic value of a new insulin preparation, Humalog Mix 25. Measured by a willingness-to-pay approach. Pharmacoeconomics. 2000; 18(3):275-287

194 Dreyer M, Prager R, Robinson A, Busch K, Ellis G, Souhami E et al. Efficacy and safety of insulin glulisine in patients with type 1 diabetes. Hormone and Metabolic Research. 2005; 37(11):702-707

195 Dufaitre-Patouraux L, Riveline JP, Renard E, Melki V, Belicar-Schaepelynck P, Selam JL et al. Continuous intraperitoneal insulin infusion does not increase the risk of organ-specific autoimmune disease in type 1 diabetic patients: results of a multicentric, comparative study. Diabetes & Metabolism. 2006; 32(5 Pt.1):427-432

196 Dunbar JM, Madden PM, Gleeson DT, Fiad TM, McKenna TJ. Premixed insulin preparations in pen syringes maintain glycemic control and are preferred by patients. Diabetes Care. 1994; 17(8):874-878

197 Edelman S, Garg S, Frias J, Maggs D, Wang Y, Zhang B et al. A double-blind, placebo-controlled trial assessing pramlintide treatment in the setting of intensive insulin therapy in type 1 diabetes. Diabetes Care. 2006; 29(10):2189-2195

198 Eeg-Olofsson K, Cederholm J, Nilsson PM, Zethelius B, Svensson AM, Gudbjornsdottir S et al. Glycemic control and cardiovascular disease in 7,454 patients with type 1 diabetes: an observational study from the Swedish National Diabetes Register (NDR). Diabetes Care. 2010; 33(7):1640-1646

199 Eli Lilly and Company. Clinical study summary: study F3Z-MC-IOAA(b). LY275585 vs. Humulin R: premeal therapy in type 1 diabetes, 1994

200 Eli Lilly and Company. Clinical study summary: study F3Z-MC-IOAC(b). LY275585 vs. Humulin R: premeal therapy in type 1 diabetes, 1995

201 Eli Lilly and Company. Clinical study summary: study F3Z-MC-IOAE. LY275585 vs. Humulin R: premeal therapy in new patients with type 1 diabetes, 1995

202 Eli Lilly and Company. Clinical study summary: study F3Z-MC-IOAG. LY275585 vs. Humulin R: premeal therapy in type 1 diabetes, 1995

203 Elliott J, Jacques RM, Kruger J, Campbell MJ, Amiel SA, Mansell P et al. Substantial reductions in the number of diabetic ketoacidosis and severe hypoglycaemia episodes requiring emergency treatment lead to reduced costs after structured education in adults with Type 1 diabetes. Diabetic Medicine. 2014; 31(7):847-853

204 Ellis D, Coonrod BA, Dorman JS, Kelsey SF, Becker DJ, Avner ED et al. Choice of urine sample predictive of microalbuminuria in patients with insulin-dependent diabetes mellitus. American Journal of Kidney Diseases. 1989; 13(4):321-328

205 Ellison JM, Stegmann JM, Colner SL, Michael RH, Sharma MK, Ervin KR et al. Rapid changes in postprandial blood glucose produce concentration differences at finger, forearm, and thigh sampling sites. Diabetes Care. 2002; 25(6):961-964

206 Elwyn GJ, Vaughan NJ, Stott NC. District diabetes registers: more trouble than they're worth?. Diabetic Medicine. 1998; 15(Suppl. 3):S44-S48

207 Engelbrecht R, Hildebrand C. DIABCARD a smart card for patients with chronic diseases. Clinical Performance & Quality Health Care. 1997; 5(2):67-70

208 Engelbrecht R, Hildebrand C. Telemedicine and diabetes. Studies in Health Technology and Informatics. 1999; 64:142-154

209 Engelbrecht R, Hildebrand C, Brugues E, de Leiva A, Corcoy R. DIABCARD--an application of a portable medical record for persons with diabetes. Medical Informatics. 1996; 21(4):273-282

210 Engelbrecht R, Hildebrand C, Kuhnel E, Brenner G, Corcoy R, Eberhard G et al. A chip card for patients with diabetes. Computer Methods and Programs in Biomedicine. 1994; 45(1-2):33-35

211 Ericsson Å, Pollock RF, Hunt B, Valentine WJ. Evaluation of the cost-utility of insulin degludec vs insulin glargine in Sweden. Journal of Medical Economics. 2013; 16(12):1442-1452

212 ETDRS Investigators. Aspirin effects on mortality and morbidity in patients with diabetes mellitus. Early Treatment Diabetic Retinopathy Study report 14. JAMA. 1992; 268(10):1292-1300

213 ETDRS Investigators. Aspirin effects on mortality and morbidity in patients with diabetes mellitus. Early Treatment Diabetic Retinopathy Study report 14. Personal communication: 2013

214 Evans JM, Newton RW, Ruta DA, MacDonald TM, Stevenson RJ, Morris AD. Frequency of blood glucose monitoring in relation to glycaemic control: observational study with diabetes database. BMJ. 1999; 319(7202):83-86

215 Ewing DJ, Clarke BF. Autonomic neuropathy: its diagnosis and prognosis. Clinics in Endocrinology and Metabolism. 1986; 15(4):855-888

216 Faes TJ, Yff GA, DeWeerdt O, Lanting P, Heimans JJ, Bertelsmann FW. Treatment of diabetic autonomic neuropathy with an aldose reductase inhibitor. Journal of Neurology. 1993; 240(3):156-160

217 Fan H, Pan Q, Zhang P, Liu J, Xu Y, Yang X. Influence of islet function on typing and prognosis of new-onset diabetes after intensive insulin therapy. Medical Science Monitor. 2013; 19:787-793

218 Fanelli C, Pampanelli S, Epifano L, Rambotti AM, Di Vincenzo A, Modarelli F et al. Long-term recovery from unawareness, deficient counterregulation and lack of cognitive dysfunction during hypoglycaemia, following institution of rational, intensive insulin therapy in IDDM. Diabetologia. 1994; 37(12):1265-1276

219 Fanelli CG, Epifano L, Rambotti AM, Pampanelli S, Di Vincenzo A, Modarelli F et al. Meticulous prevention of hypoglycemia normalizes the glycemic thresholds and magnitude of most of neuroendocrine responses to, symptoms of, and cognitive function during hypoglycemia in intensively treated patients with short-term IDDM. Diabetes. 1993; 42(11):1683-1689

220 Fanelli CG, Pampanelli S, Porcellati F, Rossetti P, Brunetti P, Bolli GB. Administration of neutral protamine Hagedorn insulin at bedtime versus with dinner in type 1 diabetes mellitus to avoid nocturnal hypoglycemia and improve control. A randomized, controlled trial. Annals of Internal Medicine. 2002; 136(137):504-514

221 Fares JE, Kanaan M, Chaaya M, Azar ST. Fluctuations in glycosylated hemoglobin (HbA1C) as a predictor for the development of diabetic nephropathy in type 1 diabetic patients. International Journal of Diabetes Mellitus. 2010; 2(1):10-14

222 Faronato P, de Bigontina G. A cost-benefit analysis of two mass screening strategies for albuminuria in diabetic patients. Diabetes, Nutrition and Metabolism - Clinical and Experimental. 1994; 7(6):325-329

223 Fendrick AM, Javitt JC, Chiang YP. Cost-effectiveness of the screening and treatment of diabetic retinopathy. What are the costs of underutilization? International Journal of Technology Assessment in Health Care. 1992; 8(4):694-707

224 Ferguson SC, Strachan MW, Janes JM, Frier BM. Severe hypoglycaemia in patients with type 1 diabetes and impaired awareness of hypoglycaemia: a comparative study of insulin lispro and regular human insulin. Diabetes/Metabolism Research and Reviews. 2001; 17(4):285-291

225 Ferrier C, Ferrari P, Weidmann P, Keller U, Beretta-Piccoli C, Riesen WF. Swiss hypertension treatment programme with verapamil and/or enalapril in diabetic patients. Drugs. 1992; 44(Suppl.1):74-84

226 Fialkow PJ, Zavala C, Nielsen R. Thyroid autoimmunity: increased frequency in relatives of insulin-dependent diabetes patients. Annals of Internal Medicine. 1975; 83(2):170-176

227 Fischer U, Salzsieder E, Menzel R, Vogt L, Ropke H, Schmidt R et al. Primary health care of diabetic patients in a specialized outpatient setting: a DIABCARE-based analysis. Diabetes & Metabolism. 1993; 19(1 Pt.2):188-194

228 Fisher EB, Auslander, W.F., Munro, J.F., Arfken et al. Neigbors for a smoke free North Side: Evaluation of a community organization approach to promoting smoking cessation among African Americans. American Journal of Public Health. 1998; 88:1658-1663

229 Fisher JN, Kitabchi AE. A randomized study of phosphate therapy in the treatment of diabetic ketoacidosis. Journal of Clinical Endocrinology & Metabolism. 1983; 57(1):177-180

230 Fisher JN, Shahshahani MN, Kitabchi AE. Diabetic ketoacidosis: low-dose insulin therapy by various routes. New England Journal of Medicine. 1977; 297(5):238-241

231 Fisher L, Chesla CA, Bartz RJ, Gilliss C, Skaff MA, Sabogal F et al. The family and type 2 diabetes: a framework for intervention. Diabetes Educator. 1998; 24(5):599-607

232 Fontvieille AM, Rizkalla SW, Penfornis A, Acosta M, Bornet FR, Slama G. The use of low glycaemic index foods improves metabolic control of diabetic patients over five weeks. Diabetic Medicine. 1992; 9(5):444-450

233 Forde R. Review of diabetes structured education. Health Services Executive, Republic of Ireland, 2009. Available from: http://www.hse.ie/eng/services/Publications/topics/Diabetes/diabetesstructureded.pdf

234 Forrest KY, Becker DJ, Kuller LH, Wolfson SK, Orchard TJ. Are predictors of coronary heart disease and lower-extremity arterial disease in type 1 diabetes the same? A prospective study. Atherosclerosis. 2000; 148(1):159-169

235 Franc S, Dardari D, Boucherie B, Riveline JP, Biedzinski M, Petit C et al. Real-life application and validation of flexible intensive insulin-therapy algorithms in type 1 diabetes patients. Diabetes & Metabolism. 2009; 35(6):463-468

236 Frank A, Deng S, Huang X, Velidedeoglu E, Bae YS, Liu C et al. Transplantation for type I diabetes: comparison of vascularized whole-organ pancreas with isolated pancreatic islets. Annals of Surgery. 2004; 240(4):631-633

237 Frank RN. Aldose reductase inhibition. The chemical key to the control of diabetic retinopathy? Archives of Ophthalmology. 1990; 108(9):1229-1231

238 Friedenberg FK, Palit A, Parkman HP, Hanlon A, Nelson DB. Botulinum toxin A for the treatment of delayed gastric emptying. American Journal of Gastroenterology. 2008; 103(2):416-423

239 Frier BM. How hypoglycaemia can affect the life of a person with diabetes. Diabetes/Metabolism Research and Reviews. 2008; 24(2):87-92

240 Fritsche A, Stefan N, Haring H, Gerich J, Stumvoll M. Avoidance of hypoglycemia restores hypoglycemia awareness by increasing beta-adrenergic sensitivity in type 1 diabetes. Annals of Internal Medicine. 2001; 134(9 Pt 1):729-736

241 Frokjaer JB, Ejskjaer N, Rask P, Due AS, Gregersen H, Drewes AM et al. Central neuronal mechanisms of gastric electrical stimulation in diabetic gastroparesis. Scandinavian Journal of Gastroenterology. 2008; 43(9):1066-1075

242 Frykberg RG. Team approach toward lower extremity amputation prevention in diabetes. Journal of the American Podiatric Medical Association. 1997; 87(7):305-312

243 Fukunishi I, Horikawa N, Yamazaki T, Shirasaka K, Kanno K, Akimoto M. Perception and utilization of social support in diabetic control. Diabetes Research and Clinical Practice. 1998; 41(3):207-211

244 Fulcher GR, Gilbert RE, Yue DK. Glargine is superior to neutral protamine Hagedorn for improving glycated haemoglobin and fasting blood glucose levels during intensive insulin therapy. Internal Medicine Journal. 2005; 35(9):536-542

245 Furnary AP. Rationale for glycemic control in cardiac surgical patients: The portland diabetic project. Insulin. 2006; 1(SUPPL. 1):S24-S29

246 Furnary AP, Wu Y, Bookin SO. Effect of hyperglycemia and continuous intravenous insulin infusions on outcomes of cardiac surgical procedures: the Portland Diabetic Project. Endocrine Practice : Official Journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists. 2004; 10(Suppl.2):21-33

247 Gale EA. A randomized, controlled trial comparing insulin lispro with human soluble insulin in patients with Type 1 diabetes on intensified insulin therapy. The UK Trial Group. Diabetic Medicine. 2000; 17(3):209-214

248 Gamba G, Oseguera J, Castrejon M, Gomez-Perez FJ. Bicarbonate therapy in severe diabetic ketoacidosis. A double blind, randomized, placebo controlled trial. Revista De Investigacion Clinica. 1991; 43(3):234-238

249 Game FL, Bartlett WA, Bayly GR, Jones AF. Comparative accuracy of cardiovascular risk prediction methods in patients with diabetes mellitus. Diabetes, Obesity & Metabolism. 2001; 3(4):279-286

250 Game FL, Jones AF. Coronary heart disease risk assessment in diabetes mellitus - A comparison of PROCAM and Framingham risk assessment functions. Diabetic Medicine. 2001; 18(5):355-359

251 Gan RM, Wong V, Cheung NW, McLean M. Effect of insulin infusion on electrocardiographic findings following acute myocardial infarction: importance of glycaemic control. Diabetic Medicine. 2009; 26(2):174-176

252 Gandhi GY, Nuttall GA, Abel MD, Mullany CJ, Schaff HV, O'Brien PC et al. Intensive intraoperative insulin therapy versus conventional glucose management during cardiac surgery: a randomized trial. Annals of Internal Medicine. 2007; 146(4):233-243

253 Gandhi GY, Nuttall GA, Abel MD, Mullany CJ, Schaff HV, Williams BA et al. Intraoperative hyperglycemia and perioperative outcomes in cardiac surgery patients. Mayo Clinic Proceedings. 2005; 80(7):862-866

254 Gandhi K, Hussain SS, Charatsi E, Dornhorst A. Investigating hypoglycaemia awareness in an outpatient Type 1 diabetes clinic. Diabetic Medicine. 2013; 30(Suppl.1):148

255 Garattini L, Brunetti M, Salvioni F, Barosi M. Economic evaluation of ACE inhibitor treatment of nephropathy in patients with insulin-dependent diabetes mellitus in Italy. Pharmacoeconomics. 1997; 12(1):67-75

256 Garg S, Zisser H, Schwartz S, Bailey T, Kaplan R, Ellis S et al. Improvement in glycemic excursions with a transcutaneous, real-time continuous glucose sensor: a randomized controlled trial. Diabetes Care. 2006; 29(1):44-50

257 Garg SK, Rosenstock J, Ways K. Optimized Basal–bolus insulin regimens in type 1 diabetes: insulin glulisine versus regular human insulin in combination with Basal insulin glargine. Endocrine Practice. 2005; 11(1):11-17

258 Geddes J, Schopman JE, Zammitt NN, Frier BM. Prevalence of impaired awareness of hypoglycaemia in adults with Type 1 diabetes. Diabetic Medicine. 2008; 25(4):501-504

259 Geddes J, Wright RJ, Zammitt NN, Deary IJ, Frier BM. An evaluation of methods of assessing impaired awareness of hypoglycemia in type 1 diabetes. Diabetes Care. 2007; 30(7):1868-1870

260 George JT, Valdovinos AP, Russell I, Dromgoole P, Lomax S, Torgerson DJ et al. Clinical effectiveness of a brief educational intervention in type 1 diabetes: Results from the BITES (Brief Intervention in Type 1 diabetes, Education for Self-efficacy) trial. Diabetic Medicine. 2008; 25(12):1447-1453

261 Gibbons CH, Freeman R. Treatment-induced diabetic neuropathy: a reversible painful autonomic neuropathy. Annals of Neurology. 2010; 67(4):534-541

262 Gibney MA, Arce CH, Byron KJ, Hirsch LJ. Skin and subcutaneous adipose layer thickness in adults with diabetes at sites used for insulin injections: implications for needle length recommendations. Current Medical Research and Opinion. 2010; 26(6):1519-1530

263 Gill JS, Williams G, Ghatei MA, Hetreed AH, Mather HM, Bloom SR. Effect of the aldose reductase inhibitor, ponalrestat, on diabetic neuropathy. Diabetes & Metabolism. 1990; 16:296-302

264 Gillespie P, O'Shea E, O'Hara MC, Dinneen SF, Irish DAFNE Study Group. Cost effectiveness of group follow-up after structured education for type 1 diabetes: a cluster randomised controlled trial. Trials. 2014; 15:227

265 Gimenez M, Lara M, Conget I. Sustained efficacy of continuous subcutaneous insulin infusion in type 1 diabetes subjects with recurrent non-severe and severe hypoglycemia and hypoglycemia unawareness: a pilot study. Diabetes Technology and Therapeutics. 2010; 12(7):517-521

266 Gimenez M, Lara M, Jimenez A, Conget I. Glycaemic profile characteristics and frequency of impaired awareness of hypoglycaemia in subjects with T1D and repeated hypoglycaemic events. Acta Diabetologica. 2009; 46(4):291-293

267 Glasgow RE, La Chance PA, Toobert DJ, Brown J, Hampson SE, Riddle MC. Long-term effects and costs of brief behavioural dietary intervention for patients with diabetes delivered from the medical office. Patient Education and Counseling. 1997; 32:175-184

268 Gold AE, MacLeod KM, Frier BM. Frequency of severe hypoglycemia in patients with type I diabetes with impaired awareness of hypoglycemia. Diabetes Care. 1994; 17(7):697-703

269 Goldberg RB, Mellies MJ, Sacks FM, Moye LA, Howard BV, Howard WJ et al. Cardiovascular events and their reduction with pravastatin in diabetic and glucose-intolerant myocardial infarction survivors with average cholesterol levels: subgroup analyses in the cholesterol and recurrent events (CARE) trial. The Care Investigators. Circulation. 1998; 98:2513-2519

270 Goldstein I, Young JM, Fischer J, Bangerter K, Segerson T, Taylor T. Vardenafil, a new phosphodiesterase type 5 inhibitor, in the treatment of erectile dysfunction in men with diabetes: a multicenter double-blind placebo-controlled fixed-dose study. Diabetes Care. 2003; 26(3):777-783

271 Golen LW, Ijzerman RG, Huisman MC, Hensbergen JF, Hoogma RP, Drent ML et al. Cerebral blood flow and glucose metabolism in appetite-related brain regions in type 1 diabetic patients after treatment with insulin detemir and NPH insulin: A randomized controlled crossover trial. Diabetes Care. 2013; 36(12):4050-4056

272 Golightly LK, Jones MA, Hamamura DH, Stolpman NM, McDermott MT. Management of diabetes mellitus in hospitalized patients: Efficiency and effectiveness of sliding-scale insulin therapy. Pharmacotherapy. 2006; 26(10):1421-1432

273 Gomez JM, Maravall FJ, Guma A, Abos R, Soler J, Fernandez-Castaner M. Thyroid volume as measured by ultrasonography in patients With type 1 diabetes mellitus without thyroid dysfunction. Hormone and Metabolic Research, Hormon Und Stoffwechselforschung, Hormones Et Métabolisme. 2003; 35(8):486-491

274 Gomez-Perez FJ, Rull JA, Dies H, Rodriquez-Rivera JG, Gonzalez-Barranco J, Lozano-Castaneda O. Nortriptyline and fluphenazine in the symptomatic treatment of diabetic neuropathy. A double-blind cross-over study. Pain. 1985; 23(4):395-400

275 Gonder-Frederick LA, Julian DM, Cox DJ, Clarke WL, Carter WR. Self-measurement of blood glucose. Accuracy of self-reported data and adherence to recommended regimen. Diabetes Care. 1988; 11(7):579-585

276 Gordon D, Semple CG, Paterson KR. Do different frequencies of self-monitoring of blood glucose influence control in type 1 diabetic patients? Diabetic Medicine. 1991; 8(7):679-682

277 Gorman C, Looker J, Fisk T, Oelke W, Erickson D, Smith S et al. A clinically useful diabetes electronic medical record: lessons from the past; pointers toward the future. European Journal of Endocrinology. 1996; 134(1):31-42

278 Gossain VV, Gunaga KP, Carella MJ, Edminster RR, Bowman KA, Rovner DR. Utility of micral test strips in screening for microalbuminuria. Archives of Pathology & Laboratory Medicine. 1996; 120(11):1015-1018

279 Grabert M, Schweiggert F, Holl RW. A framework for diabetes documentation and quality management in Germany: 10 years of experience with DPV. Computer Methods and Programs in Biomedicine. 2002; 69(2):115-121

280 Grant L, Lawton J, Hopkins D, Elliott J, Lucas S, Clark M et al. Type 1 diabetes structured education: What are the core self-management behaviours? Diabetic Medicine. 2013; 30(6):724-730

281 Grieve R, Beech R, Vincent J, Mazurkiewicz J. Near patient testing in diabetes clinics: appraising the costs and outcomes. Health Technology Assessment. 1999; 3(15):1-74

282 Grima DT, Thompson MF, Sauriol L. Modelling cost effectiveness of insulin glargine for the treatment of type 1 and 2 diabetes in Canada. Pharmacoeconomics. 2007; 25(3):253-266

283 Gross TM, Kayne D, King A, Rother C, Juth S. A bolus calculator is an effective means of controlling postprandial glycemia in patients on insulin pump therapy. Diabetes Technology and Therapeutics. 2003; 5(3):365-369

284 Grover SA, Coupal L, Zowall H, Alexander CM, Weiss TW, Gomes DR. How cost-effective is the treatment of dyslipidemia in patients with diabetes but without cardiovascular disease? Diabetes Care. 2001; 24(1):45-50

285 Grover SA, Coupal L, Zowall H, Dorais M. Cost-effectiveness of treating hyperlipidemia in the presence of diabetes : who should be treated? Circulation. 2000; 102(7):722-727

286 Gruessner RW, Gruessner AC. The current state of pancreas transplantation. Nature Reviews Endocrinology. 2013; 9(9):555-562

287 Guerci B, Meyer L, Sommer S, George JL, Ziegler O, Drouin P et al. Severity of diabetic retinopathy is linked to lipoprotein (a) in type 1 diabetic patients. Diabetes & Metabolism. 1999; 25(5):412-418

288 Guillermin AL, Samyshkin Y, Wright D, Nguyen T, Villeneuve J. Modeling the lifetime costs of insulin glargine and insulin detemir in type 1 and type 2 diabetes patients in Canada: a meta-analysis and a cost-minimization analysis. Journal of Medical Economics. 2011; 14(2):207-216

289 Hamaguchi K, Kimura A, Kusuda Y, Yamashita T, Yasunami M, Takahasi M et al. Clinical and genetic characteristics of GAD-antibody positive patients initially diagnosed as having type 2 diabetes. Diabetes Research and Clinical Practice. 2004; 66(2):163-171

290 Hampe CS, Maitland ME, Gilliam LK, Phan THT, Sweet IR, Radtke JR et al. High titers of autoantibodies to glutamate decarboxylase in type 1 diabetes patients: epitope analysis and inhibition of enzyme activity. Endocrine Practice. 2013; 19(4):663-668

291 Hanas R, John G. 2010 consensus statement on the worldwide standardization of the hemoglobin A1C measurement. Diabetes Care. 2010; 33(8):1903-1904

292 Hanestad BR, Albrektsen G. The effects of participation in a support group on self assessed quality of life in people with insulin-dependent diabetes mellitus. Diabetes Research and Clinical Practice. 1993; 19(2):163-173

293 Hannon MJ, Dinneen S, Yousif O, Thompson CJ, Quigley EMM, O'Halloran DJ. Gastric pacing for diabetic gastroparesis--does it work? Irish Medical Journal. 2011; 104(5):135-137

294 Hansen HP, Gaede PH, Jensen BR, Parving H-H. Lack of impact of low-dose acetylsalicylic acid on kidney function in type 1 diabetic patients with microalbuminuria. Diabetes Care. 2000; 23(12):1742-1745

295 Hanson CL, Henggeler SW, Burghen GA. Social competence and parental support as mediators of the link between stress and metabolic control in adolescents with insulin-dependent diabetes mellitus. Journal of Consulting and Clinical Psychology. 1987; 55:529-533

296 Hanukoglu A, Mizrachi A, Dalal I, Admoni O, Rakover Y, Bistritzer Z et al. Extrapancreatic autoimmune manifestations in type 1 diabetes patients and their first-degree relatives: A multicenter study. Diabetes Care. 2003; 26(4):1235-1240

297 Harris MF, Priddin D, Ruscoe W, Infante FA, O'Toole BI. Quality of care provided by general practitioners using or not using Division-based diabetes registers. Medical Journal of Australia. 2002; 177(5):250-252

298 Harris S, Ng R, Syed H, Hillson R. Near patient blood ketone measurements and their utility in predicting diabetic ketoacidosis. Diabetic Medicine. 2005; 22(2):221-224

299 Hartemann-Heurtier A, Sultan S, Sachon C, Bosquet F, Grimaldi A. How type 1 diabetic patients with good or poor glycemic control cope with diabetes-related stress. Diabetes & Metabolism. 2001; 27(5 Pt 1):553-559

300 Hatzichristou D, Gambla M, Rubio-Aurioles E, Buvat J, Brock GB, Spera G et al. Efficacy of tadalafil once daily in men with diabetes mellitus and erectile dysfunction. Diabetic Medicine : a Journal of the British Diabetic Association. 2008; 25(2):138-146

301 Hawa MI, Kolb H, Schloot N, Beyan H, Paschou SA, Buzzetti R et al. Adult-onset autoimmune diabetes in Europe is prevalent with a broad clinical phenotype: Action LADA 7. Diabetes Care. 2013; 36(4):908-913

302 Health and Social Care Information Centre. Prescription cost analysis - England, 2012 [NS]. 2013. [Last accessed: 6 January 2014]

303 Health Technology Board for Scotland (HTBS). Organization of services for diabetic retinopathy screening (project). Health Technology Board for Scotland (HTBS)., 2002. Available from: http://www.htbs.org.uk

304 Hearnshaw H, Hopkins J, Wild A, MacKinnon M, Gadsby R, Dale J. Mandatory, multidisciplinary education in diabetes care. Can it meet the needs of primary care organisations? Practical Diabetes International. 2001; 18(8):274-280

305 Heinemann L, Pettis RJ, Hirsch LJ, Nosek L, Kapitza C, Sutter DE et al. Microneedle-based intradermal injection of lispro or human regular insulin accelerates insulin uptake and reduces post-prandial glycaemia. Diabetologia. 2009; 52(S1):S378

306 Heise T, Hermanski L, Nosek L, Feldmann A, Rasmussen S, Stryhn TK et al. Insulin degludec: Less pharmacodynamic variability than insulin glargine under steady state conditions. Diabetologia. 2010; 53(Suppl.1):S387

307 Heise T, Nosek L, Rã¸Nn BB, Endahl L, Heinemann L, Kapitza C et al. Lower within-subject variability of insulin detemir in comparison to NPH insulin and insulin glargine in people with type 1 diabetes. Diabetes. 2004; 53(6):1614-1620

308 Heller S, Buse J, Fisher M, Garg S, Marre M, Merker L et al. Insulin degludec, an ultra-longacting basal insulin, versus insulin glargine in basal–bolus treatment with mealtime insulin aspart in type 1 diabetes (BEGIN Basal–bolus Type 1): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. Lancet. 2012; 379(9825):1489-1497

309 Heller S, Koenen C, Bode B. Comparison of insulin detemir and insulin glargine in a basal–bolus regimen, with insulin aspart as the mealtime insulin, in patients with type 1 diabetes: a 52-week, multinational, randomized, open-label, parallel-group, treat-to-target noninferiority trial. Clinical Therapeutics. 2009; 31(10):2086-2097

310 Heller SR, Amiel SA, Mansell P. Effect of the fast-acting insulin analog lispro on the risk of nocturnal hypoglycemia during intensified insulin therapy. U.K. Lispro Study Group. Diabetes Care. 1999; 22(10):1607-1611

311 Heller SR, Colagiuri S, Vaaler S, Wolffenbuttel BH, Koelendorf K, Friberg HH et al. Hypoglycaemia with insulin aspart: a double-blind, randomised, crossover trial in subjects with Type 1 diabetes. Diabetic Medicine. 2004; 21(7):769-775

312 Heller SR, Cryer PE. Reduced neuroendocrine and symptomatic responses to subsequent hypoglycemia after 1 episode of hypoglycemia in nondiabetic humans. Diabetes. 1991; 40(2):223-226

313 Henderson JN, Allen KV, Deary IJ, Frier BM. Hypoglycaemia in insulin-treated Type 2 diabetes: frequency, symptoms and impaired awareness. Diabetic Medicine. 2003; 20(12):1016-1021

314 Hendrieckx C, Halliday JA, Bowden JP, Colman PG, Cohen N, Jenkins A et al. Severe hypoglycaemia and its association with psychological well-being in Australian adults with type 1 diabetes attending specialist tertiary clinics. Diabetes Research and Clinical Practice. 2014; 103(3):430-436

315 Hendry BM, Viberti GC, Hummel S, Bagust A, Piercy J. Modelling and costing the consequences of using an ACE inhibitor to slow the progression of renal failure in type I diabetic patients. QJM: Monthly Journal of the Association of Physicians. 1997; 90(4):277-282

316 Hentinen M, Kyngas H. Diabetic adolescents' compliance with health regimens and associated factors. International Journal of Nursing Studies. 1996; 33:325-337

317 Herman WH, Dasbach EJ, Songer TJ, Eastman RC. The cost-effectiveness of intensive therapy for diabetes mellitus. Endocrinology and Metabolism Clinics of North America. 1997; 26(3):679-695

318 Hermanns N, Kulzer B, Kubiak T, Krichbaum M, Haak T. The effect of an education programme (HyPOS) to treat hypoglycaemia problems in patients with type 1 diabetes. Diabetes/Metabolism Research and Reviews. 2007; 23(7):528-538

319 Hermanns N, Kulzer B, Ehrmann D, Bergis-Jurgan N, Haak T. The effect of a diabetes education programme (PRIMAS) for people with type 1 diabetes: results of a randomized trial. Diabetes Research and Clinical Practice. 2013; 102(3):149-157

320 Hermansen K, Fontaine P, Kukolja KK, Peterkova V, Leth G, Gall MA. Insulin analogues (insulin detemir and insulin aspart) versus traditional human insulins (NPH insulin and regular human insulin) in basal–bolus therapy for patients with type 1 diabetes. Diabetologia. 2004; 47(4):622-629

321 Hermansen K, Madsbad S, Perrild H, Kristensen A, Axelsen M. Comparison of the soluble basal insulin analog insulin detemir with NPH insulin: A randomized open crossover trial in type 1 diabetic subjects on basal–bolus therapy. Diabetes Care. 2001; 24(2):296-301

322 Hernandez CA, Hume MR, Rodger NW. Evaluation of a self-awareness intervention for adults with type 1 diabetes and hypoglycemia unawareness. Canadian Journal of Nursing Research. 2008; 40(3):38-56

323 Herpertz S, Wagener R, Albus C, Kocnar M, Wagner R, Best F et al. Diabetes mellitus and eating disorders: a multicenter study on the comorbidity of the two diseases. Journal of Psychosomatic Research. 1998; 44(3-4):503-515

324 Herz M, Arora V, Sun B, Ferguson SC, Bolli GB, Frier BM. Basal–bolus insulin therapy in Type 1 diabetes: Comparative study of pre-meal administration of a fixed mixture of insulin lispro (50%) and neutral protamine lispro (50%) with human soluble insulin. Diabetic Medicine. 2002; 19(11):917-923

325 Hietala K, Waden J, Forsblom C, Harjutsalo V, Kyto J, Summanen P et al. HbA1c variability is associated with an increased risk of retinopathy requiring laser treatment in type 1 diabetes. Diabetologia. 2013; 56(4):737-745

326 Hillman M, Torn C, Landin-Olsson M, DISS study group. The glutamic acid decarboxylase 65 immunoglobulin G subclass profile differs between adult-onset type 1 diabetes and latent autoimmune diabetes in adults (LADA) up to 3 years after clinical onset. Clinical and Experimental Immunology. 2009; 157(2):255-260

327 Hillman N, Herranz L, Grande C, Vaquero PM, Pallardo LF. What is the relative contribution of blood glucose levels at different time points of the day to HbA1c in Type 1 diabetes? Diabetic Medicine. 2004; 21(5):468-470

328 Hirsch IB, Abelseth J, Bode BW, Fischer JS, Kaufman FR, Mastrototaro J et al. Sensor-augmented insulin pump therapy: results of the first randomized treat-to-target study. Diabetes Technology and Therapeutics. 2008; 10(5):377-383

329 Hirsch IB, Brownlee M. Beyond hemoglobin A1c--need for additional markers of risk for diabetic microvascular complications. JAMA : the Journal of the American Medical Association. 2010; 303(22):2291-2292

330 Hirsch IB, Bode B, Courreges JP, Dykiel P, Franek E, Hermansen K et al. Insulin degludec/insulin aspart administered once daily at any meal, with insulin aspart at other meals versus a standard basal–bolus regimen in patients with type 1 diabetes: a 26-week, phase 3, randomized, open-label, treat-to-target trial. Diabetes Care. 2012; 35(11):2174-2181

331 Hirsch LJ, Gibney MA, Albanese J, Qu S, Kassler-Taub K, Klaff LJ et al. Comparative glycemic control, safety and patient ratings for a new 4 mm x 32G insulin pen needle in adults with diabetes. Current Medical Research and Opinion. 2010; 26(6):1531-1541

332 Hirsch LJ, Gibney MA, Li L, Berube J. Glycemic control, reported pain and leakage with a 4 mm x 32 G pen needle in obese and non-obese adults with diabetes: a post hoc analysis. Current Medical Research and Opinion. 2012; 28(8):1305-1311

333 Hiscock J, Ligard R, and Snape. Listening to Diabetes Service Users: Qualitative findings for the diabetes National Service Framework. Department of Health, 2003. Available from: Department of Health website www.doh.gov.uk

334 Hislop AL, Fegan PG, Schlaeppi MJ, Duck M, Yeap BB. Prevalence and associations of psychological distress in young adults with Type 1 diabetes. Diabetic Medicine. 2008; 25(1):91-96

335 Hoi-Hansen T, Pedersen-Bjergaard U, Thorsteinsson B. Classification of hypoglycemia awareness in people with type 1 diabetes in clinical practice. Journal of Diabetes and Its Complications. 2010; 24(6):392-397

336 Holleman F, Schmitt H, Rottiers R, Rees A, Symanowski S, Anderson JH et al. Reduced frequency of severe hypoglycemia and coma well-controlled IDDM patients treated with insulin lispro. Diabetes Care. 1997; 20(12):1827-1832

337 Home P, Bartley P, Russell-Jones D, Hanaire-Broutin H, Heeg JE, Abrams P et al. Insulin detemir offers improved glycemic control compared with NPH insulin in people with type 1 diabetes: a randomized clinical trial. Diabetes Care. 2004; 27(5):1081-1087

338 Home PD. The pharmacokinetics and pharmacodynamics of rapid-acting insulin analogues and their clinical consequences. Diabetes Obesity and Metabolism. 2012; 14(9):780-788

339 Home PD, Coles J, Goldacre M, Mason A, and Wilkinson E. Health outcome indicators: Diabetes. A report of a working group to the Department of Health. Oxford. National centre for health outcomes development, 1999

340 Home PD, Hallgren P, Usadel KH, Sane T, Faber J, Grill V et al. Pre-meal insulin aspart compared with pre-meal soluble human insulin in type 1 diabetes. Diabetes Research and Clinical Practice. 2006; 71(2):131-139

341 Home PD, Lindholm A, Hylleberg B, Round P. Improved glycemic control with insulin aspart: a multicenter randomized double-blind crossover trial in type 1 diabetic patients. UK Insulin Aspart Study Group. Diabetes Care. 1998; 21(11):1904-1909

342 Home PD, Lindholm A, Riis A. Insulin aspart vs. human insulin in the management of long-term blood glucose control in Type 1 diabetes mellitus: A randomized controlled trial. Diabetic Medicine. 2000; 17(11):762-770

343 Home PD, Meneghini L, Wendisch U, Ratner RE, Johansen T, Christensen TE et al. Improved health status with insulin degludec compared with insulin glargine in people with Type1 diabetes. Diabetic Medicine. 2012; 29(6):716-720

344 Home PD, Rosskamp R, Forjanic-Klapproth J, Dressler A. A randomized multicentre trial of insulin glargine compared with NPH insulin in people with type 1 diabetes. Diabetes/Metabolism Research and Reviews. 2005; 21(6):545-553

345 Hommel E, Andersen P, Gall M-A, Nielsen F, Jensen B, Rossing P et al. Plasma lipoproteins and renal function during simvastatin treatment in diabetic nephropathy. Diabetologia. 1992; 35(5):447-451

346 Hope SV, Jones AG, Goodchild E, Shepherd M, Besser REJ, Shields B et al. Urinary C-peptide creatinine ratio detects absolute insulin deficiency in Type 2 diabetes. Diabetic Medicine. 2013; 30(11):1342-1348

347 Hopkins D, Lawrence I, Mansell P, Thompson G, Amiel S, Campbell M et al. Improved biomedical and psychological outcomes 1 year after structured education in flexible insulin therapy for people with type 1 diabetes: the U.K. DAFNE experience. Diabetes Care. 2012; 35(8):1638-1642

348 Hopkinson HE, Jacques RM, Gardner KJ, Amiel SA, Mansell P. Twice- rather than once-daily basal insulin is associated with better glycaemic control in Type 1 diabetes mellitus 12 months after skills-based structured education in insulin self-management. Diabetic Medicine : a Journal of the British Diabetic Association. 2015;

349 Horowitz M, Harding PE, Chatterton BE, Collins PJ, Shearman DJ. Acute and chronic effects of domperidone on gastric emptying in diabetic autonomic neuropathy. Digestive Diseases and Sciences. 1985; 30(1):1-9

350 Horsley W. Gastroelectrical stimulation for gastroparesis. North East Treatment Advisory Group, 2010. Available from: http://www.netag.nhs.uk/files/appraisal-reports/Gastroelectrical%20stimulation%20-%20NETAG%20appraisal%20report%20-Apr10.pdf

351 Hosszufalusi N, Vatay A, Rajczy K, Prohaszka Z, Pozsonyi E, Horvath L et al. Similar genetic features and different islet cell autoantibody pattern of latent autoimmune diabetes in adults (LADA) compared with adult-onset type 1 diabetes with rapid progression. Diabetes Care. 2003; 26(2):452-457

352 Howitt AJ, Cheales NA. Diabetes registers: a grassroots approach. BMJ. 1993; 307(6911):1046-1048

353 Huang ES, O'Grady M, Basu A, Winn A, John P, Lee J et al. The cost-effectiveness of continuous glucose monitoring in type 1 diabetes. Diabetes Care. 2010; 33(6):1269-1274

354 Huang G, Xiang Y, Pan L, Li X, Luo S, Zhou Z. Zinc transporter 8 autoantibody (ZnT8A) could help differentiate latent autoimmune diabetes in adults (LADA) from phenotypic type 2 diabetes mellitus. Diabetes/Metabolism Research and Reviews. 2013; 29(5):363-368

355 Huang Z, Chen Y, Li F, Li Y. Clinical heterogeneity of type 1 diabetes mellitus at onset. Diabetologia. 2010; 53(Suppl.1):S396

356 Husband DJ, Thai AC, Alberti KG. Management of diabetes during surgery with glucose-insulin-potassium infusion. Diabetic Medicine. 1986; 3(1):69-74

357 Hutchinson A, McIntosh A, Peters J, O'Keeffe C, Khunti K, Baker R et al. Effectiveness of screening and monitoring tests for diabetic retinopathy - A systematic review. Diabetic Medicine. 2000; 17(7):495-506

358 Hutchinson MS, Joakimsen RM, Njolstad I, Schirmer H, Figenschau Y, Jorde R. Glycated hemoglobin in diagnosis of diabetes mellitus and pre-diabetes; validation by oral glucose

tolerance test. The Tromso OGTT Study. Journal of Endocrinological Investigation. 2012; 35(9):835-840

359 Hwangbo Y, Kim JT, Kim EK, Khang AR, Oh TJ, Jang HC et al. Prevalence and clinical characteristics of recently diagnosed type 2 diabetes patients with positive anti-glutamic Acid decarboxylase antibody. Diabetes & Metabolism. 2012; 36(2):136-143

360 Ignaut DA, Fu H. Comparison of insulin diluent leakage postinjection using two different needle lengths and injection volumes in obese patients with type 1 or type 2 diabetes mellitus. Journal of Diabetes Science and Technology. 2012; 6(2):389-393

361 International Diabetes Foundation. A guide to Type 1 (insulin dependant) Diabetes Mellitus. Brussels. International Diabetes Federation, 1998

362 Ishii N, Nagao K, Fujikawa K, Tachibana T, Iwamoto Y, Kamidono S. Vardenafil 20-mg demonstrated superior efficacy to 10-mg in Japanese men with diabetes mellitus suffering from erectile dysfunction. International Journal of Urology : Official Journal of the Japanese Urological Association. 2006; 13(8):1066-1072

363 Iwamoto Y, Clauson P, Nishida T, Kaku K. Insulin degludec in Japanese patients with type 1 diabetes mellitus: A randomized controlled trial. Journal of Diabetes Investigation. 2013; 4(1):62-68

364 Jacobsen IB, Henriksen JE, Beck-Nielsen H. The effect of metformin in overweight patients with type 1 diabetes and poor metabolic control. Basic and Clinical Pharmacology and Toxicology. 2009; 105(3):145-149

365 Jacobson AM, Braffett BH, Cleary PA, Gubitosi-Klug RA, Larkin ME, DCCT/EDIC Research Group. The long-term effects of type 1 diabetes treatment and complications on health-related quality of life: a 23-year follow-up of the Diabetes Control and Complications/Epidemiology of Diabetes Interventions and Complications cohort. Diabetes Care. 2013; 36(10):3131-3138

366 Janssen MM, Snoek FJ, Heine RJ. Assessing impaired hypoglycemia awareness in type 1 diabetes: agreement of self-report but not of field study data with the autonomic symptom threshold during experimental hypoglycemia. Diabetes Care. 2000; 23(4):529-532

367 Janssen MM, Snoek FJ, Masurel N, Hoogma RP, Deville WL, Popp-Snijders C et al. Optimized basal–bolus therapy using a fixed mixture of 75% lispro and 25% NPL insulin in type 1 diabetes patients: no favorable effects on glycemic control, physiological responses to hypoglycemia, well-being, or treatment satisfaction. Diabetes Care. 2000; 23(5):629-633

368 Janssens J, Peeters TL, Vantrappen G, Tack J, Urbain JL, De Roo M et al. Improvement of gastric emptying in diabetic gastroparesis by erythromycin. Preliminary studies. New England Journal of Medicine. 1990; 322(15):1028-1031

369 Javitt JC, Aiello LP. Cost-effectiveness of detecting and treating diabetic retinopathy. Annals of Internal Medicine. 1996; 124(1 Pt 2):164-169

370 Javitt JC, Aiello LP, Bassi LJ, Chiang YP, Canner JK. Detecting and treating retinopathy in patients with type I diabetes mellitus. Savings associated with improved implementation of current guidelines. American Academy of Ophthalmology. Ophthalmology. 1991; 98(10):1565-1573

371 Javitt JC, Canner JK, Frank RG, Steinwachs DM, Sommer A. Detecting and treating retinopathy in patients with type I diabetes mellitus. A health policy model. Ophthalmology. 1990; 97(4):483-494

372 Javitt JC, Canner JK, Sommer A. Cost effectiveness of current approaches to the control of retinopathy in type I diabetics. Ophthalmology. 1989; 96(2):255-264

373 Javor KA, Kotsanos JG, McDonald RC, Baron AD, Kesterson JG, Tierney WM. Diabetic ketoacidosis charges relative to medical charges of adult patients with type I diabetes. Diabetes Care. 1997; 20(3):349-354

374 Jin P, Huang G, Lin J, Yang L, Xiang B, Zhou W et al. High titre of antiglutamic acid decarboxylase autoantibody is a strong predictor of the development of thyroid autoimmunity in patients with type 1 diabetes and latent autoimmune diabetes in adults. Clinical Endocrinology. 2011; 74(5):587-592

375 Johnston JH, Cook AT. Treatment of diabetic ketoacidosis with small doses of insulin. Journal of the Royal Army Medical Corps. 1977; 123(1):32-36

376 Johnston SD, Ritchie C, Robinson J. Application of red cell distribution width to screening for coeliac disease in insulin-dependent diabetes mellitus. Irish Journal of Medical Science. 1999; 168(3):167-170

377 Joint Diabetes UK and Department of Health patient education working group. Structured patient education in diabetes: report from the patient education working group. Department of Health; Diabetes UK, 2005. Available from: http://www.diabetes.org.uk/Documents/Reports/StructuredPatientEd.pdf

378 Joint Formulary Committee. British National Formulary (BNF). 64th edition. London: British Medical Association and The Royal Pharmaceutical Society of Great Britain; 2012. Available from: http://www.bnf.org.uk

379 Joint Formulary Committee. British National Formulary (BNF). 67th edition. London: British Medical Association and The Royal Pharmaceutical Society of Great Britain; 2014. Available from: http://www.bnf.org.uk

380 Jones AF, Walker J, Jewkes C, Game FL, Bartlett WA, Marshall T et al. Comparative accuracy of cardiovascular risk prediction methods in primary care patients. Heart. 2001; 85(1):37-43

381 Jonsson B, Cook JR, Pedersen TR. The cost-effectiveness of lipid lowering in patients with diabetes: results from the 4S trial. Diabetologia. 1999; 42(11):1293-1301

382 Junik R, Kozinski M, Debska-Kozinska K. Thyroid ultrasound in diabetic patients without overt thyroid disease. Acta Radiologica. 2006; 47(7):687-691

383 Kamenov ZA. Comparison of the first intake of vardenafil and tadalafil in patients with diabetic neuropathy and diabetic erectile dysfunction. Journal of Sexual Medicine. 2011; 8(3):851-864

384 Kanc K, Kastrin A, Kastrin M, Gonder-Frederick LA. Fear of hypoglycaemia - How to identify patients at risk in a routine clinical practice? Diabetologia. 2010; 53(Suppl.1):S237-S238

385 Kanters SDJM, Banga J-D, Stolk RP, Algra A. Incidence and determinants of mortality and cardiovascular events in diabetes mellitus: A meta-analysis. Vascular Medicine. 1999; 4(2):67-75

386 Kaplan RM, Hartwell SL. Differential effects of social support and social network on physiological and social outcomes in men and women with type II diabetes. Health Psychology. 1987; 6:387-398

387 Karges B, Boehm BO, Karges W. Early hypoglycaemia after accidental intramuscular injection of insulin glargine. Diabetic Medicine. 2005; 22(10):1444-1445

388 Karter AJ, Ackerson LM, Darbinian JA, D'Agostino RBJ, Ferrara A, Liu J et al. Self-monitoring of blood glucose levels and glycemic control: the Northern California Kaiser Permanente Diabetes registry. American Journal of Medicine. 2001; 111(1):1-9

389 Kawamori R, Kadowaki T, Ishii H, Iwasaki M, Iwamoto Y. Efficacy and safety of insulin glulisine in Japanese patients with type 1 diabetes mellitus. Diabetes Obesity and Metabolism. 2009; 11(9):891-899

390 Kelley DE. Sugars and starch in the nutritional management of diabetes mellitus. American Journal of Clinical Nutrition. 2003; 78(4):858S-864S

391 Kelly W, Bilous R, Murray G. A comprehensive register for diabetic outpatients: experience with desktop computing from 1987-1996. Computer Methods and Programs in Biomedicine. 1998; 56(2):205-210

392 Kendall DM, Rooney DP, Smets YF, Salazar BL, Robertson RP. Pancreas transplantation restores epinephrine response and symptom recognition during hypoglycemia in patients with long-standing type I diabetes and autonomic neuropathy. Diabetes. 1997; 46(2):249-257

393 Khachadurian AK, Davidson JA, Braunstein S, Redmond G, Greenfield M, Lauritano AA et al. Comparison of fixed-ratio versus variable-ratio regular and NPH semisynthetic human insulin in insulin-requiring diabetic patients. Clinical Therapeutics. 1989; 11(4):485-494

394 Khan AS, McLoughney CR, Ahmed AB. The effect of metformin on blood glucose control in overweight patients with Type 1 diabetes. Diabetic Medicine. 2006; 23(10):1079-1084

395 Kiberd BA, Jindal KK. Screening to prevent renal failure in insulin dependent diabetic patients: an economic evaluation. BMJ. 1995; 311(7020):1595-1599

396 Kielgast U, Krarup T, Holst JJ, Madsbad S. Four weeks of treatment with liraglutide reduces insulin dose without loss of glycemic control in type 1 diabetic patients with and without residual beta-cell function. Diabetes Care. 2011; 34(7):1463-1468

397 Kilbride L, Charlton J, Aitken G, Hill GW, Davison RCR, McKnight JA. Managing blood glucose during and after exercise in Type 1 diabetes: reproducibility of glucose response and a trial of a structured algorithm adjusting insulin and carbohydrate intake. Journal of Clinical Nursing. 2011; 20(23-24):3423-3429

398 Kim CS, Song MK, Park JS, Cho MH, Kim HJ, Nam JS et al. The clinical and immunogenetic characteristics of adult-onset type 1 diabetes mellitus in Korea. Acta Diabetologica. 2007; 44(2):45-54

399 Kirsten C, Manning P, Otago Diabetes Team. Establishing a regional diabetes register and a description of the registered population after one year. New Zealand Medical Journal. 2002; 115(1160):U146

400 Klein BE, Klein R, Moss SE. Self-rated health and diabetes of long duration. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. Diabetes Care. 1998; 21(2):236-240

401 Klein R. Hyperglycemia and microvascular and macrovascular disease in diabetes. Diabetes Care. 1995; 18(2):258-268

402 Klein R, Klein BE, Moss SE. Relation of glycemic control to diabetic microvascular complications in diabetes mellitus. Annals of Internal Medicine. 1996; 124(1 Pt 2):90-96

403 Klein R, Klein BE, Moss SE, Cruickshanks KJ. The Wisconsin Epidemiologic Study of Diabetic Retinopathy: XVII. The 14-year incidence and progression of diabetic retinopathy and associated risk factors in type 1 diabetes. Ophthalmology. 1998; 105(10):1801-1815

404 Klein R, Moss SE, Klein BE. Change in glycemia in a four-year interval in younger-onset insulin-dependent diabetes. Annals of Epidemiology. 1992; 2(3):283-294

405 Kleschen MZ, Holbrook J, Rothbaum AK, Stringer RA, McInerney MJ, Helgerson SD. Improving the pneumococcal immunization rate for patients with diabetes in a managed care population: a simple intervention with a rapid effect. Joint Commission Journal on Quality Improvement. 2000; 26(9):538-546

406 Klupa T, Benbenek-Klupa T, Malecki M, Szalecki M, Sieradzki J. Clinical usefulness of a bolus calculator in maintaining normoglycaemia in active professional patients with type 1 diabetes treated with continuous subcutaneous insulin infusion. Journal of International Medical Research. 2008; 36(5):1112-1116

407 Knight BG, Lutzky SM, Macofsky-Urban. A meta-analytic review of interventions for caregiver distress: recommendations for future research. Gerontologist. 1993; 33(2):240-248

408 Koblik T, Sieradzki J, Friedlein J, Legutko J. First polish multidisciplinary diabetic foot team: Results of the first three years of operation - The Cracow study. Diabetologia Polska. 1999; 6(4):233-238

409 Kolendorf K, Ross GP, Pavlic-Renar I, Perriello G, Philotheou A, Jendle J et al. Insulin detemir lowers the risk of hypoglycaemia and provides more consistent plasma glucose levels compared with NPH insulin in Type 1 diabetes. Diabetic Medicine. 2006; 23(7):729-735

410 Kolterman OG, Schwartz S, Corder C, Levy B, Klaff L, Peterson J et al. Effect of 14 days' subcutaneous administration of the human amylin analogue, pramlintide (AC137), on an intravenous insulin challenge and response to a standard liquid meal in patients with IDDM. Diabetologia. 1996; 39(4):492-499

411 Kong MF, Stubbs TA, King P, Macdonald IA, Lambourne JE, Blackshaw PE et al. The effect of single doses of pramlintide on gastric emptying of two meals in men with IDDM. Diabetologia. 1998; 41(5):577-583

412 Kontopoulos AG, Athyros VG, Didangelos TP, Papageorgiou AA, Avramidis MJ, Mayroudi MC et al. Effect of chronic quinapril administration on heart rate variability in patients with diabetic autonomic neuropathy. Diabetes Care. 1997; 20(3):355-361

413 Kopelman PG, Michell JC, Sanderson AJ. DIAMOND: a computerized system for the management and evaluation of district-wide diabetes care. Diabetic Medicine. 1995; 12(1):83-87

414 Koproski J, Pretto Z, Poretsky L. Effects of an intervention by a diabetes team in hospitalized patients with diabetes. Diabetes Care. 1997; 20(10):1553-1555

415 Korhonen T, Huttunen JK, Aro A, Hentinen M, Ihalainen O, Majander H et al. A controlled trial on the effects of patient education in the treatment of insulin-dependent diabetes. Diabetes Care. 1983; 6(3):256-261

416 Kouri TT, Viikari JS, Mattila KS, Irjala KM. Microalbuminuria. Invalidity of simple concentration-based screening tests for early nephropathy due to urinary volumes of diabetic patients. Diabetes Care. 1991; 14(7):591-593

417 Kouris I, Mougiakakou S, Scarnato L, Iliopoulou D, Diem P, Vazeou A et al. Mobile phone technologies and advanced data analysis towards the enhancement of diabetes self-management. International Journal of Electronic Healthcare. 2010; 5(4):386-402

418 Kovatchev BP, Cox DJ, Straume M, Farhy LS. Association of self-monitoring blood glucose profiles with glycosylated hemoglobin in patients with insulin-dependent diabetes. Methods in Enzymology. 2000; 321:410-417

419 Kovatchev BP, Crean J, McCall A. Pramlintide reduces the risks associated with glucose variability in type 1 diabetes. Diabetes Technology and Therapeutics. 2008; 10(5):391-396

420 Kowalske KJ, Agre JC. Neuromuscular rehabilitation and electrodiagnosis. 3. Generalized peripheral neuropathy. Archives of Physical Medicine and Rehabilitation. 2000; 81(3 Suppl 1):S20-S26

421 Kreugel G, Keers JC, Kerstens MN, Wolffenbuttel BH. Randomized trial on the influence of the length of two insulin pen needles on glycemic control and patient preference in obese patients with diabetes. Diabetes Technology and Therapeutics. 2011; 13(7):737-741

422 Kruger J, Brennan A, Thokala P, Basarir H, Jacques R, Elliott J et al. The cost-effectiveness of the Dose Adjustment for Normal Eating (DAFNE) structured education programme: An update using the Sheffield Type 1 Diabetes Policy Model. Diabetic Medicine. 2013; 30(10):1236-1244

423 Kucera P, Novakova D, Behanova M, Novak J, Tlaskalova-Hogenova H, Andel M. Gliadin, endomysial and thyroid antibodies in patients with latent autoimmune diabetes of adults (LADA). Clinical and Experimental Immunology. 2003; 133(1):139-143

424 Kullberg CE, Finnstrom K, Arnqvist HJ. Severity of background retinopathy in type 1 diabetes increases with the level of long-term glycated haemoglobin. Acta Opthalmologica. 1994; 72(2):181-188

425 Laadhar L, Zitouni M, Kallel-Sellami M, Bouguerra R, Chaabouni H, Makni S. Spectrum of autoantibodies in Tunisian adult type 1 diabetes mellitus. Annals of the New York Academy of Sciences. 2007; 1107:356-362

426 Laaksonen DE, Atalay M, Niskanen LK, Mustonen J, Sen CK, Lakka TA et al. Aerobic exercise and the lipid profile in type 1 diabetic men: a randomized controlled trial. Medicine & Science in Sports & Exercise. 2000; 32(9):1541-1548

427 Labrecque MS, Peak T. Long term effectiveness of a group program for caregivers of frail elderly veterans. American Journal of Orthopsychiatry. 1992; 62(4):575-588

428 Lachin JM, Orchard TJ, Nathan DM, DCCT/EDIC Research Group. Update on cardiovascular outcomes at 30 years of the diabetes control and complications trial/epidemiology of diabetes interventions and complications study. Diabetes Care. 2014; 37(1):39-43

429 Lacy BE, Crowell MD, Schettler-Duncan A, Mathis C, Pasricha PJ. The treatment of diabetic gastroparesis with botulinum toxin injection of the pylorus. Diabetes Care. 2004; 27(10):2341-2347

430 Laffel LMB, Wentzell K, Loughlin C, Tovar A, Moltz K, Brink S. Sick day management using blood 3-hydroxybutyrate (3-OHB) compared with urine ketone monitoring reduces hospital visits in young people with T1DM: A randomized clinical trial. Diabetic Medicine. 2006; 23(3):278-284

431 Lafrance L, Rabasa-Lhoret R, Poisson D, Ducros F, Chiasson JL. Effects of different glycaemic index foods and dietary fibre intake on glycaemic control in type 1 diabetic patients on intensive insulin therapy. Diabetic Medicine. 1998; 15(11):972-978

432 Lalli C, Ciofetta M, Del Sindaco P, Torlone E, Pampanelli S, Compagnucci P et al. Long-term intensive treatment of type 1 diabetes with the short-acting insulin analog lispro in variable combination with NPH insulin at mealtime. Diabetes Care. 1999; 22(3):468-477

433 Langendam M, Luijf YM, Hooft L, DeVries JH, Mudde AH, Scholten Rob JPM. Continuous glucose monitoring systems for type 1 diabetes mellitus. Cochrane Database of Systematic Reviews. 2012; Issue 1:CD008101. DOI:10.1002/14651858.CD008101.pub2

434 Larsen ML, Horder M, Mogensen EF. Effect of long-term monitoring of glycosylated hemoglobin levels in insulin-dependent diabetes mellitus. New England Journal of Medicine. 1990; 323(15):1021-1025

435 Larsson J, Apelqvist J, Agardh CD, Stenstrom A. Decreasing incidence of major amputation in diabetic patients: a consequence of a multidisciplinary foot care team approach? Diabetic Medicine. 1995; 12(9):770-776

436 Laurenzi A, Bolla AM, Panigoni G, Doria V, Uccellatore A, Peretti E et al. Effects of carbohydrate counting on glucose control and quality of life over 24 weeks in adult patients with type 1 diabetes on continuous subcutaneous insulin infusion: a randomized, prospective clinical trial (GIOCAR). Diabetes Care. 2011; 34(4):823-827

437 Lawrenson R, Williams J. Antidepressant use in people with diabetes. Diabetes Primary Care. 2001; 3(3):70-74

438 Lawton J, Rankin D, Cooke D, Elliott J, Amiel S, Heller S. Patients' experiences of adjusting insulin doses when implementing flexible intensive insulin therapy: a longitudinal, qualitative investigation. Diabetes Research and Clinical Practice. 2012; 98(2):236-242

439 Lawton J, Rankin D, Elliott J, Heller SR, Rogers HA, de ZN et al. Experiences, views, and support needs of family members of people with hypoglycemia unawareness: interview study. Diabetes Care. 2014; 37(1):109-115

440 Le Floch JP, Charles MA, Philippon C, Perlemuter L. Cost-effectiveness of screening for microalbuminuria using immunochemical dipstick tests or laboratory assays in diabetic patients. Diabetic Medicine. 1994; 11(4):349-356

441 Le Floch JP, Lévy M, Mosnier-Pudar H, Nobels F, Laroche S, Gonbert S et al. Comparison of once- versus twice-daily administration of insulin detemir, used with mealtime insulin aspart,

in basal–bolus therapy for type 1 diabetes: assessment of detemir administration in a progressive treat-to-target trial (ADAPT). Diabetes Care. 2009; 32(1):32-37

442 Le Floch JP, Marre M, Rodier M, Passa P. Interest of Clinitek Microalbumin in screening for microalbuminuria: results of a multicentre study in 302 diabetic patients. Diabetes & Metabolism. 2001; 27(1):36-39

443 Lecaire TJ, Palta M, Klein R, Klein BEK, Cruickshanks KJ. Assessing progress in retinopathy outcomes in type 1 diabetes: comparing findings from the Wisconsin Diabetes Registry Study and the Wisconsin Epidemiologic Study of Diabetic Retinopathy. Diabetes Care. 2013; 36(3):631-637

444 Lee SA, Lee WJ, Kim EH, Yu JH, Jung CH, Koh EH et al. Progression to insulin deficiency in Korean patients with Type 2 diabetes mellitus positive for anti-GAD antibody. Diabetic Medicine. 2011; 28(3):319-324

445 Leelarathna L, Little SA, Walkinshaw E, Tan HK, Lubina-Solomon A, Kumareswaran K et al. Restoration of self-awareness of hypoglycemia in adults with long-standing type 1 diabetes: hyperinsulinemic-hypoglycemic clamp substudy results from the HypoCOMPaSS trial. Diabetes Care. 2013; 36(12):4063-4070

446 Leeuw I, Vague P, Selam JL, Skeie S, Lang H, Draeger E et al. Insulin detemir used in basal–bolus therapy in people with type 1 diabetes is associated with a lower risk of nocturnal hypoglycaemia and less weight gain over 12 months in comparison to NPH insulin. Diabetes Obesity and Metabolism. 2005; 7(1):73-82

447 Lehmann R, Kaplan V, Bingisser R, Bloch KE, Spinas GA. Impact of physical activity on cardiovascular risk factors in IDDM. Diabetes Care. 1997; 20(10):1603-1611

448 Lehto S, Ronnemaa T, Pyorala K, Laakso M. Poor glycemic control predicts coronary heart disease events in patients with type 1 diabetes without nephropathy. Arteriosclerosis, Thrombosis, and Vascular Biology. 1999; 19(4):1014-1019

449 Leitao CB, Tharavanij T, Cure P, Pileggi A, Baidal DA, Ricordi C et al. Restoration of hypoglycemia awareness after islet transplantation. Diabetes Care. 2008; 31(11):2113-2115

450 Lennon GM, Taylor KG, Debney L, Bailey CJ. Knowledge, attitudes, technical competence, and blood glucose control of Type 1 diabetic patients during and after an education programme. Diabetic Medicine. 1990; 7(9):825-832

451 Lepore M, Pampanelli S, Fanelli C, Porcellati F, Bartocci L, Vincenzo AD et al. Pharmacokinetics and pharmacodynamics of subcutaneous injection of long-acting human insulin analog glargine, NPH insulin, and ultralente human insulin and continuous subcutaneous infusion of insulin lispro. Diabetes. 2000; 49(12):2142-2148

452 Levetan C, Want LL, Weyer C, Strobel SA, Crean J, Wang Y et al. Impact of pramlintide on glucose fluctuations and postprandial glucose, glucagon, and triglyceride excursions among patients with type 1 diabetes intensively treated with insulin pumps. Diabetes Care. 2003; 26(1):1-8

453 Levetan CS, Salas JR, Wilets IF, Zumoff B. Impact of endocrine and diabetes team consultation on hospital length of stay for patients with diabetes. American Journal of Medicine. 1995; 99(1):22-28

454 Levitt Katz LE, Jawad AF, Ganesh J, Abraham M, Murphy K, Lipman TH. Fasting c-peptide and insulin-like growth factor-binding protein-1 levels help to distinguish childhood type 1 and type 2 diabetes at diagnosis. Pediatric Diabetes. 2007; 8(2):53-59

455 Levitt NS, Stansberry KB, Wynchank S, Vinik AI. The natural progression of autonomic neuropathy and autonomic function tests in a cohort of people with IDDM. Diabetes Care. 1996; 19(7):751-754

456 Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. New England Journal of Medicine. 1993; 329(20):1456-1462

457 Lewis JB. Microalbuminuria: accuracy or economics. American Journal of Kidney Diseases. 1998; 32(3):524-528

458 Ligtenberg PC, Blans M, Hoekstra JB, van dT, I, Erkelens DW. No effect of long-term physical activity on the glycemic control in type 1 diabetes patients: a cross-sectional study. Netherlands Journal of Medicine. 1999; 55(2):59-63

459 Lin SF, Lin JD, Huang YY. Diabetic ketoacidosis: comparisons of patient characteristics, clinical presentations and outcomes today and 20 years ago. Chang Gung Medical Journal. 2005; 28(1):24-30

460 Lind M, Bounias I, Olsson M, Gudbjornsdottir S, Svensson AM, Rosengren A. Glycaemic control and incidence of heart failure in 20,985 patients with type 1 diabetes: an observational study. Lancet. 2011; 378(9786):140-146

461 Lindholm E, Hallengren B, Agardh CD. Gender differences in GAD antibody-positive diabetes mellitus in relation to age at onset, C-peptide and other endocrine autoimmune diseases. Diabetes/Metabolism Research and Reviews. 2004; 20(2):158-164

462 Little SA, Walkinshaw E, Tan HK, Chapple O, Lubina-Solomon A, Chadwick TJ et al. Recovery of hypoglycemia awareness in long-standing type 1 diabetes: a multicenter 2 x 2 factorial randomized controlled trial comparing insulin pump with multiple daily injections and continuous with conventional glucose self-monitoring (HypoCOMPaSS). Diabetes Care. 2014; 37(8):2114-2122

463 Liu D, McManus RM, Ryan EA. Improved counter-regulatory hormonal and symptomatic responses to hypoglycemia in patients with insulin-dependent diabetes mellitus after 3 months of less strict glycemic control. Clinical and Investigative Medicine. 1996; 19(2):71-82

464 Livingstone SJ, Looker HC, Hothersall EJ, Wild SH, Lindsay RS, Chalmers J et al. Risk of cardiovascular disease and total mortality in adults with type 1 diabetes: Scottish registry linkage study. PLoS Medicine. 2012; 9(10):e1001321

465 Lloyd CE, Wing RR, Orchard TJ, Becker DJ. Psychosocial correlates of glycemic control: the Pittsburgh Epidemiology of Diabetes Complications (EDC) Study. Diabetes Research and Clinical Practice. 1993; 21(2-3):187-195

466 Loveman E, Royle P, Waugh N. Specialist nurses in diabetes mellitus. Cochrane Database of Systematic Reviews. 2003;(2):CD003286

467 Lu H, Hu F, Zeng Y, Zou L, Luo S, Sun Y et al. Ketosis onset type 2 diabetes had better islet beta-cell function and more serious insulin resistance. Journal of Diabetes Research. 2014; 2014:510643

468 Lund SS, Tarnow L, Astrup AS, Hovind P, Jacobsen PK, Alibegovic AC et al. Effect of adjunct metformin treatment in patients with type-1 diabetes and persistent inadequate glycaemic control. A randomized study. PloS One. 2008; 3(10):e3363

469 Lupi I, Raffaelli V, Di CG, Caturegli P, Manetti L, Ciccarone AM et al. Pituitary autoimmunity in patients with diabetes mellitus and other endocrine disorders. Journal of Endocrinological Investigation. 2013; 36(2):127-131

470 Lustman PJ, Anderson RJ, Freedland KE, de Groot M, Carney RM, Clouse RE. Depression and poor glycemic control: a meta-analytic review of the literature. Diabetes Care. 2000; 23(7):934-942

471 Lustman PJ, Clouse RE, Ciechanowski PS, Hirsch IB, Freedland KE. Depression-related hyperglycemia in type 1 diabetes: a mediational approach. Psychosomatic Medicine. 2005; 67(2):195-199

472 Lustman PJ, Freedland KE, Griffith LS, Clouse RE. Fluoxetine for depression in diabetes: a randomized double-blind placebo-controlled trial. Diabetes Care. 2000; 23(5):618-623

473 Lustman PJ, Griffith LS, Clouse RE, Freedland KE, Eisen SA, Rubin EH et al. Effects of alprazolam on glucose regulation in diabetes. Results of double-blind, placebo-controlled trial. Diabetes Care. 1995; 18(8):1133-1139

474 Lustman PJ, Griffith LS, Clouse RE, Freedland KE, Eisen SA, Rubin EH et al. Effects of nortriptyline on depression and glycemic control in diabetes: results of a double-blind, placebo-controlled trial. Psychosomatic Medicine. 1997; 59(3):241-250

475 Maberley D, Walker H, Koushik A, Cruess A. Screening for diabetic retinopathy in James Bay, Ontario: a cost-effectiveness analysis. Canadian Medical Association Journal. 2003; 168(2):160-164

476 MacIsaac RJ, Lee LY, McNeil KJ, Tsalamandris C, Jerums G. Influence of age on the presentation and outcome of acidotic and hyperosmolar diabetic emergencies. Internal Medicine Journal. 2002; 32(8):379-385

477 Mahadeb YP, Gruson D, Buysschaert M, Hermans MP. What are the characteristics of phenotypic type 2 diabetic patients with low-titer GAD65 antibodies? Acta Diabetologica. 2014; 51(1):103-111

478 Maioli M, Pes GM, Delitala G, Puddu L, Falorni A, Tolu F et al. Number of autoantibodies and HLA genotype, more than high titers of glutamic acid decarboxylase autoantibodies, predict insulin dependence in latent autoimmune diabetes of adults. European Journal of Endocrinology. 2010; 163(4):541-549

479 Mallamaci F, Zuccala A, Zoccali C, Testa A, Gaggi R, Spoto B et al. The deletion polymorphism of the angiotensin-converting enzyme is associated with nephroangiosclerosis. American Journal of Hypertension. 2000; 13(4 I):433-437

480 Maran A, Lomas J, Macdonald IA, Amiel SA. Lack of preservation of higher brain function during hypoglycaemia in patients with intensively-treated IDDM. Diabetologia. 1995; 38(12):1412-1418

481 Maraschin JdF, Weinert LS, Murussi N, Witter V, Rodrigues TdC, Rossato ER et al. Influence of age at diagnosis and duration of diabetes on the positivity of glutamic acid decarboxylase antibody in South-Brazilian type 1 diabetes mellitus. Annals of Clinical Biochemistry. 2013; 50(Pt 3):262-266

482 Marrero DG, Crean J, Zhang B, Kellmeyer T, Gloster M, Herrmann K et al. Effect of adjunctive pramlintide treatment on treatment satisfaction in patients with type 1 diabetes. Diabetes Care. 2007; 30(2):210-216

483 Marshall SM, Collins A, Gregory W, Goodwin A, Hill C, Jarrett RJ et al. Predictors of the development of microalbuminuria in patients with type I diabetes mellitus: A seven-year prospective study. Diabetic Medicine. 1999; 16(11):918-925

484 Mathiesen ER, Feldt-Rasmussen B, Hommel E, Deckert T, Parving HH. Stable glomerular filtration rate in normotensive IDDM patients with stable microalbuminuria. A 5-year prospective study. Diabetes Care. 1997; 20(3):286-289

485 Mathieu C, Hollander P, Miranda-Palma B, Cooper J, Franek E, Russell-Jones D et al. Efficacy and safety of insulin degludec in a flexible dosing regimen vs insulin glargine in patients with type 1 diabetes (BEGIN: Flex T1): a 26-week randomized, treat-to-target trial with a 26-week extension. Journal of Clinical Endocrinology and Metabolism. 2013; 98(3):1154-1162

486 Matteucci E, Cinapri V, Quilici S, Lucchetti A, Mugnaini P, Giampietro O. Screening for coeliac disease in families of adults with Type 1 diabetes based on serological markers. Diabetes, Nutrition and Metabolism - Clinical and Experimental. 2001; 14(1):37-42

487 Maurizi AR, Lauria A, Maggi D, Palermo A, Fioriti E, Manfrini S et al. A novel insulin unit calculator for the management of type 1 diabetes. Diabetes Technology and Therapeutics. 2011; 13(4):425-428

488 Maxwell AE, Hunt IF, Bush MA. Effects of a social support group, as an adjunct to diabetes training, on metabolic control and psychosocial outcomes. Diabetes Educator. 1992; 18(4):303-309

489 McAlister FA, Zarnke KB, Campbell NRC, Feldman RD, Levine M, Mahon J et al. The 2001 Canadian recommendations for the management of hypertension: Part two - Therapy. Canadian Journal of Cardiology. 2002; 18(6):625-641

490 Mccallum RW, Ricci DA, Rakatansky H, Behar J, Rhodes JB, Salen G et al. A multicenter placebo-controlled clinical trial of oral metoclopramide in diabetic gastroparesis. Diabetes Care. 1983; 6(5):463-467

491 Mccallum RW, Snape W, Brody F, Wo J, Parkman HP, Nowak T. Gastric electrical stimulation with Enterra therapy improves symptoms from diabetic gastroparesis in a prospective study. Clinical Gastroenterology and Hepatology. 2010; 8(11):947-954

492 McCavert M, Mone F, Dooher M, Brown R, O'Donnell ME. Peri-operative blood glucose management in general surgery - a potential element for improved diabetic patient outcomes - an observational cohort study. International Journal of Surgery. 2010; 8(6):494-498

493 McClean MT, Andrews WJ, McElnay JC. Characteristics associated with neuropathy and/or retinopathy in a hospital outpatient diabetic clinic. Pharmacy World and Science. 2005; 27(3):154-158

494 McCulloch DK. Impact of endocrine and diabetes team consultation on hospital length of stay for patients with diabetes... [commentary on Levetan CS, Salas R, Wiltes IF et al. Am.J.Med. 99:22-8, 1995]. Diabetes Spectrum. 1996; 9(3):180-181

495 McCulloch DK, Mitchell RD, Ambler J, Tattersall RB. A prospective comparison of 'conventional' and high carbohydrate/high fibre/low fat diets in adults with established type 1 (insulin-dependent) diabetes. Diabetologia. 1985; 28(4):208-212

496 McDonald TJ, Colclough K, Brown R, Shields B, Shepherd M, Bingley P et al. Islet autoantibodies can discriminate maturity-onset diabetes of the young (MODY) from Type 1 diabetes. Diabetic Medicine. 2011; 28(9):1028-1033

497 McEwan P, Poole CD, Tetlow T, Holmes P, Currie CJ. Evaluation of the cost-effectiveness of insulin glargine versus NPH insulin for the treatment of type 1 diabetes in the UK. Current Medical Research and Opinion. 2007; 23(Suppl.1):S7-S19

498 McGill M, Constantino M, Yue DK. Integrating telemedicine into a National Diabetes Footcare Network. Practical Diabetes International. 2000; 17(7):235-238

499 McHardy KC, Gann ME, Ross IS, Pearson DW. A simple approach to screening for microalbuminuria in a type 1 (insulin-dependent) diabetic population. Annals of Clinical Biochemistry. 1991; 28(Pt 5):450-455

500 Mckay M, Compion G, Lytzen L. A comparison of insulin injection needles on patients' perceptions of pain, handling, and acceptability: a randomized, open-label, crossover study in subjects with diabetes. Diabetes Technology and Therapeutics. 2009; 11(3):195-201

501 McQueen RB, Ellis SL, Campbell JD, Nair K, V, Sullivan PW. Cost-effectiveness of continuous glucose monitoring and intensive insulin therapy for type 1 diabetes. Cost Effectiveness and Resource Allocation. 2011; 9:13-21

502 Medicines and Healthcare products Regulatory Agency, Commission on Human Medicines. Aspirin: not licensed for primary prevention of thrombotic vascular disease. Drug Safety Update. 2014; 3(3):10

503 Merimee TJ, Gardner DF, Zapf J, Froesch ER. Effect of glycemic control on serum insulin-like growth factors in diabetes mellitus. Diabetes. 1984; 33(8):790-793

504 Meyer C, Hering BJ, Grossmann R, Brandhorst H, Brandhorst D, Gerich J et al. Improved glucose counterregulation and autonomic symptoms after intraportal islet transplants alone in patients with long-standing type I diabetes mellitus. Transplantation. 1998; 66(2):233-240

505 Meyer L, Bohme P, Delbachian I, Lehert P, Cugnardey N, Drouin P et al. The benefits of metformin therapy during continuous subcutaneous insulin infusion treatment of type 1 diabetic patients. Diabetes Care. 2002; 25(12):2153-2158

506 Miller KM, Beck RW, Bergenstal RM, Goland RS, Haller MJ, McGill JB et al. Evidence of a strong association between the frequency of selfmonitoring of blood glucose and haemoglobin A1c levels in type 1 diabetes exchange participants. Diabetes Care. 2013; 36(7):2009-2014

507 Minder AE, Albrecht D, Schafer J, Zulewski H. Frequency of blood glucose testing in well educated patients with diabetes mellitus type 1: How often is enough? Diabetes Research and Clinical Practice. 2013; 101(1):57-61

508 Miwa T, Itoh R, Kobayashi T, Tanabe T, Shikuma J, Takahashi T et al. Comparison of the effects of a new 32-Gaugex4-mm pen needle and a 32-Gaugex6-mm pen needle on glycemic control, safety, and patient ratings in japanese adults with diabetes. Diabetes Technology and Therapeutics. 2012; 14(12):1084-1090

509 Miyakoshi M, Kamoi K, Iwanaga M, Hoshiyama A, Yamada A. Comparison of patient's preference, pain perception, and usability between Micro Fine Plus 31-gauge needle and Microtapered NanoPass 33-gauge needle for insulin therapy. Journal of Diabetes Science and Technology. 2007; 1(5):718-724

510 Moheet A, Kumar A, Chow L, Eberly LE, Seaquist ER. History of severe hypoglycemia and score on clarke questionnaire is associated with blunted counterregulatory response to experimental hypoglycemia in patients with type 1 diabetes. Diabetes. 2012; 61(Suppl.1):A99

511 Mok PH, Cheng MW. Outcomes and perceptions of 4mm pen needle use in diabetes patients: Results from a multi-center survey pilot study in Hong Kong. Value in Health: the Journal of the International Society for Pharmacoeconomics and Outcomes Research. 2012; 15(7):A664

512 Monge L, Bruno G, Pinach S, Grassi G, Maghenzani G, Dani F et al. A clinically orientated approach increases the efficiency of screening for latent autoimmune diabetes in adults (LADA) in a large clinic-based cohort of patients with diabetes onset over 50 years. Diabetic Medicine. 2004; 21(5):456-459

513 Morris DB. A rural diabetes support group. Diabetes Educator. 1998; 24(4):493-497

514 Morris LR, Murphy MB, Kitabchi AE. Bicarbonate therapy in severe diabetic ketoacidosis. Annals of Internal Medicine. 1986; 105(6):836-840

515 Moss SE, Klein R, Klein BE. The 14-year incidence of lower-extremity amputations in a diabetic population. The Wisconsin Epidemiologic Study of Diabetic Retinopathy. Diabetes Care. 1999; 22(6):951-959

516 Moss SE, Klein R, Klein BE, Meuer SM. The association of glycemia and cause-specific mortality in a diabetic population. Archives of Internal Medicine. 1994; 154(21):2473-2479

517 Mota MC, Leite E, Ruas MA, Verjans HL, Blakemore CB, Cunha-Vaz JG. Effect of cyclospasmol on early diabetic retinopathy. International Ophthalmology. 1987; 10(1):3-9

518 Muhlhauser I, Overmann H, Bender R, Bott U, Berger M. Risk factors of severe hypoglycaemia in adult patients with Type I diabetes--a prospective population based study. Diabetologia. 1998; 41(11):1274-1282

519 Murao S, Kondo S, Ohashi J, Fujii Y, Shimizu I, Fujiyama M et al. Anti-thyroid peroxidase antibody, IA-2 antibody, and fasting C-peptide levels predict beta cell failure in patients with latent autoimmune diabetes in adults (LADA)--a 5-year follow-up of the Ehime study. Diabetes Research and Clinical Practice. 2008; 80(1):114-121

520 Nagai Y, Ohshige T, Arai K, Kobayashi H, Sada Y, Ohmori S et al. Comparison between shorter straight and thinner microtapered insulin injection needles. Diabetes Technology and Therapeutics. 2013; 15(7):550-555

521 Nathan DM, Cleary PA, Backlund JY, Genuth SM, Lachin JM, Orchard TJ et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. New England Journal of Medicine. 2005; 353(25):2643-2653

522 Nathan DM, McKitrick C, Larkin M, Schaffran R, Singer DE. Glycemic control in diabetes mellitus: have changes in therapy made a difference? American Journal of Medicine. 1996; 100(2):157-163

523 Nathan DM, DCCT/EDIC Research Group. The diabetes control and complications trial/epidemiology of diabetes interventions and complications study at 30 years: overview. Diabetes Care. 2014; 37(1):9-16

524 Nathan DM, McGee P, Steffes MW, Lachin JM, DCCT/EDIC Research Group. Relationship of glycated albumin to blood glucose and HbA1c values and to retinopathy, nephropathy, and cardiovascular outcomes in the DCCT/EDIC study. Diabetes. 2014; 63(1):282-290

525 National Collaborating Centre for Women's and Children's Health. Diabetes in pregnancy: management of diabetes and its complications from preconception to the postnatal period. NICE clinical guideline 63. London. RCOG Press, 2008. Available from: http://guidance.nice.org.uk/CG63

526 National Institute for Health and Care Excellence. Neuropathic pain - pharmacological management: the pharmacological management of neuropathic pain in adults in non-specialist settings. NICE clinical guideline 173. London. National Institute for Health and Care Excellence, 2013. Available from: http://guidance.nice.org.uk/CG173

527 National Institute for Health and Clinical Excellence. Diabetes type 1 and 2: the clinical effectiveness and cost effectiveness of long acting insulin analogues for diabetes. NICE technology appraisal guidance 53. London. National Institute for Health and Clinical Excellence, 2002. Available from: http://www.nice.org.uk/TA053

528 National Institute for Health and Clinical Excellence. The clinical effectiveness and cost effectiveness of patient education models for diabetes. NICE technology appraisal guidance 60. London. National Institute for Health and Clinical Excellence, 2003. Available from: http://guidance.nice.org.uk/TA60

529 National Institute for Health and Clinical Excellence. Diagnosis and management of type 1 diabetes in children, young people and adults. London. NICE, 2004. Available from: http://guidance.nice.org.uk/CG15

530 National Institute for Health and Clinical Excellence. Costing report. Nutrition support in adults: oral nutrition support, enteral tube feeding and parenteral nutrition. NICE clinical guideline 32. London. National Institute for Health and Clinical Excellence, 2006

531 National Institute for Health and Clinical Excellence. Allogeneic pancreatic islet cell transplantation for type 1 diabetes mellitus. NICE interventional procedure guidance 257. London. National Institute for Health and Clinical Excellence (NICE), 2008. Available from: http://www.nice.org.uk/IPG257

532 National Institute for Health and Clinical Excellence. Allogeneic pancreatic islet cell transplantation for type 1 diabetes mellitus. NICE interventional procedure guidance 257. London. National Institute for Health and Clinical Excellence (NICE), 2008. Available from: http://www.nice.org.uk/IPG257

533 National Institute for Health and Clinical Excellence. Diabetes in adults. NICE quality standard 6. 2011. Available from: http://guidance.nice.org.uk/QS6 [Last accessed: 8 October 2014]

534 National Institute for Health and Clinical Excellence. Management of hyperglycaemia in people with acute coronary syndromes. NICE clinical guideline 130. London. National Institute for Health and Clinical Excellence, 2011. Available from: http://guidance.nice.org.uk/CG130

535 National Institute for Health and Clinical Excellence. The guidelines manual. London: National Institute for Health and Clinical Excellence; 2012. Available from: http://publications.nice.org.uk/the-guidelines-manual-pmg6/

536 National Institute for Health and Clinical Excellence. Guide to the methods of technology appraisal 2013. 2nd edition. London: National Institute for Health and Clinical Excellence; 2013. Available from: http://publications.nice.org.uk/pmg9

537 National Patient Safety Agency. The adult patient's passport to safer use of insulin. 2011. Available from: http://www.nrls.npsa.nhs.uk/resources/?EntryId45=130397 [Last accessed: 11 September 2014]

538 Nayak AU, Holland MR, Viswanath AK, Singh BM. HbA1c may not accurately reflect glycaemia in diabetes-examina tion of the relationship between HbA1c and self blood glucose monitoring independent of glycation gap. Diabetes. 2011; 60(Suppl.1):A245

539 Newman SP, Cooke D, Casbard A, Walker S, Meredith S, Nunn A et al. A randomised controlled trial to compare minimally invasive glucose monitoring devices with conventional monitoring in the management of insulin-treated diabetes mellitus (MITRE). Health Technology Assessment. 2009; 13(28):1-194

540 NHS Business Services Authority. NHS Electronic Drug Tariff: December 2013. 2013. Available from: http://www.ppa.org.uk/edt/December_2013/mindex.htm [Last accessed: 12 December 2013]

541 NHS Business Services Authority. NHS Electronic Drug Tariff: November 2014. 2014. Available from: http://www.ppa.org.uk/edt/November_2014/mindex.htm [Last accessed: 27 November 2014]

542 NHS Centre for Reviews and Dissemination. Aspirin for the secondary prophylaxis of vascular disease in primary care. University of Newcastle upon Tyne, Centre for Health Services Research; York: University of York, Centre for Health Economics., 1998. Available from: http://www.ncl.ac.uk/chsr/publications/guide/aspirin.pdf

543 NHS Diabetes and Royal College of General Practitioners. Coding, classification and diagnosis of diabetes: A review of the coding, classification and diagnosis of diabetes in primary care in England with recommendations for improvement. London. Department of Health, 2011

544 NHS England. UK Islet cell transplantation service specifications (contract A17/S(NHSS)c. NHS England, 2013. Available from: http://www.england.nhs.uk/wp-content/uploads/2013/06/a17-islet-trans-serv-ad.pdf

545 NICE. Management of type 2 diabetes: Retinopathy - screening and early management. London. NICE, 2002. Available from: http://www.wales.nhs.uk/sites3/documents/334/diabetesretinopathyguideline.pdf

546 Nicholson WK, Robinson KA, Smallridge RC, Ladenson PW, Powe NR. Prevalence of postpartum thyroid dysfunction: a quantitative review. Thyroid. 2006; 16(6):573-582

547 Nielsen FS, Jorgensen LN, Ipsen M, Voldsgaard AI, Parving HH. Long-term comparison of human insulin analogue B10Asp and soluble human insulin in IDDM patients on a basal/bolus insulin regimen. Diabetologia. 1995; 38(5):592-598

548 Nielsen JK, Gravholt CH, Djurhuus CB, Brandt D, Becker J, Heinemann L et al. Continuous subcutaneous glucose monitoring shows a close correlation between mean glucose and time spent in hyperglycemia and hemoglobin A1c. Journal of Diabetes Science and Technology. 2007; 1(6):857-863

549 Nielsen S. Eating disorders in females with type 1 diabetes: An update of a meta-analysis. European Eating Disorders Review. 2002; 10(4):241-254

550 Nordwall M, Arnqvist HJ, Bojestig M, Ludvigsson J. Good glycemic control remains crucial in prevention of late diabetic complications--the Linkoping Diabetes Complications Study. Pediatric Diabetes. 2009; 10(3):168-176

551 Nuffield Trust. Sharing,Stories: a feasibility study of facilitated small group learning by the oral tradition in diabetes education for British Bangladesh's in Tower Hamlets., 2000

552 Nyholm B, Orskov L, Hove KY, Gravholt CH, Møller N, Alberti KG et al. The amylin analog pramlintide improves glycemic control and reduces postprandial glucagon concentrations in patients with type 1 diabetes mellitus. Metabolism: Clinical and Experimental. 1999; 48(7):935-941

553 O'Connell MA, Donath S, O'Neal DN, Colman PG, Ambler GR, Jones TW et al. Glycaemic impact of patient-led use of sensor-guided pump therapy in type 1 diabetes: a randomised controlled trial. Diabetologia. 2009; 52(7):1250-1257

554 Olausson EA, Alpsten M, Larsson A, Mattsson H, Andersson H, Attvall S. Small particle size of a solid meal increases gastric emptying and late postprandial glycaemic response in diabetic subjects with gastroparesis. Diabetes Research and Clinical Practice. 2008; 80(2):231-237

555 Olausson EA, Storsrud S, Grundin H, Isaksson M, Attvall S, Simren M. A small particle size diet reduces upper gastrointestinal symptoms in patients with diabetic gastroparesis: a randomized controlled trial. American Journal of Gastroenterology. 2014; 109(3):375-385

556 Olson JC, Erbey JR, Forrest KY, Williams K, Becker DJ, Orchard TJ. Glycemia (or, in women, estimated glucose disposal rate) predict lower extremity arterial disease events in type 1 diabetes. Metabolism: Clinical and Experimental. 2002; 51(2):248-254

557 Orchard TJ, Olson JC, Erbey JR, Williams K, Forrest KY, Smithline KL et al. Insulin resistance-related factors, but not glycemia, predict coronary artery disease in type 1 diabetes: 10-year follow-up data from the Pittsburgh Epidemiology of Diabetes Complications Study. Diabetes Care. 2003; 26(5):1374-1379

558 Organisation for Economic Co-operation and Development (OECD). Purchasing power parities (PPP). 2011. Available from: http://www.oecd.org/std/ppp [Last accessed: 16 October 2014]

559 Organisation for Economic Co-operation and Development (OECD). Purchasing power parities (PPP). 2012. Available from: http://www.oecd.org/std/ppp [Last accessed: 17 October 2014]

560 Ostwald SK, Hepburn KW, Caron W, Burns T. Reducing caregiver burden: a randomised psychoeducational intervention for caregivers of persons with dementia. Gerontologist. 1999; 39(3):299-309

561 Ota T, Takamura T, Nagai Y, Bando Y, Usuda R. Significance of IA-2 antibody in Japanese type 1 diabetes: its association with GAD antibody. Diabetes Research and Clinical Practice. 2005; 67(1):63-69

562 Pagani A, Greco G, Tagliaferro V, Marena S, Pagano G. Dipyridamole administration in insulin-dependent diabetics with background retinopathy: A 36-month follow-up. Current Therapeutic Research, Clinical & Experimental. 1989; 45(3):469-475

563 Palma CCSS, Pavesi M, Nogueira VG, Clemente ELS, Vasconcellos MDFB, Pereira LC et al. Prevalence of thyroid dysfunction in patients with diabetes mellitus. Diabetology and Metabolic Syndrome. 2013; 5(1)

564 Palmer AJ, Roze S, Valentine WJ, Minshall ME, Foos V, Lurati FM et al. The CORE Diabetes Model: projecting long-term clinical outcomes, costs and cost-effectiveness of interventions in diabetes mellitus (types 1 and 2) to support clinical and reimbursement decision-making. Current Medical Research and Opinion. 2004; 20(S1):S5-S26

565 Palmer AJ, Roze S, Valentine WJ, Smith I, Wittrup-Jensen KU. Cost-effectiveness of detemir-based basal/bolus therapy versus NPH-based basal/bolus therapy for Type 1 diabetes in a UK setting: an economic analysis based on meta-analysis results of four clinical trials. Current Medical Research and Opinion. 2004; 20(11):1729-1746

566 Palmer AJ, Sendi PP, Spinas GA. Applying some UK Prospective Diabetes Study results to Switzerland: the cost-effectiveness of intensive glycaemic control with metformin versus conventional control in overweight patients with type-2 diabetes. Schweizerische Medizinische Wochenscrift. 2000; 130(27-28):1034-1040

567 Palmer AJ, Valentine WJ, Ray JA, Foos V, Lurati F, Smith I et al. An economic assessment of analogue basal–bolus insulin versus human basal–bolus insulin in subjects with type 1 diabetes in the UK. Current Medical Research and Opinion. 2007; 23(4):895-901

568 Palmer AJ, Weiss C, Sendi PP, Neeser K, Brandt A, Singh G et al. The cost-effectiveness of different management strategies for type I diabetes: a Swiss perspective. Diabetologia. 2000; 43(1):13-26

569 Pandit RJ, Taylor R. Quality assurance in screening for sight-threatening diabetic retinopathy. Diabetic Medicine. 2002; 19(4):285-291

570 Paschke A, Grzelka A, Zawada A, Zozulinska-Ziolkiewicz D. Clinical characteristics and autoantibody pattern in newly diagnosed adult-onset autoimmune diabetes. Polskie Archiwum Medycyny Wewnetrznej. 2013; 123(7-8):401-408

571 Patrick AW, Collier A, Hepburn DA, Steedman DJ, Clarke BF, Robertson C. Comparison of intramuscular glucagon and intravenous dextrose in the treatment of hypoglycaemic coma in an accident and emergency department. Archives of Emergency Medicine. 1990; 7(2):73-77

572 Patterson D. A multicenter placebo-controlled study of dompiderone in diabetic gastroparesis. Gastroenterology. 1993; 104(A564)

573 Patterson D, Abell T, Rothstein R, Koch K, Barnett J. A double-blind multicenter comparison of domperidone and metoclopramide in the treatment of diabetic patients with symptoms of gastroparesis. American Journal of Gastroenterology. 1999; 94(5):1230-1234

574 Pedersen-Bjergaard U, Pramming S, Thorsteinsson B. Recall of severe hypoglycaemia and self-estimated state of awareness in type 1 diabetes. Diabetes/Metabolism Research and Reviews. 2003; 19(3):232-240

575 Pegoraro A, Singh A, Bakir AA, Arruda JA, Dunea G. Simplified screening for microalbuminuria. Annals of Internal Medicine. 1997; 127(9):817-819

576 Perez Mendez LF, Alvarez-Garcia E, Alvarez-Vazquez P, Hervas E, Casteras A, Fajar L et al. Long-term improvement of metabolic control without increased risk of hypoglycaemia by intensive insulin regimens in type 1 diabetes patients treated in a regular clinical setting. Experimental and Clinical Endocrinology & Diabetes. 2007; 115(3):182-186

577 Perros P, McCrimmon RJ, Shaw G, Frier BM. Frequency of thyroid dysfunction in diabetic patients: value of annual screening. Diabetic Medicine. 1995; 12(7):622-627

578 Perry TL, Mann JI, Lewis-Barned NJ, Duncan AW, Waldron MA, Thompson C. Lifestyle intervention in people with insulin-dependent diabetes mellitus (IDDM). European Journal of Clinical Nutrition. 1997; 51:757-763

579 Pfohl M, Schadlich PK, Dippel FW, Koltermann KC. Health economic evaluation of insulin glargine vs NPH insulin in intensified conventional therapy for type 1 diabetes in Germany. Journal of Medical Economics. 2012; 15(Suppl.2):14-27

580 Pfutzner A, Kustner E, Forst T, Schulze-Schleppinghoff B, Trautmann ME, Haslbeck M et al. Intensive insulin therapy with insulin lispro in patients with type 1 diabetes reduces the frequency of hypoglycemic episodes. Experimental and Clinical Endocrinology. 1996; 104(1):25-30

581 Pickup JC, Freeman SC, Sutton AJ. Glycaemic control in type 1 diabetes during real time continuous glucose monitoring compared with self monitoring of blood glucose: meta-analysis of randomised controlled trials using individual patient data. BMJ. 2011; 343:d3805

582 Pieber TR, Draeger E, Kristensen A, Grill V. Comparison of three multiple injection regimens for Type 1 diabetes: morning plus dinner or bedtime administration of insulin detemir vs. morning plus bedtime NPH insulin. Diabetic Medicine. 2005; 22(7):850-857

583 Pieber TR, Eugene-Jolchine I, Derobert E. Efficacy and safety of HOE 901 versus NPH insulin in patients with type 1 diabetes. The European Study Group of HOE 901 in type 1 diabetes. Diabetes Care. 2000; 23(2):157-162

584 Piehlmeier W, Renner R, Kimmerling T, Schramm W, Garbe S, Proetzsch R et al. Evaluation of the Micral-Test S, a qualitative immunologic patient self-test for microalbuminuria: the PROSIT project. Proteinuria Screening and Intervention. Diabetic Medicine. 1998; 15(10):883-885

585 Pignone MP, Phillips CJ, Atkins D, Teutsch SM, Mulrow CD, Lohr KN. Screening and treating adults for lipid disorders. American Journal of Preventive Medicine. 2001; 20(3:Suppl):Suppl-89

586 Piters KM, Kumar D, Pei E, Bessman AN. Comparison of continuous and intermittent intravenous insulin therapies for diabetic ketoacidosis. Diabetologia. 1977; 13(4):317-321

587 Pitocco D, Zaccardi F, Tarzia P, Milo M, Scavone G, Rizzo P et al. Metformin improves endothelial function in type 1 diabetic subjects: a pilot, placebo-controlled randomized study. Diabetes Obesity and Metabolism. 2013; 15(5):427-431

588 Piwernetz K, Renner R, Mohrlein A, Steiner M, Hepp KD, Engelbrecht R et al. Analysis and processing of data in a hospital-based diabetes management system. Hormone and Metabolic Research Supplement Series. 1990; 24:109-115

589 Plank J, Bodenlenz M, Sinner F, Magnes C, Gorzer E, Regittnig W et al. A double-blind, randomized, dose-response study investigating the pharmacodynamic and pharmacokinetic properties of the long-acting insulin analog detemir. Diabetes Care. 2005; 28(5):1107-1112

590 Poggioli R, Faradji RN, Ponte G, Betancourt A, Messinger S, Baidal DA et al. Quality of life after islet transplantation. American Journal of Transplantation. 2006; 6(2):371-378

591 Polak BC, Crijns H, Casparie AF, Niessen LW. Cost-effectiveness of glycemic control and ophthalmological care in diabetic retinopathy. Health Policy. 2003; 64(1):89-97

592 Poppe AY, Vautour L, Yale J-F, Wing SS. Evaluation of a protocol for the perioperative administration of intravenous insulin in patients with diabetes. Canadian Journal of Diabetes. 2004; 28(2):134-141

593 Porcellati F, Rossetti P, Pampanelli S, Fanelli CG, Torlone E, Scionti L et al. Better long-term glycaemic control with the basal insulin glargine as compared with NPH in patients with Type 1 diabetes mellitus given meal-time lispro insulin. Diabetic Medicine. 2004; 21(11):1213-1220

594 Pratoomsoot C, Smith HT, Kalsekar A, Boye KS, Arellano J, Valentine WJ. An estimation of the long-term clinical and economic benefits of insulin lispro in type 1 diabetes in the UK. Diabetic Medicine. 2009; 26(8):803-814

595 Prazny M, Skrha J, Limanova Z, Hilgertova J. The evaluation of thyroid and islet autoantibodies in type 1 diabetes mellitus. Sbornik Lekarsky. 1999; 100(3):205-211

596 Preiser JC, Devos P, Ruiz-Santana S, Melot C, Annane D, Groeneveld J et al. A prospective randomised multi-centre controlled trial on tight glucose control by intensive insulin therapy in adult intensive care units: the Glucontrol study. Intensive Care Medicine. 2009; 35(10):1738-1748

597 Raccah D, Sulmont V, Reznik Y, Guerci B, Renard E, Hanaire H et al. Incremental value of continuous glucose monitoring when starting pump therapy in patients with poorly controlled type 1 diabetes: the RealTrend study. Diabetes Care. 2009; 32(12):2245-2250

598 Radermecker RP, Saint Remy A, Scheen AJ, Bringer J, Renard E. Continuous glucose monitoring reduces both hypoglycaemia and HbA1c in hypoglycaemia-prone type 1 diabetic patients treated with a portable pump. Diabetes & Metabolism. 2010; 36(5):409-413

599 Radtke MA, Midthjell K, Nilsen TIL, Grill V. Heterogeneity of patients with latent autoimmune diabetes in adults: linkage to autoimmunity is apparent only in those with perceived need for insulin treatment: results from the Nord-Trondelag Health (HUNT) study. Diabetes Care. 2009; 32(2):245-250

600 Rajalakshmi R, Amutha A, Ranjani H, Ali MK, Unnikrishnan R, Anjana RM et al. Prevalence and risk factors for diabetic retinopathy in Asian Indians with young onset type 1 and type 2 diabetes. Journal of Diabetes and Its Complications. 2014; 28(3):291-297

601 Ramsay L, Williams B, Johnston G, MacGregor G, Poston L, Potter J et al. Guidelines for management of hypertension: report of the third working party of the British Hypertension Society. J Hum Hypertens. 1999; 13(9):569-592

602 Rankin D, Elliott J, Heller S, Amiel S, Rogers H, DeZoysa N et al. Experiences of hypoglycaemia unawareness amongst people with Type 1 diabetes: A qualitative investigation. Chronic Illness. 2013; 10(3):180-191

603 Rapid Reviews Team SHc. Patient education models for diabetes. Southampton. NICE, 2002. Available from: http://www.nice.org.uk/guidance/ta60/resources/assessment-report-patient-education-models-for-diabetes-2

604 Raskin P, Ganda OP, Schwartz S, Willard D, Rosenstock J, Lodewick PA et al. Efficacy and safety of pravastatin in the treatment of patients with type I or type II diabetes mellitus and hypercholesterolemia. American Journal of Medicine. 1995; 99(4):362-369

605 Raskin P, Guthrie RA, Leiter L, Riis A, Jovanovic L. Use of insulin aspart, a fast-acting insulin analog, as the mealtime insulin in the management of patients with type 1 diabetes. Diabetes Care. 2000; 23(5):583-588

606 Raskin P, Klaff L, Bergenstal R, Halle J-P, Donley D, Mecca T. A 16-week comparison of the novel insulin analog insulin glargine (HOE 901) and NPH human insulin used with insulin lispro in patients with type 1 diabetes. Diabetes Care. 2000; 23(11):1666-1671

607 Ratner RE, Dickey R, Fineman M, Maggs DG, Shen L, Strobel SA et al. Amylin replacement with pramlintide as an adjunct to insulin therapy improves long-term glycaemic and weight control in Type 1 diabetes mellitus: a 1-year, randomized controlled trial. Diabetic Medicine. 2004; 21(11):1204-1212

608 Ratner RE, Hirsch IB, Neifing JL, Garg SK, Mecca TE, Wilson CA. Less hypoglycemia with insulin glargine in intensive insulin therapy for type 1 diabetes. U.S. Study Group of Insulin Glargine in Type 1 Diabetes. Diabetes Care. 2000; 23(5):639-643

609 Rattarasarn C, Diosdado MA, Ortego J, Leelawattana R, Soonthornpun S, Setasuban W et al. Thyroid autoantibodies in Thai type 1 diabetic patients: clinical significance and their relationship with glutamic acid decarboxylase antibodies. Diabetes Research and Clinical Practice. 2000; 49(2-3):107-111

610 Ray T, Choudhary P, Mansell P, Heller S, Amiel SA, Hopkins D. Dose adjustment for normal eating (DAFNE) structured education reduces progression to continuous subcutaneous insulin infusion (CSII) among patients being considered for insulin pump therapy at enrolment. Diabetic Medicine. 2013; 30(Suppl.1):7-8

611 Reichard P. Are there any glycemic thresholds for the serious microvascular diabetic complications? Journal of Diabetes and Its Complications. 1995; 9(1):25-30

612 Reichard P, Nilsson BY, Rosenqvist U. The effect of long-term intensified insulin treatment on the development of microvascular complications of diabetes mellitus. New England Journal of Medicine. 1993; 329(5):304-309

613 Reichard P, Pihl M, Rosenqvist U, Sule J. Complications in IDDM are caused by elevated blood glucose level: the Stockholm Diabetes Intervention Study (SDIS) at 10-year follow up. Diabetologia. 1996; 39(12):1483-1488

614 Renard E, Dubois-Laforgue D, Guerci B. Non-inferiority of insulin glargine versus insulin detemir on blood glucose variability in type 1 diabetes patients: A multicenter, randomized, crossover study. Diabetes Technology and Therapeutics. 2011; 13(12):1213-1218

615 Rendell MS, Rajfer J, Wicker PA, Smith MD. Sildenafil for treatment of erectile dysfunction in men with diabetes: a randomized controlled trial. Sildenafil Diabetes Study Group. JAMA. 1999; 281(5):421-426

616 Reviriego J, Gomis R, Maranes JP, Ricart W, Hudson P. Cost of severe hypoglycaemia in patients with type 1 diabetes in Spain and the cost-effectiveness of insulin lispro compared with regular human insulin in preventing severe hypoglycaemia. International Journal of Clinical Practice. 2008; 62(7):1026-1032

617 Riazi A, Hammersley S, Eiser C, Eiser JR, Tooke JE. Patients' experiences of the diabetes annual review. Practical Diabetes International. 2000; 17(7):226-230

618 Ricci DA, Saltzman MB, Meyer C, Callachan C, Mccallum RW. Effect of metoclopramide in diabetic gastroparesis. Journal of Clinical Gastroenterology. 1985; 7(1):25-32

619 Roach P, Bai S, Charbonnel B, Consoli A, Taboga C, Tiengo A et al. Effects of multiple daily injection therapy with Humalog mixtures versus separately injected insulin lispro and NPH insulin in adults with type I diabetes mellitus. Clinical Therapeutics. 2004; 26(4):502-510

620 Roach P, Strack T, Arora V, Zhao Z. Improved glycaemic control with the use of self-prepared mixtures of insulin lispro and insulin lispro protamine suspension in patients with types 1 and 2 diabetes. International Journal of Clinical Practice. 2001; 55(3):177-182

621 Roach P, Trautmann M, Arora V, Sun B, Anderson JH, Jr. Improved postprandial blood glucose control and reduced nocturnal hypoglycemia during treatment with two novel insulin lispro-protamine formulations, insulin lispro mix25 and insulin lispro mix50. Mix50 Study Group. Clinical Therapeutics. 1999; 21(3):523-534

622 Rodby RA, Firth LM, Lewis EJ. An economic analysis of captopril in the treatment of diabetic nephropathy. The Collaborative Study Group. Diabetes Care. 1996; 19(10):1051-1061

623 Rodin G, Olmsted MP, Rydall AC, Maharaj SI, Colton PA, Jones JM et al. Eating disorders in young women with type 1 diabetes mellitus. Journal of Psychosomatic Research. 2002; 53(4):943-949

624 Roffi M, Chew DP, Mukherjee D, Bhatt DL, White JA, Heeschen C et al. Platelet glycoprotein IIb/IIIa inhibitors reduce mortality in diabetic patients with non-ST-segment-elevation acute coronary syndromes. Circulation. 2001; 23:2767-2771

625 Rogers HA, de ZN, Amiel SA. Patient experience of hypoglycaemia unawareness in Type 1 diabetes: are patients appropriately concerned? Diabetic Medicine. 2012; 29(3):321-327

626 Rogowicz-Frontczak A, Zozulilska-Ziolkiewicz D, Litwinowicz M, Niedzwiecki P, Wyka K, Wierusz-Wysocka B. Are zinc transporter type 8 antibodies a marker of autoimmune thyroiditis in non-obese adults with new-onset diabetes? European Journal of Endocrinology. 2014; 170(4):651-658

627 Roh MO, Jung CH, Kim BY, Mok JO, Kim CH. The prevalence and characteristics of latent autoimmune diabetes in adults (LADA) and its relation with chronic complications in a clinical department of a university hospital in Korea. Acta Diabetologica. 2013; 50(2):129-134

628 Rosenstock J, Park G, Zimmerman J. Basal insulin glargine (HOE 901) versus NPH insulin in patients with type 1 diabetes on multiple daily insulin regimens. U.S. Insulin Glargine (HOE 901) Type 1 Diabetes Investigator Group. Diabetes Care. 2000; 23(8):1137-1142

629 Rossetti P, Pampanelli S, Fanelli C, Porcellati F, Costa E, Torlone E et al. Intensive replacement of basal insulin in patients with type 1 diabetes given rapid-acting insulin analog at mealtime: a 3-month comparison between administration of NPH insulin four times daily and glargine insulin at dinner or bedtime. Diabetes Care. 2003; 26(5):1490-1496

630 Rossi MC, Nicolucci A, Di Bartolo P, Bruttomesso D, Girelli A, Ampudia FJ et al. Diabetes Interactive Diary: a new telemedicine system enabling flexible diet and insulin therapy while improving quality of life: an open-label, international, multicenter, randomized study. Diabetes Care. 2010; 33(1):109-115

631 Rossi MC, Nicolucci A, Lucisano G, Pellegrini F, Di Bartolo P, Miselli V et al. Impact of the "diabetes interactive diary" telemedicine system on metabolic control, risk of hypoglycemia, and quality of life: a randomized clinical trial in type 1 diabetes. Diabetes Technology and Therapeutics. 2013; 15(8):670-679

632 Rossing P, Hougaard P, Borch-Johnsen K, Parving HH. Predictors of mortality in insulin dependent diabetes: 10 year observational follow up study. BMJ. 1996; 313(7060):779-784

633 Russell-Jones D, Simpson R, Hylleberg B, Draeger E, Bolinder J. Effects of QD insulin detemir or neutral protamine Hagedorn on blood glucose control in patients with type I diabetes mellitus using a basal–bolus regimen. Clinical Therapeutics. 2004; 26(5):724-736

634 Rustemeijer C, Schouten JA, Janssens ENW, Spooren PFM, van Doormaal JJ. Pravastatin in diabetes associated hypercholesterolemia. Acta Diabetologica. 1997; 34(4):294-300

635 Ryan EA, Paty BW, Senior PA, Bigam D, Alfadhli E, Kneteman NM et al. Five-year follow-up after clinical islet transplantation. Diabetes. 2005; 54(7):2060-2069

636 Ryan EA, Shandro T, Green K, Paty BW, Senior PA, Bigam D et al. Assessment of the severity of hypoglycemia and glycemic lability in type 1 diabetic subjects undergoing islet transplantation. Diabetes. 2004; 53(4):955-962

637 Ryan EA, Germsheid J. Use of continuous glucose monitoring system in the management of severe hypoglycemia. Diabetes Technology and Therapeutics. 2009; 11(10):635-639

638 Ryder J, Cavan DA, Ziegler R, Cranston I, Barnard K, Vogel C et al. Use of an automated bolus advisor may improve carbohydrate counting competence in patients treated with multiple daily insulin injection therapy: Results from ABACUS. Diabetologia. 2013; 56:S425

639 Ryder REJ, Dent MT, Ward JD. Testing for diabetic neuropathy, part two: Autonomic neuropathy. Practical Diabetes. 1992; 9(2):56-60

640 Sacks HS, Shahshahani M, Kitabchi AE, Fisher JN, Young RT. Similar responsiveness of diabetic ketoacidosis to low-dose insulin by intramuscular injection and albumin-free infusion. Annals of Internal Medicine. 1979; 90(1):36-42

641 Sadur CN, Moline N, Costa M, Michalik D, Mendlowitz D, Roller S et al. Diabetes management in a health maintenance organization. Efficacy of care management using cluster visits. Diabetes Care. 1999; 22:2011-2017

642 Saenz dT, I, Anglin G, Knight JR, Emmick JT. Effects of tadalafil on erectile dysfunction in men with diabetes. Diabetes Care. 2002; 25(12):2159-2164

643 Safarinejad MR. Oral sildenafil in the treatment of erectile dysfunction in diabetic men: a randomized double-blind and placebo-controlled study. Journal of Diabetes and Its Complications. 2004; 18(4):205-210

644 Samann A, Muhlhauser I, Bender R, Kloos C, Muller UA. Glycaemic control and severe hypoglycaemia following training in flexible, intensive insulin therapy to enable dietary freedom in people with type 1 diabetes: a prospective implementation study. Diabetologia. 2005; 48(10):1965-1970

645 Samsom M, Jebbink RJ, Akkermans LM, Bravenboer B, van Berge-Henegouwen GP, Smout AJ. Effects of oral erythromycin on fasting and postprandial antroduodenal motility in patients with type I diabetes, measured with an ambulatory manometric technique. Diabetes Care. 1997; 20(2):129-134

646 Samsom M, Szarka LA, Camilleri M, Vella A, Zinsmeister AR, Rizza RA. Pramlintide, an amylin analog, selectively delays gastric emptying: potential role of vagal inhibition. American Journal of Physiology, Gastrointestinal and Liver Physiology. 2000; 278(6):G946-G951

647 Sarkar G, Alattar M, Brown RJ, Quon MJ, Harlan DM, Rother KI. Exenatide treatment for 6 months improves insulin sensitivity in adults with type 1 diabetes. Diabetes Care. 2014; 37(3):666-670

648 Sartor G, Katzman P, Eizyk E, Kalen J, Nilsson A, Ugander L et al. Simvastatin treatment of hypercholesterolemia in patients with insulin dependent diabetes mellitus. International Journal of Clinical Pharmacology and Therapeutics. 1995; 33(1):3-6

649 Sategna-Guidetti C, Grosso S, Pulitano R, Benaduce E, Dani F, Carta Q. Celiac disease and insulin-dependent diabetes mellitus. Screening in an adult population. Digestive Diseases and Sciences. 1994; 39(8):1633-1637

650 Savage MW, Dhatariya KK, Kilvert A, Rayman G, Rees JAE, Courtney CH et al. Joint British Diabetes Societies guideline for the management of diabetic ketoacidosis. Diabetic Medicine. 2011; 28(5):508-515

651 Scavone G, Manto A, Pitocco D, Gagliardi L, Caputo S, Mancini L et al. Effect of carbohydrate counting and medical nutritional therapy on glycaemic control in Type 1 diabetic subjects: a pilot study. Diabetic Medicine. 2010; 27(4):477-479

652 Schachinger H, Hegar K, Hermanns N, Straumann M, Keller U, Fehm-Wolfsdorf G et al. Randomized controlled clinical trial of blood glucose awareness training (BGAT III) in Switzerland and Germany. Journal of Behavioral Medicine. 2005; 28(6):587-594

653 Schafer LC, McCaul KD, Glasgow RE. Supportive and nonsupportive family behaviors: relationships to adherence and metabolic control in persons with type I diabetes. Diabetes Care. 1986; 9:179-185

654 Schernthaner G, Wein W, Sandholzer K, Equiluz-Bruck S, Bates PC, Birkett MA. Postprandial insulin lispro. A new therapeutic option for type 1 diabetic patients. Diabetes Care. 1998; 21(4):570-573

655 Schiffrin A, Belmonte M. Multiple daily self-glucose monitoring: its essential role in long-term glucose control in insulin-dependent diabetic patients treated with pump and multiple subcutaneous injections. Diabetes Care. 1982; 5(5):479-484

656 Schmidt S, Meldgaard M, Serifovski N, Storm C, Christensen TM, Gade-Rasmussen B et al. Use of an automated bolus calculator in MDI-treated type 1 diabetes: the BolusCal Study, a randomized controlled pilot study. Diabetes Care. 2012; 35(5):984-990

657 Schneider SH, Khachadurian AK, Amorosa LF, Clemow L, Ruderman NB. Ten-year experience with an exercise-based outpatient life-style modification program in the treatment of diabetes mellitus. Diabetes Care. 1992; 15(11):1800-1810

658 Scholin A, Bjorklund L, Borg H, Arnqvist H, Bjork E, Blohme G et al. Islet antibodies and remaining beta-cell function 8 years after diagnosis of diabetes in young adults: a prospective follow-up of the nationwide Diabetes Incidence Study in Sweden. Journal of Internal Medicine. 2004; 255(3):384-391

659 Scholin A, Nystrom L, Arnqvist H, Bolinder J, Bjork E, Berne C et al. Proinsulin/C-peptide ratio, glucagon and remission in new-onset Type 1 diabetes mellitus in young adults. Diabetic Medicine. 2011; 28(2):156-161

660 Scholin A, Torn C, Nystrom L, Berne C, Arnqvist H, Blohme G et al. Normal weight promotes remission and low number of islet antibodies prolong the duration of remission in Type 1 diabetes. Diabetic Medicine. 2004; 21(5):447-455

661 Scholin A, Siegbahn A, Lind L, Berne C, Sundkvist G, Bjork E et al. CRP and IL-6 concentrations are associated with poor glycemic control despite preserved beta-cell function during the first year after diagnosis of type 1 diabetes. Diabetes/Metabolism Research and Reviews. 2004; 20(3):205-210

662 Schopman JE, Geddes J, Frier BM. Frequency of symptomatic and asymptomatic hypoglycaemia in Type 1 diabetes: effect of impaired awareness of hypoglycaemia. Diabetic Medicine. 2011; 28(3):352-355

663 Schutt M, Kern W, Krause U, Busch P, Dapp A, Grziwotz R et al. Is the frequency of self-monitoring of blood glucose related to long-term metabolic control? Multicenter analysis including 24,500 patients from 191 centers in Germany and Austria. Experimental and Clinical Endocrinology & Diabetes. 2006; 114(7):384-388

664 Schwartz SL, Hanson C, Lucas C, Rosenblatt S, Rosenstock J, Whittier F et al. Double-blind, placebo-controlled study of ramipril in diabetics with mild to moderate hypertension. Clinical Therapeutics. 1993; 15(1):79-87

665 Scottish Intercollegiate Guidelines Network. Lipids and the primary prevention of coronary heart disease. SIGN, 1999. Available from: http://www.nhsggc.org.uk/content/mediaassets/pdf/HSD/sign40.pdf

666 Scottish Intercollegiate Guidelines Network. Hypertension in older people; Treatment of special groups of older people. SIGN, 2001. Available from: http://www.nhsggc.org.uk/content/mediaassets/pdf/HSD/sign49.pdf

667 Scottish Intercollegiate Guidelines Network. Management of diabetes. A national clinical guideline. SIGN Publication No.55. Edinburgh. Scottish Intercollegiate Guidelines Network, 2001

668 Scottish Intercollegiate Guidelines Network. Management of diabetes: a national clinical guideline. Edinburgh. SIGN, 2010. Available from: http://www.sign.ac.uk/pdf/sign116.pdf

669 Seaquist ER, Anderson J, Childs B, Cryer P, Dagogo-Jack S, Fish L et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. Diabetes Care. 2013; 36(5):1384-1395

670 Sequeira PA, Montoya L, Ruelas V, Xing D, Chen V, Beck R et al. Continuous glucose monitoring pilot in low-income type 1 diabetes patients. Diabetes Technology and Therapeutics. 2013; 15(10):855-858

671 Service FJ, O'Brien PC. The relation of glycaemia to the risk of development and progression of retinopathy in the Diabetic Control and Complications Trial. Diabetologia. 2001; 44(10):1215-1220

672 Service FJ, O'Brien PC. Influence of glycemic variables on hemoglobin A1c. Endocrine Practice. 2007; 13(4):350-354

673 Shaban MC, Fosbury J, Kerr D, Cavan DA. The prevalence of depression and anxiety in adults with Type 1 diabetes. Diabetic Medicine. 2006; 23(12):1381-1384

674 Shapiro AM, Ricordi C, Hering BJ, Auchincloss H, Lindblad R, Robertson RP et al. International trial of the Edmonton protocol for islet transplantation. New England Journal of Medicine. 2006; 355(13):1318-1330

675 Shapiro AM, Ricordi C, Hering BJ, Auchincloss H, Lindblad R, Robertson RP et al. International trial of the Edmonton protocol for islet transplantation. New England Journal of Medicine. 2006; 355(13):1318-1330

676 Sharma D, Morrison G, Joseph F, Purewal TS, Weston PJ. The role of continuous subcutaneous insulin infusion therapy in patients with diabetic gastroparesis. Diabetologia. 2011; 54(11):2768-2770

677 Shearer A, Bagust A, Sanderson D, Heller S, Roberts S. Cost-effectiveness of flexible intensive insulin management to enable dietary freedom in people with Type 1 diabetes in the UK. Diabetic Medicine. 2004; 21(5):460-467

678 Shephard MD, Barratt LJ, Simpson-Lyttle W. Is the Bayer DCA 2000 acceptable as a screening instrument for the early detection of renal disease? Annals of Clinical Biochemistry. 1999; 36(Pt 3):393-394

679 Shimizu H, Uehara Y, Okada S, Mori M. Contribution of fasting and postprandial hyperglycemia to hemoglobin A1c in insulin-treated Japanese diabetic patients. Endocrine Journal. 2008; 55(4):753-756

680 Shishikura K, Tanimoto K, Sakai S, Tanimoto Y, Terasaki J, Hanafusa T. Association between skeletal muscle mass and insulin secretion in patients with type 2 diabetes mellitus. Endocrine Journal. 2014; 61(3):281-287

681 Siebenhofer A, Plank J, Berghold A, Jeitler K, Horvath K, Narath M et al. Short acting insulin analogues versus regular human insulin in patients with diabetes mellitus. Cochrane Database of Systematic Reviews. 2006; Issue 2:CD003287. DOI:10.1002/14651858.CD003287.pub4

682 Siegel JE, Krolewski AS, Warram JH, Weinstein MC. Cost-effectiveness of screening and early treatment of nephropathy in patients with insulin-dependent diabetes mellitus. Journal of the American Society of Nephrology. 1992; 3(4 Suppl.):S111-S119

683 Siegmund T, Blankenfeld H, Schumm-Draeger PM. Comparison of usability and patient preference for insulin pen needles produced with different production techniques: "thin-wall" needles compared to "regular-wall" needles: an open-label study. Diabetes Technology and Therapeutics. 2009; 11(8):523-528

684 Silvers D, Kipnes M, Broadstone V, Patterson D, Quigley EMM, Mccallum R et al. Domperidone in the management of symptoms of diabetic gastroparesis: Efficacy, tolerability, and quality-of-life outcomes in a multicenter controlled trial. Clinical Therapeutics. 1998; 20(3):438-453

685 Simmons D, Morton K, Laughton SJ, Scott DJ. A comparison of two intravenous insulin regimens among surgical patients with insulin-dependent diabetes mellitus. Diabetes Educator. 1994; 20(5):422-427

686 Sjoberg K, Eriksson KF, Bredberg A, Wassmuth R, Eriksson S. Screening for coeliac disease in adult insulin-dependent diabetes mellitus. Journal of Internal Medicine. 1998; 243(2):133-140

687 Sjoberg S, Carlson A, Rosenqvist U, Ostman J. Health attitudes, self-monitoring of blood glucose, metabolic control and residual insulin secretion in type 1 diabetic patients. Diabetic Medicine. 1988; 5(5):449-453

688 Skeie S, Kristensen GBB, Carlsen S, Sandberg S. Self-monitoring of blood glucose in type 1 diabetes patients with insufficient metabolic control: focused self-monitoring of blood glucose intervention can lower glycated hemoglobin A1C. Journal of Diabetes Science and Technology. 2009; 3(1):83-88

689 Smith CB, Choudhary P, Pernet A, Hopkins D, Amiel SA. Hypoglycemia unawareness is associated with reduced adherence to therapeutic decisions in patients with type 1 diabetes: evidence from a clinical audit. Diabetes Care. 2009; 32(7):1196-1198

690 Smith KJ, Roberts MS. The cost-effectiveness of sildenafil. Annals of Internal Medicine. 2000; 132(12):933-937

691 Smith SA, Murphy ME, Huschka TR, Dinneen SF, Gorman CA, Zimmerman BR et al. Impact of a diabetes electronic management system on the care of patients seen in a subspecialty diabetes clinic. Diabetes Care. 1998; 21(6):972-976

692 Snape WJ, Jr., Battle WM, Schwartz SS, Braunstein SN, Goldstein HA, Alavi A. Metoclopramide to treat gastroparesis due to diabetes mellitus: a double-blind, controlled trial. Annals of Internal Medicine. 1982; 96(4):444-446

693 Snoek FJ, Van Der Ven NCW, Twisk JWR, Hogenelst MHE, Tromp-Wever AME, van der Ploeg HM et al. Cognitive behavioural therapy (CBT) compared with blood glucose awareness training (BGAT) in poorly controlled Type 1 diabetic patients: Long-term effects on HbA1c moderated by depression. A randomized controlled trial. Diabetic Medicine. 2008; 25(11):1337-1342

694 Sorgjerd EP, Skorpen F, Kvaloy K, Midthjell K, Grill V. Time dynamics of autoantibodies are coupled to phenotypes and add to the heterogeneity of autoimmune diabetes in adults: the HUNT study, Norway. Diabetologia. 2012; 55(5):1310-1318

695 Speight J, Barendse S, Singh H, Amiel SA, Elliot J, Evans M et al. The Hypo Awareness Questionnaire: design of a novel measure of awareness of hypoglycaemia for use in the UK Hypo COMPaSS trial. Diabetic Medicine. 2011; 28(Suppl.1):181

696 Spiess K, Sachs G, Pietschmann P, Prager R. A program to reduce onset distress in unselected type I diabetic patients: effects on psychological variables and metabolic control. European Journal of Endocrinology. 1995; 132(5):580-586

697 Stades AM, Hoekstra JB, van dT, I, Erkelens DW, Holleman F, STABILITY Study Group. Additional lunchtime basal insulin during insulin lispro intensive therapy in a randomized, multicenter, crossover study in adults : a real-life design. Diabetes Care. 2002; 25(4):712-717

698 Stadler M, Shuttlewood EM, Rogers H, Gianfrancesco C, Beveridge S, Britneff E et al. DAFNE-HART, a psycho-educational programme to reverse hypoglycaemia unawareness in Type 1 diabetes: Report on sustained biomedical benefit at 1 year, and the user experience. Diabetic Medicine. 2014; 31:8-9

699 Standl E, Lang H, Roberts A. The 12-month efficacy and safety of insulin detemir and NPH insulin in basal–bolus therapy for the treatment of type 1 diabetes. Diabetes Technology and Therapeutics. 2004; 6(5):579-588

700 Stern Z, Levy R. Analysis of direct cost of standard compared with intensive insulin treatment of insulin-dependent diabetes mellitus and cost of complications. Acta Diabetologica. 1996; 33(1):48-52

701 Stolk EA, Busschbach JJ, Caffa M, Meuleman EJ, Rutten FF. Cost utility analysis of sildenafil compared with papaverine-phentolamine injections. BMJ (Clinical Research Ed). 2000; 320(7243):1165-1168

702 Storms FE, Lutterman JA, van't Laar A. Comparison of efficacy of human and porcine insulin in treatment of diabetic ketoacidosis. Diabetes Care. 1987; 10(1):49-55

703 Streja D. Can continuous glucose monitoring provide objective documentation of hypoglycemia unawareness? Endocrine Practice. 2005; 11(2):83-90

704 Stroebel RJ, Scheitel SM, Fitz JS, Herman RA, Naessens JM, Scott CG et al. A randomized trial of three diabetes registry implementation strategies in a community internal medicine practice. Joint Commission Journal on Quality Improvement. 2002; 28:441-450

705 Stuckey BG, Jadzinsky MN, Murphy LJ, Montorsi F, Kadioglu A, Fraige F et al. Sildenafil citrate for treatment of erectile dysfunction in men with type 1 diabetes: results of a randomized controlled trial. Diabetes Care. 2003; 26(2):279-284

706 Sundkvist G, Armstrong FM, Bradbury JE, Chaplin C, Ellis SH, Owens DR et al. Peripheral and autonomic nerve function in 259 diabetic patients with peripheral neuropathy treated with ponalrestat (an aldose reductase inhibitor) or placebo for 18 months. Journal of Diabetes & Its Complications. 1992; 6(2):123-130

707 Szepietowska B, Glebocka A, Puch U, Gorska M, Szelachowska M. Latent autoimmune diabetes in adults in a population-based cohort of Polish patients with newly diagnosed diabetes mellitus. Archives of Medical Research. 2012; 8(3):491-495

708 Tabaei BP, Al Kassab AS, Ilag LL, Zawacki CM, Herman WH. Does microalbuminuria predict diabetic nephropathy? Diabetes Care. 2001; 24(9):1560-1566

709 Tabaei BP, Shillnovak J, Brandle M, Burke R, Kaplan RM, Herman WH. Glycemia and the quality of well-being in patients with diabetes. Quality of Life Research: an International Journal of Quality of Life Aspects of Treatment, Care and Rehabilitation. 2004; 13(6):1153-1161

710 Taboulet P, Deconinck N, Thurel A, Haas L, Manamani J, Porcher R et al. Correlation between urine ketones (acetoacetate) and capillary blood ketones (3-beta-hydroxybutyrate) in hyperglycaemic patients. Diabetes & Metabolism. 2007; 33(2):135-139

711 Talal AH, Murray JA, Goeken JA, Sivitz WI. Celiac disease in an adult population with insulin-dependent diabetes mellitus: Use of endomysial antibody testing. American Journal of Gastroenterology. 1997; 92(8):1280-1284

712 Tamas G, Marre M, Astorga R, Dedov I, Jacobsen J, Lindholm A. Glycaemic control in type 1 diabetic patients using optimised insulin aspart or human insulin in a randomised multinational study. Diabetes Research and Clinical Practice. 2001; 54(2):105-114

713 Tamborlane WV, Beck RW, Bode BW, Buckingham B, Chase HP, Clemons R et al. Continuous glucose monitoring and intensive treatment of type 1 diabetes. New England Journal of Medicine. 2008; 359(14):1464-1476

714 Tan HK, Flanagan DE. Impaired hypoglycaemia awareness in Type 1 diabetes in an outpatient setting. Diabetic Medicine. 2012; 29(Suppl.1):130

715 Tanenberg R, Bode B, Lane W, Levetan C, Mestman J, Harmel AP et al. Use of the Continuous Glucose Monitoring System to guide therapy in patients with insulin-treated diabetes: a randomized controlled trial. Mayo Clinic Proceedings. 2004; 79(12):1521-1526

716 Taylor R. Practical community screening for diabetic retinopathy using the mobile retinal camera: report of a 12 centre study. British Diabetic Association Mobile Retinal Screening Group. Diabetic Medicine. 1996; 13(11):946-952

717 Taylor TN, Chrischilles EA. Economic evaluation of interventions in endocrinology. Endocrinology and Metabolism Clinics of North America. 1997; 26(1):67-87

718 Terent A, Hagfall O, Cederholm U. The effect of education and self-monitoring of blood glucose on glycosylated hemoglobin in type I diabetes. A controlled 18-month trial in a representative population. Acta Medica Scandinavica. 1985; 217(1):47-53

719 Testa MA, Gill J, Su M, Turner RR, Blonde L, Simonson DC. Comparative Effectiveness of Basal–bolus Versus Premix Analog Insulin on Glycemic Variability and Patient-Centered Outcomes during Insulin Intensification in Type 1 and Type 2 Diabetes: A Randomized, Controlled, Crossover Trial. Journal of Clinical Endocrinology and Metabolism. 2012; 97(10):3504-3514

720 Thanabalasingham G, Pal A, Selwood MP, Dudley C, Fisher K, Bingley PJ et al. Systematic assessment of etiology in adults with a clinical diagnosis of young-onset type 2 diabetes is a successful strategy for identifying maturity-onset diabetes of the young. Diabetes Care. 2012; 35(6):1206-1212

721 The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. New England Journal of Medicine. 1993; 329(14):977-986

722 The Diabetes Control and Complications Trial Research Group. Lifetime benefits and costs of intensive therapy as practiced in the diabetes control and complications trial. JAMA. 1996; 276(17):1409-1415

723 The TIMAD Study Group. Ticlopidine treatment reduces the progression of nonproliferative diabetic retinopathy. Archives of Ophthalmology. 1990; 108(11):1577-1583

724 Thomas RM, Aldibbiat A, Griffin W, Cox MA, Leech NJ, Shaw JA. A randomized pilot study in Type 1 diabetes complicated by severe hypoglycaemia, comparing rigorous hypoglycaemia avoidance with insulin analogue therapy, CSII or education alone. Diabetic Medicine. 2007; 24(7):778-783

725 Thompson DM, Kozak SE, Sheps S. Insulin adjustment by a diabetes nurse educator improves glucose control in insulin-requiring diabetic patients: a randomized trial. Canadian Medical Association Journal. 1999; 161(8):959-962

726 Thompson RG, Pearson L, Kolterman OG. Effects of 4 weeks' administration of pramlintide, a human amylin analogue, on glycaemia control in patients with IDDM: effects on plasma glucose profiles and serum fructosamine concentrations. Diabetologia. 1997; 40(11):1278-1285

727 Thompson RG, Peterson J, Gottlieb A, Mullane J. Effects of pramlintide, an analog of human amylin, on plasma glucose profiles in patients with IDDM: results of a multicenter trial. Diabetes. 1997; 46(4):632-636

728 Tildesley HD, Johns KW. Long-term treatment of type 1 diabetes in the outpatient setting: Results of 934 patients during up to 10 years' follow-up. Canadian Journal of Diabetes. 2004; 28(3):190-195

729 Timratana P, El-Hayek K, Shimizu H, Kroh M, Chand B. Laparoscopic Gastric Electrical Stimulation for Medically Refractory Diabetic and Idiopathic Gastroparesis. Journal of Gastrointestinal Surgery. 2013; 17(3):461-470

730 Timratana P, El-Hayek KM, Shimizu H, Kroh M, Chand B. Laparoscopic gastric pacer therapy for medical refractory diabetic and idiopathic gastroparesis. Gastroenterology. 2012; 142(5 SUPPL. 1):S1065

731 Toseland RW, Labrecque MS, Gobel ST, Whitney MH. An evaluation of a group program for spouses of frail elderly veterans. Gerontologist. 1992; 32(3):382-390

732 Toso C, Shapiro AM, Bowker S, Dinyari P, Paty B, Ryan EA et al. Quality of life after islet transplant: impact of the number of islet infusions and metabolic outcome. Transplantation. 2007; 84(5):664-666

733 Trabucchi A, Faccinetti NI, Guerra LL, Puchulu FM, Frechtel GD, Poskus E et al. Detection and characterization of ZnT8 autoantibodies could help to screen latent autoimmune diabetes in adult-onset patients with type 2 phenotype. Autoimmunity. 2012; 45(2):137-142

734 Trento M, Passera P, Borgo E, Tomalino M, Bajardi M, Brescianini A et al. A 3-year prospective randomized controlled clinical trial of group care in type 1 diabetes. Nutrition, Metabolism, and Cardiovascular Diseases. 2005; 15(4):293-301

735 Trento M, Trinetta A, Kucich C, Grassi G, Passera P, Gennari S et al. Carbohydrate counting improves coping ability and metabolic control in patients with Type 1 diabetes managed by Group Care. Journal of Endocrinological Investigation. 2011; 34(2):101-105

736 Tridgell DM, Spiekerman C, Wang RS, Greenbaum CJ. Interaction of onset and duration of diabetes on the percent of gad and ia-2 antibody-positive subjects in the type 1 diabetes genetics consortium database. Diabetes Care. 2011; 34(4):988-993

737 Tung YC, Lee JS, Tsai WY, Hsiao PH. Evaluation of beta-cell function in diabetic Taiwanese children using a 6-min glucagon test. European Journal of Pediatrics. 2008; 167(7):801-805

738 Tunis SL, Minshall ME, Conner C, McCormick J, I, Kapor J, Yale J-F et al. Cost-effectiveness of insulin detemir compared to NPH insulin for type 1 and type 2 diabetes mellitus in the Canadian payer setting: modeling analysis. Current Medical Research and Opinion. 2009; 25(5):1273-1284

739 Umpierrez GE, Latif KA, Murphy MB, Lambeth HC, Stentz F, Bush A et al. Thyroid dysfunction in patients with type 1 diabetes: a longitudinal study. Diabetes Care. 2003; 26(4):1181-1185

740 University College London Hospitals. Provider to provider services 2012-2013 tariff. London. Unversity College London Hospitals NHS Foundation Trust, 2012. Available from: https://www.uclh.nhs.uk/aboutus/wwd/Documents/Provider%20to%20Provider%20Tariff%202012-13.pdf

741 Vague P, Selam JL, Skeie S, Leeuw I, Elte JW, Haahr H et al. Insulin detemir is associated with more predictable glycemic control and reduced risk of hypoglycemia than NPH insulin in patients with type 1 diabetes on a basal–bolus regimen with premeal insulin aspart. Diabetes Care. 2003; 26(3):590-596

742 Valentine WJ, Aagren M, Haglund M, Ericsson A, Gschwend MH. Evaluation of the long-term cost-effectiveness of insulin detemir compared with neutral protamine hagedorn insulin in patients with type 1 diabetes using a basal–bolus regimen in Sweden. Scandinavian Journal of Public Health. 2011; 39(1):79-87

743 Valentine WJ, Jendle J, Saraheimo M, Thorsteinsson B, Pollock RF, Lammert M. Evaluating the cost-effectiveness of reduced mild hypoglycaemia in subjects with Type1 diabetes treated with insulin detemir or NPH insulin in Denmark, Sweden, Finland and the Netherlands. Diabetic Medicine. 2012; 29(3):303-312

744 Valentine WJ, Palmer AJ, Erny-Albrecht KM, Ray JA, Cobden D, Foos V et al. Cost-effectiveness of basal insulin from a US health system perspective: comparative analyses of detemir, glargine and NPH. Advances in Therapy. 2006; 23(2):191-207

745 Van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M et al. Intensive insulin therapy in critically ill patients. New England Journal of Medicine. 2001; 345(19):1359-1367

746 van der Voort IR, Becker JC, Dietl KH, Konturek JW, Domschke W, Pohle T. Gastric electrical stimulation results in improved metabolic control in diabetic patients suffering from gastroparesis. Experimental and Clinical Endocrinology & Diabetes. 2005; 113(1):38-42

747 van Dyk J. Insulin glargine (HOE901) lowers fasting blood glucose in children with type 1 diabetes mellitus without increasing the risk of hypoglycaemia. Journal of Pediatric Endocrinology and Metabolism. 2000; 13 (suppl.):34

748 van Os N, Niessen LW, Bilo HJ, Casparie AF, van Hout BA. Diabetes nephropathy in the Netherlands: a cost effectiveness analysis of national clinical guidelines. Health Policy. 2000; 51(3):135-147

749 Van Tilburg MAL, McCaskill CC, Lane JD, Edwards CL, Bethel A, Feinglos MN et al. Depressed mood is a factor in glycemic control in type 1 diabetes. Psychosomatic Medicine. 2001; 63(4):551-555

750 Vardi M, Jacobson E, Nini A, Bitterman H. Intermediate acting versus long acting insulin for type 1 diabetes mellitus. Cochrane Database of Systematic Reviews. 2008; Issue 3:CD006297. DOI:10.1002/14651858.CD006297.pub2

751 Vaughan NJ, Shaw M, Boer F, Billett D, Martin C. Creation of a District Diabetes Register using the DIALOG system. Diabetic Medicine. 1996; 13(2):175-181

752 Vaziri-Sani F, Oak S, Radtke J, Lernmark K, Lynch K, Agardh CD et al. ZnT8 autoantibody titers in type 1 diabetes patients decline rapidly after clinical onset. Autoimmunity. 2010; 43(8):598-606

753 Venhaus A, Chantelau E. Self-selected unrefined and refined carbohydrate diets do not affect metabolic control in pump-treated diabetic patients. Diabetologia. 1988; 31(3):153-157

754 Vermeulen I, Weets I, Asanghanwa M, Ruige J, Van GL, Mathieu C et al. Contribution of antibodies against IA-2beta and zinc transporter 8 to classification of diabetes diagnosed under 40 years of age. Diabetes Care. 2011; 34(8):1760-1765

755 Vervoort G, Goldschmidt HM, van Doorn LG. Nocturnal blood glucose profiles in patients with type 1 diabetes mellitus on multiple (> or = 4) daily insulin injection regimens. Diabetic Medicine. 1996; 13(9):794-799

756 Viallon A, Zeni F, Lafond P, Venet C, Tardy B, Page Y et al. Does bicarbonate therapy improve the management of severe diabetic ketoacidosis? Critical Care Medicine. 1999; 27(12):2690-2693

757 Vignati L, Anderson JH, Jr., Iversen PW. Efficacy of insulin lispro in combination with NPH human insulin twice per day in patients with insulin-dependent or non-insulin-dependent diabetes mellitus. Multicenter Insulin Lispro Study Group. Clinical Therapeutics. 1997; 19:1408-1421

758 Vlad A, Serban V, Sima A, Timar R, Rosu M. The value of basal C peptide and its relationship with pancreatic autoantibodies in young adults with type 2 diabetes mellitus. Romanian Journal of Internal Medicine. 2004; 42(2):333-341

759 Vondra K, Vrbikova J, Sterzl I, Bilek R, Vondrova M, Zamrazil V. Thyroid autoantibodies and their clinical relevance in young adults with type 1 diabetes during the first 12 yr after diabetes onset. Journal of Endocrinological Investigation. 2004; 27(8):728-732

760 Vriesendorp TM, Morelis QJ, DeVries JH, Legemate DA, Hoekstra JB. Early post-operative glucose levels are an independent risk factor for infection after peripheral vascular surgery. A retrospective study. European Journal of Vascular and Endovascular Surgery : the Official Journal of the European Society for Vascular Surgery. 2004; 28(5):520-525

761 Wagner A, Risse A, Brill HL, Wienhausen-Wilke V, Rottmann M, Sondern K et al. Therapy of severe diabetic ketoacidosis. Zero-mortality under very-low-dose insulin application. Diabetes Care. 1999; 22(5):674-677

762 Walter M, McDonald CG, Paty BW, Shapiro AMJ, Ryan EA, Senior PA. Prevalence of autoimmune diseases in islet transplant candidates with severe hypoglycaemia and glycaemic

lability: previously undiagnosed coeliac and autoimmune thyroid disease is identified by screening. Diabetic Medicine. 2007; 24(2):161-165

763 Warren E, Weatherley-Jones E, Chilcott J, Beverley C. Systematic review and economic evaluation of a long-acting insulin analogue, insulin glargine. Health Technology Assessment. 2004; 8(45):iii-41

764 Waugh N, Cummins E, Royle P, Clar C, Marien M, Richter B et al. Newer agents for blood glucose control in type 2 diabetes: systematic review and economic evaluation. Health Technology Assessment. 2010; 14(36):1-248

765 Webb DJ, Newman DJ, Chaturvedi N, Fuller JH. The use of the Micral-Test strip to identify the presence of microalbuminuria in people with insulin dependent diabetes mellitus (IDDM) participating in the EUCLID study. Diabetes Research and Clinical Practice. 1996; 31:93-102

766 Wehrmann T, Lembcke B, Caspary WF. Influence of cisapride on antroduodenal motor function in healthy subjects and diabetics with autonomic neuropathy. Alimentary Pharmacology and Therapeutics. 1991; 5(6):599-608

767 Wei N, Zheng H, Nathan DM. Empirically Establishing Blood Glucose Targets to Achieve HbA1c Goals. Diabetes Care. 2014; 37(4):1048-1051

768 Weinstock RS, Xing D, Maahs DM, Michels A, Rickels MR, Peters AL et al. Severe hypoglycemia and diabetic ketoacidosis in adults with type 1 diabetes: results from the T1D Exchange clinic registry. Journal of Clinical Endocrinology and Metabolism. 2013; 98(8):3411-3419

769 Weitgasser R, Schnoll F, Pretsch I, Gruber U. Evaluation of self-monitoring of blood glucose after five years of intensive insulin therapy following a basal–bolus regimen. Diabetologia Croatica. 1994; 23(1):13-17

770 Wenzlau JM, Walter M, Gardner TJ, Frisch LM, Yu L, Eisenbarth GS et al. Kinetics of the post-onset decline in zinc transporter 8 autoantibodies in type 1 diabetic human subjects. Journal of Clinical Endocrinology and Metabolism. 2010; 95(10):4712-4719

771 Weyer C, Gottlieb A, Kim DD, Lutz K, Schwartz S, Gutierrez M et al. Pramlintide reduces postprandial glucose excursions when added to regular insulin or insulin lispro in subjects with type 1 diabetes: a dose-timing study. Diabetes Care. 2003; 26(11):3074-3079

772 White NH, Sun W, Cleary PA, Danis RP, Davis MD, Hainsworth DP et al. Prolonged effect of intensive therapy on the risk of retinopathy complications in patients with type 1 diabetes mellitus: 10 years after the Diabetes Control and Complications Trial. Archives of Ophthalmology. 2008; 126(12):1707-1715

773 White NH, Waltman SR, Krupin T, Santiago JV. Reversal of abnormalities in ocular fluorophotometry in insulin-dependent diabetes after five to nine months of improved metabolic control. Diabetes. 1982; 31(1):80-85

774 Whitehead C, Lunt H, Pearson JF, Cawood TJ. Is screening for hypothyroidism in the diabetes clinic effective? Practical Diabetes International. 2010; 27(3):113-117

775 Whitehouse F, Kruger DF, Fineman M, Shen L, Ruggles JA, Maggs DG et al. A randomized study and open-label extension evaluating the long-term efficacy of pramlintide as an adjunct to insulin therapy in type 1 diabetes. Diabetes Care. 2002; 25(4):724-730

776 Wiggam MI, O'Kane MJ, Harper R, Atkinson AB, Hadden DR, Trimble ER et al. Treatment of diabetic ketoacidosis using normalization of blood 3- hydroxybutyrate concentration as the endpoint of emergency management: A randomized controlled study. Diabetes Care. 1997; 20(9):1347-1352

777 Wikblad K, Leksell J, Wibell L. Health-related quality of life in relation to metabolic control and late complications in patients with insulin dependent diabetes mellitus. Quality of Life Research: an International Journal of Quality of Life Aspects of Treatment, Care and Rehabilitation. 1996; 5(1):123-130

778 Wikblad K, Montin K, Wibell L. Metabolic control, residual insulin secretion and self-care behaviours in a defined group of patients with type 1 diabetes. Upsala Journal of Medical Sciences. 1991; 96(1):47-61

779 Willey KA, Twigg SM, Constantino MI, Yue DK, Turtle JR. Home blood glucose monitoring: How often? Practical Diabetes. 1993; 10(1):22-25

780 Wilmot-Roussel H, Levy DJ, Carette C, Caillat-Zucman S, Boitard C, Timsit J et al. Factors associated with the presence of glutamic acid decarboxylase and islet antigen-2 autoantibodies in patients with long-standing type 1 diabetes. Diabetes & Metabolism. 2013; 39(3):244-249

781 Wilson HK, Keuer SP, Lea AS, Boyd AE, III, Eknoyan G. Phosphate therapy in diabetic ketoacidosis. Archives of Internal Medicine. 1982; 142(3):517-520

782 Winocour PH, Durrington PN, Bhatnagar D, Ishola M, Arrol S, Lalor BC et al. Double-blind placebo-controlled study of the effects of bezafibrate on blood lipids, lipoproteins, and fibrinogen in hyperlipidaemic type 1 diabetes mellitus. Diabetic Medicine. 1990; 7(8):736-743

783 Woo V, Clendenan J. Association of frequency of Self-Monitoring of Blood Glucose (SMBG) and HbA1c in the clinical practice. Diabetes. 2011; 60(Suppl.1):A241

784 Wright J, Ruck K, Rabbitts R, Charlton M, De P, Barrett T. Diabetic ketoacidosis (DKA) in Birmingham, UK, 2000–2009: an evaluation of risk factors for recurrence and mortality. British Journal of Diabetes and Vascular Disease. 2009; 9:278-282

785 Wright RJ, Frier BM, Deary IJ. Effects of acute insulin-induced hypoglycemia on spatial abilities in adults with type 1 diabetes. Diabetes Care. 2009; 32(8):1503-1506

786 Wu SY, Lung BC, Chang S, Lee SC, Critchley JA, Chan JC. Evaluation of drug usage and expenditure in a hospital diabetes clinic. Journal of Clinical Pharmacy and Therapeutics. 1998; 23(1):49-56

787 Yale JF, Begg I, Gerstein H, Houlden R, Jones H, Maheux P et al. 2001 Canadian Diabetes Association Clinical Practice Guidelines for the Prevention and Management of Hypogyceamia in Diabetes. Canadian Journal of Diabetes Care. 2001; 26(1):22-35

788 Yamaguchi K, Fukushima H, Uzawa H. Response of human growth hormone, prolactin and thyrotropin to thyrotropin releasing hormone in liver cirrhosis and diabetes mellitus. Endocrinologia Japonica. 1979; 26(1):81-88

789 Yamaguchi Y, Chikuba N, Ueda Y, Yamamoto H, Yamasaki H, Nakanishi T et al. Islet cell antibodies in patients with autoimmune thyroid disease. Diabetes. 1991; 40(3):319-322

790 Yang L, Zhou ZG, Tan SZ, Huang G, Jin P, Yan X et al. Carboxypeptidase-H autoantibodies differentiate a more latent subset of autoimmune diabetes from phenotypic type 2 diabetes among Chinese adults. Annals of the New York Academy of Sciences. 2008; 1150:263-266

791 Yasmin T, Ghafoor F, Malik T, Ruhy N, Khan AU. Pattern of thyroid autoimmunity in type 1 and type 2 diabetics. Journal of the College of Physicians and Surgeons--Pakistan. 2006; 16(12):751-754

792 Yip JW, Jones SL, Wiseman MJ, Hill C, Viberti G. Glomerular hyperfiltration in the prediction of nephropathy in IDDM: a 10-year follow-up study. Diabetes. 1996; 45(12):1729-1733

793 Yokoyama KK, Cryar AK, Griffin KC, Godley PJ, Woodward BW. Cost-effectiveness of a multidisciplinary diabetes care clinic. Drug Benefit Trends. 2002; 14(Suppl. D):36-44

794 Yun YS, Lee HC, Park CS, Chang KH, Cho CH, Song YD et al. Effects of long-acting somatostatin analogue (Sandostatin) on manifest diabetic ketoacidosis. Journal of Diabetes & Its Complications. 1999; 13(5-6):288-292

795 Yusuf S, Dagenais G, Pogue J, Bosch J, Sleight P. Vitamin E supplementation and cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. New England Journal of Medicine. 2000; 342:154-160

796 Zachariah S, Sheldon B, Shojaee-Moradie F, Jackson NC, Backhouse K, Johnsen S et al. Insulin detemir reduces weight gain as a result of reduced food intake in patients with type 1 diabetes. Diabetes Care. 2011; 34(7):1487-1491

797 Zambanini A, Newson RB, Maisey M, Feher MD. Injection related anxiety in insulin-treated diabetes. Diabetes Research and Clinical Practice. 1999; 46(3):239-246

798 Zampetti S, Capizzi M, Spoletini M, Campagna G, Leto G, Cipolloni L et al. GADA titer-related risk for organ-specific autoimmunity in LADA subjects subdivided according to gender (NIRAD study 6). Journal of Clinical Endocrinology and Metabolism. 2012; 97(10):3759-3765

799 Zelmanovitz T, Gross JL, Oliveira J, De Azevedo MJ. Proteinuria is still useful for the screening and diagnosis of overt diabetic nephropathy. Diabetes Care. 2003; 21(7):1076-1079

800 Zhang S, Sun Q, Feng K, Fu Y, Wang O, Ping F et al. Clinical, biochemical, and immunological characteristics of newly diagnosed nonobese diabetic patients aged 18-45 years in China. Journal of Diabetes and Its Complications. 2012; 26(1):40-43

801 Ziegler D, Merfort F, van AH, Yassin A, Reblin T, Neureither M. Efficacy and safety of flexible-dose vardenafil in men with type 1 diabetes and erectile dysfunction. Journal of Sexual Medicine. 2006; 3(5):883-891

802 Ziegler O, Kolopp M, Got I, Genton P, Debry G, Drouin P. Reliability of self-monitoring of blood glucose by CSII-treated patients with type I diabetes. Diabetes Care. 1989; 12(3):184-188

803 Ziegler O, Kolopp M, Louis J, Musse JP, Patris A, Debry G et al. Self-monitoring of blood glucose and insulin dose alteration in type 1 diabetes mellitus. Diabetes Research and Clinical Practice. 1993; 21(1):51-59

804 Ziegler R, Cavan DA, Cranston I, Barnard K, Ryder J, Vogel C et al. More frequent SMBG is associated with more frequent insulin boluses and lower HbA1c: Baseline results from the ABACUS. Diabetologia. 2012; 55(Suppl.1):S425

805 Ziegler R, Cavan DA, Cranston I, Barnard K, Ryder J, Vogel C et al. Use of an Insulin Bolus Advisor Improves Glycemic Control in Multiple Daily Insulin Injection (MDI) Therapy Patients With Suboptimal Glycemic Control: First results from the ABACUS trial. Diabetes Care. 2013; 36(11):3613-3619

806 Zoffmann V, Vistisen D, Due-Christensen M. A cross-sectional study of glycaemic control, complications and psychosocial functioning among 18- to 35-year-old adults with Type 1 diabetes. Diabetic Medicine. 2014; 31(4):493-499

18 Acronyms and abbreviations

Acronym or abbreviation	Description
ADA	American Diabetes Association
anti-TGL	anti-triglyceride Lipase
BGAT	Blood Glucose Awareness Training
BMI	Body mass index
CGM	Continuous glucose monitoring
CHO	Carbohydrate
CSII	Continuous subcutaneous insulin infusion
COPD	Chronic obstructive pulmonary disease
CV	Cardiovascular
DAFNE	Dose adjustment for normal eating
DKA	Diabetic ketoacidosis
GAD/GADA/GAD65	Glutamic acid decarboxylase autoantibodies
GI	Glycaemic index
HbA1c	Glycated haemoglobin
HFS	Hypoglycaemia fear survey
IA2A	Inslet antigen 2 antibody 2A
IAA	Insulin autoantibodies
IAH	Impaired awareness of hypoglycaemia
ICA	Islet cell antibodies
ICU	Intensive care unit
LADA	Latent autoimmune diabetes of adulthood
MI	Myocardial infarction
MODY	Maturity onset diabetes of the young
NICE	National Institute for Health and Care Excellence
NCGC	National Clinical Guideline Centre
PAID	Problem areas in diabetes
SMBG	Self-monitoring of blood glucose
SIGN	Scottish Intercollegiate Guideline Network
TA	Technology appraisal
T-Ab	Thyroxine Antibody
TSH	Thyroid stimulating hormone
TPO	Thyroid peroxidase antibodies
TFT	Thyroid function tests
UCPCR	Urine C-peptide creatinine ratio
VAS	Visual analogue scale

19 Glossary

Term	Definition
Abstract	Summary of a study, which may be published alone or as an introduction to a full scientific paper.
Acute painful neuropathy of rapid glycaemic control	A very small proportion of individuals with diabetes who achieve a rapid improvement in blood glucose levels with insulin therapy develop a painful paraesthesia in limbs, especially the legs and feet, that can have a considerable impact on sleep and activities of daily living. The aetiology has not been clearly identified and no satisfactory explanation for the phenomenon has been agreed; symptoms usually improve over time but individuals may require additional treatments for pain relief.
Algorithm (in guidelines)	A flow chart of the clinical decision pathway described in the guideline, where decision points are represented with boxes, linked with arrows.
Allocation concealment	The process used to prevent advance knowledge of group assignment in an RCT. The allocation process should be impervious to any influence by the individual making the allocation, by being administered by someone who is not responsible for recruiting participants.
Applicability	How well the results of a study or NICE evidence review can answer a clinical question or be applied to the population being considered.
Arm (of a clinical study)	Subsection of individuals within a study who receive one particular intervention, for example placebo arm.
Association	Statistical relationship between 2 or more events, characteristics or other variables. The relationship may or may not be causal.
Autonomic neuropathy	Late stage complication of diabetes where the neurons of the autonomic nervous system become damaged following exposure to chronically raised blood glucose levels. Manifestations include gastroparesis, diarrhoea, sweating, orthostatic hypotension, cardiac arrest, erectile dysfunction, bladder dysfunction and cardiac arrest.
Baseline	The initial set of measurements at the beginning of a study (after run-in period where applicable), with which subsequent results are compared.
Bias	Influences on a study that can make the results look better or worse than they really are. (Bias can even make it look as if a treatment works when it does not.) Bias can occur by chance, deliberately or as a result of systematic errors in the design and execution of a study. It can also occur at different stages in the research process, for example, during the collection, analysis, interpretation, publication or review of research data. For examples see selection bias, performance bias, information bias, confounding factor, and publication bias.
Blinding	A way to prevent researchers, doctors and patients in a clinical trial from knowing which study group each patient is in so they cannot influence the results. The best way to do this is by sorting patients into study groups randomly. The purpose of 'blinding' or 'masking' is to protect against bias. A single-blinded study is one in which patients do not know which study group they are in (for example whether they are taking the experimental drug or a placebo). A double-blinded study is one in which neither patients nor the researchers and doctors know which study group the patients are in. A triple blind study is one in which neither the patients, clinicians or the people carrying out the statistical analysis know which treatment patients received.
BMI	An indicator of body density as determined by the relationship of body weight to body height. BMI=weight (kg)/height squared (m^2). BMI correlates

Term	Definition
	with body fat (adipose tissue). Their relationship varies with age and gender. For adults, BMI falls into these categories: below 18.5 (underweight); 18.5-24.9 (normal); 25.0-29.9 (overweight); 30.0 and above (obese). (National Center for Health Statistics, Centers for Disease Control and Prevention)
Carer (caregiver)	Someone who looks after family, partners or friends in need of help because they are ill, frail or have a disability.
Case–control study	A study to find out the cause(s) of a disease or condition. This is done by comparing a group of patients who have the disease or condition (cases) with a group of people who do not have it (controls) but who are otherwise as similar as possible (in characteristics thought to be unrelated to the causes of the disease or condition). This means the researcher can look for aspects of their lives that differ to see if they may cause the condition. For example, a group of people with lung cancer might be compared with a group of people the same age that do not have lung cancer. The researcher could compare how long both groups had been exposed to tobacco smoke. Such studies are retrospective because they look back in time from the outcome to the possible causes of a disease or condition.
Case series	Report of a number of cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison (control) group of patients.
Clinical efficacy	The extent to which an intervention is active when studied under controlled research conditions.
Clinical effectiveness	How well a specific test or treatment works when used in the 'real world' (for example, when used by a doctor with a patient at home), rather than in a carefully controlled clinical trial. Trials that assess clinical effectiveness are sometimes called management trials. Clinical effectiveness is not the same as efficacy.
Clinician	A healthcare professional who provides patient care. For example, a doctor, nurse or physiotherapist.
Cochrane Review	The Cochrane Library consists of a regularly updated collection of evidence-based medicine databases including the Cochrane Database of Systematic Reviews (reviews of randomised controlled trials prepared by the Cochrane Collaboration).
Cohort study	A study with 2 or more groups of people – cohorts – with similar characteristics. One group receives a treatment, is exposed to a risk factor or has a particular symptom and the other group does not. The study follows their progress over time and records what happens. See also observational study.
Comorbidity	A disease or condition that someone has in addition to the health problem being studied or treated.
Comparability	Similarity of the groups in characteristics likely to affect the study results (such as health status or age).
Concordance	This is a recent term whose meaning has changed. It was initially applied to the consultation process in which doctor and patient agree therapeutic decisions that incorporate their respective views, but now includes patient support in medicine taking as well as prescribing communication. Concordance reflects social values but does not address medicine-taking and may not lead to improved adherence.
Confidence interval (CI)	There is always some uncertainty in research. This is because a small group of patients is studied to predict the effects of a treatment on the wider population. The confidence interval is a way of expressing how certain we are about the findings from a study, using statistics. It gives a range of

Term	Definition
	results that is likely to include the 'true' value for the population. The CI is usually stated as '95% CI', which means that the range of values has a 95 in a 100 chance of including the 'true' value. For example, a study may state that 'based on our sample findings, we are 95% certain that the 'true' population blood pressure is not higher than 150 and not lower than 110'. In such a case the 95% CI would be 110 to 150. A wide confidence interval indicates a lack of certainty about the true effect of the test or treatment – often because a small group of patients has been studied. A narrow confidence interval indicates a more precise estimate (for example, if a lot of patients have been studied).
Confounding factor	Something that influences a study and can result in misleading findings if it is not understood or appropriately dealt with. For example, a study of heart disease may look at a group of people that exercises regularly and a group that does not exercise. If the ages of the people in the 2 groups are different, then any difference in heart disease rates between the 2 groups could be because of age rather than exercise. Therefore age is a confounding factor.
Consensus methods	Techniques used to reach agreement on a particular issue. Consensus methods may be used to develop NICE guidance if there is not enough good quality research evidence to give a clear answer to a question. Formal consensus methods include Delphi and nominal group techniques.
Continuous subcutaneous infusion insulin infusion (or insulin pump therapy)	A device that delivers rapid-acting insulin constantly into subcutaneous tissue for blood glucose control. The device requires input from the user to administer bolus insulin doses with food but has the advantage that it can be set up to deliver a variable basal rate of rapid-acting insulin according to the user's needs.
Control group	A group of people in a study who do not receive the treatment or test being studied. Instead, they may receive the standard treatment (sometimes called 'usual care') or a dummy treatment (placebo). The results for the control group are compared with those for a group receiving the treatment being tested. The aim is to check for any differences. Ideally, the people in the control group should be as similar as possible to those in the treatment group, to make it as easy as possible to detect any effects due to the treatment.
Cost-effectiveness analysis (CEA)	Cost-effectiveness analysis is one of the tools used to carry out an economic evaluation. The benefits are expressed in non-monetary terms related to health, such as symptom-free days, heart attacks avoided, deaths avoided or life years gained (that is, the number of years by which life is extended as a result of the intervention).
Cost-effectiveness model	An explicit mathematical framework, which is used to represent clinical decision problems and incorporate evidence from a variety of sources in order to estimate the costs and health outcomes.
Cost–utility analysis (CUA)	Cost–utility analysis is one of the tools used to carry out an economic evaluation. The benefits are assessed in terms of both quality and duration of life, and expressed as quality-adjusted life years (QALYs). See also utility.
Credible interval (CrI)	The Bayesian equivalent of a confidence interval.
Decision analysis	An explicit quantitative approach to decision-making under uncertainty, based on evidence from research. This evidence is translated into probabilities, and then into diagrams or decision trees which direct the clinician through a succession of possible scenarios, actions and outcomes.
Diabetic ketoacidosis	A medical emergency which occurs when the body is unable to use glucose as an energy source due to a lack of insulin. The body breaks down fat as an alternative source of energy. Ketone formation is a by-product of this

Term	Definition
	process and contributes to the development of an acidotic state. Diabetic ketoacidosis is a medical emergency as it can lead to coma and death. It requires urgent treatment with intravenous fluids, insulin and electrolyte replacement, typically in a hospital setting.
Diabetic nephropathy	A microvascular complication of diabetes that results in progressive kidney disease caused by angiopathy of capillaries in kidney glomeruli.
Diabetic retinopathy	An ocular manifestation of diabetes that occurs as a result of microvascular retinal changes in response to chronic hyperglycaemia exposure. It can be associated with visual loss, although, screening programmes aim to detect early changes and time specialist referral for treatment interventions.
Discounting	Costs and perhaps benefits incurred today have a higher value than costs and benefits occurring in the future. Discounting health benefits reflects individual preference for benefits to be experienced in the present rather than the future. Discounting costs reflects individual preference for costs to be experienced in the future rather than the present.
Economic evaluation	An economic evaluation is used to assess the cost effectiveness of healthcare interventions (that is, to compare the costs and benefits of a healthcare intervention to assess whether it is worth doing). The aim of an economic evaluation is to maximise the level of benefits – health effects – relative to the resources available. It should be used to inform and support the decision-making process; it is not supposed to replace the judgement of healthcare professionals. There are several types of economic evaluation: cost–benefit analysis, cost–consequences analysis, cost-effectiveness analysis, cost–minimisation analysis and cost–utility analysis. They use similar methods to define and evaluate costs, but differ in the way they estimate the benefits of a particular drug, programme or intervention.
Effect (as in effect measure, treatment effect, estimate of effect, effect size)	A measure that shows the magnitude of the outcome in one group compared with that in a control group. For example, if the absolute risk reduction is shown to be 5% and it is the outcome of interest, the effect size is 5%. The effect size is usually tested, using statistics, to find out how likely it is that the effect is a result of the treatment and has not just happened by chance (that is, to see if it is statistically significant).
Effectiveness	How beneficial a test or treatment is under usual or everyday conditions, compared with doing nothing or opting for another type of care.
Efficacy	How beneficial a test, treatment or public health intervention is under ideal conditions (for example, in a laboratory), compared with doing nothing or opting for another type of care.
Epidemiological study	The study of a disease within a population, defining its incidence and prevalence and examining the roles of external influences (for example, infection, diet) and interventions.
EQ-5D (EuroQol 5 dimensions)	A standardised instrument used to measure health-related quality of life. It provides a single index value for health status.
Evidence	Information on which a decision or guidance is based. Evidence is obtained from a range of sources including randomised controlled trials, observational studies, expert opinion (of clinical professionals or patients).
Exclusion criteria (literature review)	Explicit standards used to decide which studies should be excluded from consideration as potential sources of evidence.
Exclusion criteria (clinical study)	Criteria that define who is not eligible to participate in a clinical study.
Extrapolation	An assumption that the results of studies of a specific population will also

Term	Definition
	hold true for another population with similar characteristics.
Follow-up	Observation over a period of time of an individual, group or initially defined population whose appropriate characteristics have been assessed in order to observe changes in health status or health-related variables.
Gold standard	A method, procedure or measurement that is widely accepted as being the best available to test for or treat a disease.
GRADE, GRADE profile	A system developed by the GRADE Working Group to address the shortcomings of present grading systems in healthcare. The GRADE system uses a common, sensible and transparent approach to grading the quality of evidence. The results of applying the GRADE system to clinical trial data are displayed in a table known as a GRADE profile.
Harms	Adverse effects of an intervention.
Health economics	Study or analysis of the cost of using and distributing healthcare resources.
Health-related quality of life (HRQoL)	A measure of the effects of an illness to see how it affects someone's day-to-day life.
Heterogeneity or Lack of homogeneity	The term is used in meta-analyses and systematic reviews to describe when the results of a test or treatment (or estimates of its effect) differ significantly in different studies. Such differences may occur as a result of differences in the populations studied, the outcome measures used or because of different definitions of the variables involved. It is the opposite of homogeneity.
Hyperglycaemia	Abnormally high blood glucose level, typically considered to be >7.0 mmol/litre fasting and >11.1 mmol/litre post-prandially. Prolonged hyperglycaemia can lead to osmotic symptoms of thirst, passing urine frequently and weight loss in the short term, and retinopathy, nephropathy and neuropathy in the long-term.
Hypoglycaemia	Abnormally low blood glucose level, typically considered to be a level of <3.5 mmol/litre. An individual with a hypoglycaemic blood glucose level typically experiences autonomic symptoms (sweating, palpitations, tremor) and neuroglycopenic symptoms (emotional lability, paraesthesia, blurred vision, incoordination, reduced orientation) that warn them to consume carbohydrate to correct their glucose levels.
Impaired awareness of hypoglycaemia	Repeated episodes of hypoglycaemia can result in reduced autonomic and neuroglycopenic warning signs when low blood glucose levels occur in individuals with diabetes. Eventually, an individual with diabetes can develop hypoglycaemia awareness such that they do not have any warning signs that they have a low blood glucose level, and this can predispose them to episodes of severe hypoglycaemia.
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of effect.
Inclusion criteria (literature review)	Explicit criteria used to decide which studies should be considered as potential sources of evidence.
Incremental analysis	The analysis of additional costs and additional clinical outcomes with different interventions.
Incremental cost	The extra cost linked to using one test or treatment rather than another. Or the additional cost of doing a test or providing a treatment more frequently.
Incremental cost-effectiveness ratio (ICER)	The difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest for one treatment compared with another.
Indirectness	The available evidence is different from the review question being addressed, in terms of PICO (population, intervention, comparison and

Term	Definition
	outcome).
Intervention	In medical terms this could be a drug treatment, surgical procedure, diagnostic or psychological therapy. Examples of public health interventions could include action to help someone to be physically active or to eat a more healthy diet.
Long-term care	Residential care in a home that may include skilled nursing care and help with everyday activities. This includes nursing homes and residential homes.
Ketogenesis	The process by which ketone bodies are produced as a result of fatty acid breakdown. In individuals with type 1 diabetes, this typically occurs when blood glucose cannot be taken up by cells as a consequence of insufficient insulin levels; ketone body production is then initiated to make energy available to cells from the breakdown of stored fatty acids.
Ketosis	Ketosis occurs when ketogenesis is happening at an abnormally high level to form raised concentrations of acetone, acetoacetate and β-hydroxybutyrate from acetyl-CoA to provide energy supplies to the body. Acetoacetate and β-hydroxybutyrate are acidic, and high levels result in ketoacidosis, a medical emergency which can lead to a comatose state, if left untreated.
Latent autoimmune diabetes of adulthood (LADA)	A form of diabetes mellitus that is caused by autoimmune destruction of pancreatic β cells, but typically the destruction is considerably slower than that seen in classic presentations of type 1 diabetes, and it presents in adults rather than in childhood. Clinical onset of osmotic symptoms is therefore slower (over several years), and in its early stages good glycaemic control can be achieved with very small doses of insulin. LADA has been likened to a slow onset form of type 1 diabetes.
Lipolysis	The breakdown of fat (lipid) cells.
Macrovascular complications of diabetes	Diabetes is associated with disease of large blood vessels in the body, including the coronary arteries, aorta, carotid arteries and peripheral vascular arteries to the limbs. Chronic exposure to hyperglycaemia leads to an increased incidence of coronary heart disease, cerebrovascular disease and peripheral vascular disease.
Markov model	A method for estimating long-term costs and effects for recurrent or chronic conditions, based on health states and the probability of transition between them within a given time period (cycle).
Maturity onset diabetes of the young (MODY)	Rare forms of diabetes different from type 1 and type 2 diabetes caused by mutation of a single gene – it is thought that 1-2% of people with diabetes in the UK have this form of diabetes. Key features are: Presentation with diabetes at <25 years of age Diabetes in at least two preceding generations, with diagnosis at <25 years of age Absence of ketones at diagnosis such that insulin may not be immediately required for management of the diabetes in its early stages
Meta-analysis	A method often used in systematic reviews. Results from several studies of the same test or treatment are combined to estimate the overall effect of the treatment.
Microalbuminuria	An increase in the level of albumin in the urine (>30 to 300 mg/litre, >30-300 mg/24 hours, urine albumin/creatinine ratio of >2.5 mg/mmol in men and >3.5 mg/mmol in women) that occurs when the permeability of the renal glomerulus is abnormally increased in response to chronic hyperglycaemia exposure. The diagnosis of microalbuminuria should be confirmed on a repeat urine sample within 3 to 6 months of the first positive test. Microalbuminuria is an important prognostic marker for kidney disease, and its detection should prompt a clinical review of treatment options in adults with diabetes mellitus.

Term	Definition
Microvascular complications of diabetes	Diabetes is associated with disease of small blood vessels in the body caused by direct damage from hyperglycaemia, with microvascular complications, including damage to the eyes (retinopathy), kidneys (nephropathy) and nerves (neuropathy). Treatments aimed at improving glycaemic control aim to reduce the incidence of each of these complications in individuals with diabetes.
Micturition	Passing urine from the body; urination.
Observational study	Individuals or groups are observed or certain factors are measured. No attempt is made to affect the outcome. For example, an observational study of a disease or treatment would allow 'nature' or usual medical care to take its course. Changes or differences in one characteristic (for example, whether or not people received a specific treatment or intervention) are studied without intervening. There is a greater risk of selection bias than in experimental studies.
Odds ratio	Odds are a way to represent how likely it is that something will happen (the probability). An odds ratio compares the probability of something in one group with the probability of the same thing in another. An odds ratio of 1 between 2 groups would show that the probability of the event (for example a person developing a disease, or a treatment working) is the same for both. An odds ratio greater than 1 means the event is more likely in the first group. An odds ratio less than 1 means that the event is less likely in the first group. Sometimes probability can be compared across more than 2 groups – in this case, one of the groups is chosen as the 'reference category', and the odds ratio is calculated for each group compared with the reference category. For example, to compare the risk of dying from lung cancer for non-smokers, occasional smokers and regular smokers, non-smokers could be used as the reference category. Odds ratios would be worked out for occasional smokers compared with non-smokers and for regular smokers compared with non-smokers. See also confidence interval, relative risk, risk ratio.
Outcome	The impact that a test, treatment, policy, programme or other intervention has on a person, group or population. Outcomes from interventions to improve the public's health could include changes in knowledge and behaviour related to health, societal changes (for example, a reduction in crime rates) and a change in people's health and wellbeing or health status. In clinical terms, outcomes could include the number of patients who fully recover from an illness or the number of hospital admissions, and an improvement or deterioration in someone's health, functional ability, symptoms or situation. Researchers should decide what outcomes to measure before a study begins.
Pvalue	The p value is a statistical measure that indicates whether or not an effect is statistically significant. For example, if a study comparing 2 treatments found that one seems more effective than the other, the p value is the probability of obtaining these results by chance. By convention, if the p value is below 0.05 (that is, there is less than a 5% probability that the results occurred by chance) it is considered that there probably is a real difference between treatments. If the p value is 0.001 or less (less than a 1% probability that the results occurred by chance), the result is seen as highly significant. If the p value shows that there is likely to be a difference between treatments, the confidence interval describes how big the difference in effect might be.
Perioperative	The period from admission through surgery until discharge, encompassing the preoperative and postoperative periods.

Term	Definition
Peripheral sensory neuropathy	Damage or disease affecting the sensation nerves of the peripheral nervous system. In individuals with diabetes, this can occur as a microvascular complication in response to chronic hyperglycaemia exposure. The condition results in reduced sensation, classically in a stocking distribution in the lower limbs and feet, and can be associated with symptoms of painful paraesthesia, especially at night. Its diagnosis is important as it is associated with increased risk of skin injury and ulcer formation in individuals with diabetes.
Placebo	A fake (or dummy) treatment given to participants in the control group of a clinical trial. It is indistinguishable from the actual treatment (which is given to participants in the experimental group). The aim is to determine what effect the experimental treatment has had – over and above any placebo effect caused because someone has received (or thinks they have received) care or attention.
Postoperative	Pertaining to the period after patients leave the operating theatre, following surgery.
Preoperative	The period before surgery commences.
Primary care	Healthcare delivered outside hospitals. It includes a range of services provided by GPs, nurses, health visitors, midwives and other healthcare professionals and allied health professionals such as dentists, pharmacists and opticians.
Primary outcome	The outcome of greatest importance, usually the one in a study that the power calculation is based on.
Problematic hypoglycaemia	Hypoglycaemia is defined as problematic in any of the following circumstances: more than 1 episode per year of severe hypoglycaemia with no obviously preventable precipitating cause complete loss of awareness of hypoglycaemia frequent (more than 2 episodes per week) asymptomatic hypoglycaemia that is causing problems with daily activities extreme fear of hypoglycaemia.
Prodrome	Early phase of an illness before the full array of disease-specific symptoms occur
Prospective study	A research study in which the health or other characteristic of participants is monitored (or 'followed up') for a period of time, with events recorded as they happen. This contrasts with retrospective studies.
Publication bias	Publication bias occurs when researchers publish the results of studies showing that a treatment works well and don't publish those showing it did not have any effect. If this happens, analysis of the published results will not give an accurate idea of how well the treatment works. This type of bias can be assessed by a funnel plot.
Quality of life	See 'Health-related quality of life'.
Quality-adjusted life year (QALY)	A measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life. One QALY is equal to 1 year of life in perfect health. QALYS are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality of life score (on a scale of 0 to 1). It is often measured in terms of the person's ability to perform the activities of daily life, freedom from pain and mental disturbance.
Randomisation	Assigning participants in a research study to different groups without taking any similarities or differences between them into account. For example, it

Term	Definition
	could involve using a random numbers table or a computer-generated random sequence. It means that each individual (or each group in the case of cluster randomisation) has the same chance of receiving each intervention.
Randomised controlled trial (RCT)	A study in which a number of similar people are randomly assigned to 2 (or more) groups to test a specific drug or treatment. One group (the experimental group) receives the treatment being tested, the other (the comparison or control group) receives an alternative treatment, a dummy treatment (placebo) or no treatment at all. The groups are followed up to see how effective the experimental treatment was. Outcomes are measured at specific times and any difference in response between the groups is assessed statistically. This method is also used to reduce bias.
RCT	See 'Randomised controlled trial'.
Receiver operated characteristic (ROC) curve	A graphical method of assessing the accuracy of a diagnostic test. Sensitivity is plotted against 1 minus specificity. A perfect test will have a positive, vertical linear slope starting at the origin. A good test will be somewhere close to this ideal.
Reference standard	The test that is considered to be the best available method to establish the presence or absence of the outcome – this may not be the one that is routinely used in practice.
Relative risk (RR)	The ratio of the risk of disease or death among those exposed to certain conditions compared with the risk for those who are not exposed to the same conditions (for example, the risk of people who smoke getting lung cancer compared with the risk for people who do not smoke). If both groups face the same level of risk, the relative risk is 1. If the first group had a relative risk of 2, subjects in that group would be twice as likely to have the event happen. A relative risk of less than one means the outcome is less likely in the first group. Relative risk is sometimes referred to as risk ratio.
Review question	In guideline development, this term refers to the questions about treatment and care that are formulated to guide the development of evidence-based recommendations.
Secondary outcome	An outcome used to evaluate additional effects of the intervention deemed a priori as being less important than the primary outcomes.
Sensitivity	How well a test detects the thing it is testing for. If a diagnostic test for a disease has high sensitivity, it is likely to pick up all cases of the disease in people who have it (that is, give a 'true positive' result). But if a test is too sensitive it will sometimes also give a positive result in people who don't have the disease (that is, give a 'false positive'). For example, if a test were developed to detect if a woman is 6 months pregnant, a very sensitive test would detect everyone who was 6 months pregnant, but would probably also include those who are 5 and 7 months pregnant. If the same test were more specific (sometimes referred to as having higher specificity), it would detect only those who are 6 months pregnant, and someone who was 5 months pregnant would get a negative result (a 'true negative'). But it would probably also miss some people who were 6 months pregnant (that is, give a 'false negative'). Breast screening is a 'real-life' example. The number of women who are recalled for a second breast screening test is relatively high because the test is very sensitive. If it were made more specific, people who don't have the disease would be less likely to be called back for a second test but more women who have the disease would be missed.

Term	Definition
Sensitivity analysis	A means of representing uncertainty in the results of economic evaluations. Uncertainty may arise from missing data, imprecise estimates or methodological controversy. Sensitivity analysis also allows for exploring the generalisability of results to other settings. The analysis is repeated using different assumptions to examine the effect on the results. One-way simple sensitivity analysis (univariate analysis): each parameter is varied individually in order to isolate the consequences of each parameter on the results of the study. Multi-way simple sensitivity analysis (scenario analysis): 2 or more parameters are varied at the same time and the overall effect on the results is evaluated. Threshold sensitivity analysis: the critical value of parameters above or below which the conclusions of the study will change are identified. Probabilistic sensitivity analysis: probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques (for example, Monte Carlo simulation).
Severe hypoglycaemia	Severe hypoglycaemia is defined as a blood glucose level that is sufficiently low to cause a reduced level of function in an individual such that they are unable to self-manage a hypoglycaemia episode and require help from another individual to achieve normoglycaemia.
Significance (statistical)	A result is deemed statistically significant if the probability of the result occurring by chance is less than 1 in 20 ($p<0.05$).
Specificity	The proportion of true negatives that are correctly identified as such. For example in diagnostic testing the specificity is the proportion of non-cases correctly diagnosed as non-cases. See related term ‘Sensitivity’. In terms of literature searching a highly specific search is generally narrow and aimed at picking up the key papers in a field and avoiding a wide range of papers.
Stakeholder	An organisation with an interest in a topic that NICE is developing a clinical guideline or piece of public health guidance on. Organisations that register as stakeholders can comment on the draft scopeand the draft guidance. Stakeholders may be: • manufacturers of drugs or equipment • national patient and carer organisations • NHS organisations • organisations representing healthcare professionals.
Systematic review	A review in which evidence from scientific studies has been identified, appraised and synthesised in a methodical way according to predetermined criteria. It may include a meta-analysis.
Time horizon	The time span over which costs and health outcomes are considered in a decision analysis or economic evaluation.
Univariate	Analysis which separately explores each variable in a data set.
Utility	In health economics, a 'utility' is the measure of the preference or value that an individual or society places upon a particular health state. It is generally a number between 0 (representing death) and 1 (perfect health). The most widely used measure of benefit in cost–utility analysis is the quality-adjusted life year, but other measures include disability-adjusted life years (DALYs) and healthy year equivalents (HYEs).