NCC-WCH

Final version 1.0

Diabetes (type 1 and type 2) in children and young people:

Diagnosis and management

NICE Guideline 18

Methods, evidence and recommendations

August 2015

May 2023: NICE's original guidance on diabetes in children and young people was published in 2004. It was updated in 2015, 2020, 2022 and 2023. See the NICE website for the guideline recommendations and the evidence reviews for the 2020, 2022 and 2023 updates. This document preserves evidence reviews and committee discussions for areas of the guideline that were not updated in 2020, 2022 and 2023.

Final version

Commissioned by the National Institute for Health and Care Excellence

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.

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Contents

1 Guideline summary

1.1 Guideline development group membership, NCC-WCH staff and acknowledgements

1.1.1 2004 original guideline

Table 1: Guideline development group members

Name	Role
Stephen Greene	Paediatrician and Group Leader
Jeremy Allgrove	Paediatrician
Timothy Barrett	Paediatrician
Vincent Connolly	Physician
James Cripps	Consumer Representative
Jo Dalton	Specialist Nurse Practitioner, Paediatric Diabetes
Alan English	Clinical Psychologist
Jane Houghton	Nurse Consultant
Mustafa Kapasi	General Practitioner
Gill Regan	Paediatric Dietitian
Carol Williams	Consumer Representative

Table 2: National Collaborating Centre for Women's and Children's Health staff

Name	Role
Jane Thomas	Director
Moira Mugglestone	Deputy Director
Anna Burt	Research Fellow
Gregory Eliovson	Informatics Specialist
Alex McNeil	Research Assistant
Anna Bancsi	Work Programme Coordinator
Hannah Rose Douglas	Health Economist, London School of Hygiene and Tropical Medicine
Dimitra Lambrelli	Health Economist

1.1.1.1 Acknowledgements

Additional support was received from:

Heather Brown, Helena Campbell, Susan Davidson, Jennifer Gray, Ann-Britt Jones, Irene Kwan, Susan Murray, Deirdre Quinlan, Felix Ram, Amanda Sage and Natalie Terry at the NCC- WCH; Carol Carson at the Royal Hospital for Sick Children, Edinburgh; Jessica Datta and Hannah Olle at the National Children's Bureau; Rob Grant, Stephen Barnes and Hilary Jackson at the National Collaborating Centre for Chronic Conditions; and Laura Price, freelance medical writer and editor. We also thank the Patient Involvement Unit for NICE (whose glossary was adapted for use in this guideline) and the young people who participated in the consultation day, including: Rhian Anderson, Lowri Barrett, Luna Begum, Ruth Davidson, Sarah Greig, Brian Henderson, Cherelle Hurndall, Jennifer Hurst, Alex Lipinski, Louisa Oram, Stacey Phillips, Andrew Souter, Melanie Stephenson, James Titmuss and Rosie Westwell.

1.1.2 2015 update

This section was updated in 2015.

Table 3: Guideline development group members

Name	Role
Jerry Wales	Paediatric Endocrinologist and Chair
Francesca Annan	Paediatric Diabetes Dietitian
Jo Dalton	Paediatric Diabetes Specialist Nurse
Jacqueline Double	Lay Member
Sarah Eaton	General Practitioner
Julie Edge	Paediatric Diabetologist and Chair of the diabetic ketoacidosis (DKA) subgroup
Nikhil Gokani	Lay Member
William Lamb	Paediatric Diabetologist
Carol Metcalfe	Paediatric Diabetes Specialist Nurse (from June 2014)
Claire Pesterfield	Paediatric Diabetes Specialist Nurse (to June 2014)

Table 4: National Collaborating Centre for Women's and Children's Health staff

Names	Role
Sarah Bailey	Research Associate (from August 2013 to June 2014)
Frauke Becker	Research Assistant – Health Economist (from March 2013 to March 2014)
Zosia Beckles	Information Scientist
Anne Carty	Project Manager (from June 2015)
Rupert Franklin	Project Manager (from September 2013 to June 2014)
Yelan Guo	Research Fellow (from October 2013)
Paul Jacklin	Senior Research Fellow – Health Economist
Sadia Janjua	Research Fellow (from July 2014)
Juliet Kenny	Project Manager (from May 2012 to March 2015)
Hugh McGuire	Senior Research Fellow (to March 2014)
Paul Mitchell	Research Fellow – Health Economist (from April to August 2014)
Moira Mugglestone	Director (from October 2012)
M Stephen Murphy	Clinical Director for Children's Health
Su Park	Research Assistant (from April to August 2013)
Nitara Prasannan	Research Associate (from March to June 2013)
Wendy Riches	Executive Director (to September 2012)
Grammati Sarri	Senior Research Fellow and Guideline Lead (from October 2014 to May 2015)
Lilian Stevens	Project Manager (from March to April 2015)
Cristina Visintin	Project Manager (to April 2012)
Amy Wang	Research Fellow (from June to December 2014)
Katie Webster	Research Fellow (from September 2013 to June 2015)

Table 5: Expert advisers

Name	Role
Katharine Barnard	Clinical Psychologist
Andrew Durward	Paediatric Intensivist

1.1.2.1 Acknowledgements

Additional support was received from:

Alex Allen, Paul Miller, Rachel O'Mahony, Nancy Pursey and Richard Whittome at the National Clinical Guideline Centre (NCGC) who undertook the evidence review for the question about diagnosis of diabetes; Fiona Beyer, Taryn Krause and Nancy Turnbull who contributed to the guideline as freelance consultants; Nicole Glaser at University of California, Davis, USA, who contributed individual patient data for the review question about the rate of rehydration during diabetic ketoacidosis (DKA); David Dunger and M. Loredana Marcovecchio of the University of Cambridge and Julie Edge of the University of Oxford who contributed data from the Oxford Regional Prospective Study for the review question about monitoring for nephropathy in children and young people with type 1 diabetes; and Karen Packham, editor.

1.2 Foreword

This guideline is a partial update of the NICE clinical guideline Type 1 diabetes: diagnosis and management of type 1 diabetes (CG15, published July 2004) and replaces the part of CG15 that relates to children and young people.

New and updated recommendations have been included on the role of C-peptide and antibody testing in the diagnosis of type 1 and type 2 diabetes and the following areas related to type 1 diabetes:

- structured education programmes
- psychological interventions to improve adherence
- multiple daily injections versus mixed insulin injections
- HbA1c (glycated haemoglobin) targets
- glucose monitoring strategies
- blood ketone monitoring compared with urine ketone monitoring
- dietary advice, including carbohydrate counting and glycaemic index
- recognition and management of diabetic ketoacidosis (DKA)
- recognition of complications (retinopathy and nephropathy).

Additionally, recommendations have been added on the following areas related to type 2 diabetes:

- structured education programmes
- psychological interventions to improve adherence
- dietary advice to optimise glycaemic control
- weight management in children and young people who are overweight or obese to improve glycaemic control
- metformin monotherapy
- HbA1c targets
- recognition and management of DKA
- recognition of complications and comorbidities (hypertension, dyslipidaemia, retinopathy and nephropathy).

Recommendations in this guideline are marked as **[new 2015]**, **[2015]**, **[2004]** or **[2004, amended 2015]**:

- **[new 2015]** indicates that the evidence has been reviewed and the recommendation has been added or updated

- **[2015]** indicates that the evidence has been reviewed but no change has been made to the recommended action
- **[2004]** indicates that the evidence has not been reviewed since the original guideline
- **[2004, amended 2015**] indicates that the evidence has not been reviewed but either changes have been made to the recommendation wording that change the meaning or NICE has made editorial changes to the original wording to clarify the action to be taken. Explanations of the reasons for the changes are presented in Appendix A:.

Material from the original guideline which has been superseded by the 2015 update is presented in Appendix N:.

1.3 Care pathway/algorithm

The pathway for this guideline can be found at the following link:

https://pathways.nice.org.uk/pathways/diabetes-in-children-and-young-people

.

1.4 Recommendations

The current recommendations can be found at https://www.nice.org.uk/guidance/ng18.

1.5 Research recommendations

1. What is the clinical and cost effectiveness of a programme of structured education from diagnosis for children and young people with type 1 diabetes?
2. What is the impact of training in teaching skills for healthcare professionals on the effectiveness of education for children and young people with type 1 diabetes?
3. What is the effectiveness of education programmes in which young people with type 1 diabetes provide training for their peers?
4. [2004] Research is needed to compare the effectiveness of continuous subcutaneous insulin infusion (or insulin pump therapy) and multiple daily injection regimens in children and young people with type 1 diabetes.
5. [2004] Research is needed to evaluate the effectiveness of long-acting insulin analogues in children and young people with type 1 diabetes.
6. [2004] Further research is required to evaluate the effectiveness of insulin delivery systems in children and young people with type 1 diabetes.
7. [2004] Research is needed to compare the effectiveness of insulin delivery modes (for example, dermal, nasal, oral and pulmonary) in children and young people with type 1 diabetes.
8. What is the clinical and cost effectiveness of non-insulin agents (for example, metformin) combined with insulin treatment in children and young people with type 1 diabetes?
9. What is the impact of educating children and young people with type 1 diabetes and their family members or carers (as appropriate) about their glycaemic index from diagnosis?
10. What is the optimal upper limit and timing for blood glucose measurements after meals for children and young people with type 1 diabetes to reach an HbA1c level of 48 mmol/mol (6.5%) without unacceptable hypoglycaemia?
11. What is the clinical and cost effectiveness of real-time continuous glucose monitoring systems compared to 5 or more capillary blood glucose tests per day in children aged 5 years or younger with type 1 diabetes who use insulin pump therapy?
12. [2004] Research is needed to investigate the clinical implications of alternative site monitoring (for example, the arm as opposed to the finger) in children and young people with type 1 diabetes.
13. [2004] Further research is needed to evaluate the effects of persistent hypoglycaemia and recurrent diabetic ketoacidosis on neurocognitive function.
14. [2004] Further studies are needed to evaluate the effectiveness of behavioural and social interventions on anxiety and depression, eating disorders, behavioural and

conduct disorders, and adherence to therapy in children and young people with type 1 diabetes, especially in adolescence, from diagnosis and in established diabetes.

15. [2004] Further research is needed to evaluate the effectiveness of screening for cardiovascular risk factors in children and young people with type 1 diabetes.

16. What is the correlation between changes in body mass index standard deviation scores and absolute HbA1c measurements or changes in HbA1c in children and young people with type 2 diabetes?

17. What is the long-term comparative clinical and cost effectiveness of different metformin preparations for treating type 2 diabetes in children and young people?

18. What is the clinical and cost effectiveness of psychological interventions for children and young people with type 2 diabetes?

19. What is the optimal dosage of intravenous insulin for managing diabetic ketoacidosis (DKA) in children and young people?

20. [2004] Further research is needed to evaluate the effects of low blood glucose levels on learning, attendance at school and educational attainment.

21. [2004] Further research is needed to investigate young people's experiences of transition from paediatric to adult services for people with type 1 diabetes.

1.6 Schedule for updating the guideline

NICE is currently reviewing its schedule for guideline updates. For the most up-to-date information about the guideline review schedule, please see the latest version of the NICE guidelines manual available from the NICE website.

2 Introduction

2.1 Diabetes in children and young people

Diabetes is a long-term condition that can have a major impact on the life of a child or young person, as well as their family or carers. In addition to insulin therapy, diabetes management should include education, support and access to psychological services, as detailed here and in this guideline. Preparations should also be made for the transition from paediatric to adult services, which have a somewhat different model of care and evidence base.

Type 1 diabetes is becoming more common in the UK and since 2004 type 2 diabetes has also been diagnosed with increasing frequency. The 2013 to 2014 National Diabetes Audit identified 26,500 children and young people in the UK with type 1 diabetes and 500 with type 2[a]. Much of the general care for type 2 diabetes is the same as for type 1 diabetes, but the initial management is different. In addition, the overweight and obesity associated with type 2 diabetes bring an increased risk of renal complications in particular, and of problems such as hypertension and dyslipidaemia. These differences in management and complications need guidance specific to type 2 diabetes, which is included here for the first time.

A variety of genetic conditions (such as maturity-onset diabetes in the young) and other conditions (such as cystic fibrosis-related diabetes) may also lead to diabetes in children and young people, but the care of these diverse conditions is beyond the scope of this guideline.

Since 2004 there have been major changes to the routine management of type 1 diabetes in an attempt to achieve much stricter targets for blood glucose control in order to further reduce the long-term risks associated with the condition. This national guidance is the first for children and young people to recommend attempting to reach a glycated haemoglobin (HbA1c) level in the normal range and near normoglycaemia. This tight control may be achieved by intensive insulin management (multiple daily injections or insulin pump therapy) from diagnosis, accompanied by carbohydrate counting. Newer technology, such as continuous subcutaneous glucose monitoring, may also help children and young people to have better blood glucose control, although this is not currently recommended for all children and young people with type 1 diabetes.

The guideline development group believes that by implementing the strict blood glucose control recommended in this guideline, improvements can be made to diabetes care that reduce the impact of the condition on the future health of children and young people.

2.2 For whom is this guideline intended

This guideline is of relevance to those who work in or use the National Health Service (NHS) in England and Wales, in particular:

- paediatric endocrinologists, paediatric dietitians, paediatric diabetes specialist nurses, general practitioners (GPs, mental health professionals and paediatric intensivists
- those responsible for commissioning and planning healthcare services, including primary care trust and local health board commissioners, Wales commissioners and public health and trust managers
- children and young people with type 1 or type 2 diabetes and their families or carers.

[a] http://www.rcpch.ac.uk/child-health/standards-care/clinical-audit-and-quality-improvement/national-paediatric-diabetes-au-1

2.3 Related NICE guidance

Details are correct at the time of publication of the guideline (August 2015). Further information is available on the NICE website.

2.3.1 Published

2.3.1.1 General

- Medicines optimisation (2015) NICE guideline NG5
- Medicines adherence (2009) NICE guideline CG76

2.3.1.2 Condition-specific

- Diabetic foot problems (2015) NICE guideline NG19
- Type 1 diabetes in adults (2015) NICE guideline NG17
- Maintaining a healthy weight and preventing excess weight gain among adults and children (2015) NICE guideline NG7
- Diabetes in pregnancy (2015) NICE guideline NG3
- Obesity: identification, assessment and management of overweight and obesity in children, young people and adults (2014) NICE guideline CG189
- Antisocial behaviour and conduct disorders in children and young people (2013) NICE guideline CG158
- Smoking cessation in secondary care (2013) NICE guideline PH48
- Tobacco: harm-reduction approaches to smoking (2013) NICE guideline PH45
- School-based interventions to prevent smoking (2010) NICE guideline PH23
- Promoting physical activity for children and young people (2009) NICE guideline PH17
- Coeliac disease (2009) NICE guideline CG86
- Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus (2008) NICE technology appraisal guidance 151
- Preventing the uptake of smoking by children and young people (2008) NICE guideline PH14
- Smoking cessation services (2010) NICE guideline PH10
- Obesity: guidance on the prevention of overweight and obesity in adults and children (2006) NICE guideline CG43
- Brief interventions and referral for smoking cessation (2006) NICE guideline PH1
- Depression in children and young people (2005) NICE guideline CG28
- Dental recall: Recall interval between routine dental examinations (2004) NICE guideline CG19
- Eating disorders (2004) NICE guideline CG9

2.3.2 Under development

NICE is developing the following guidance:

- Type 1 diabetes: Integrated sensor-augmented pump therapy systems for managing blood glucose levels (The MiniMed Paradigm Veo System and the Vibe and G4 PLATINUM CGM system). NICE diagnostics guidance (publication expected October 2015).
- Type 2 diabetes in adults. NICE guideline (publication expected November 2015)
- Intravenous fluids therapy in children. NICE guideline (publication expected November 2015).
- Sepsis. NICE guideline (publication expected July 2016).

3 Guideline development methodology

3.1 Original (2004) methodology

This guideline was commissioned by NICE and developed in accordance with the guideline development process outlined in The Guideline Development Process – Information for National Collaborating Centres and Guideline Development Groups (available at www.nice.org.uk)

3.1.1 Literature search strategy

The aim of the literature review was to identify and synthesise relevant published evidence to answer specific clinical questions formulated and agreed by the guideline development group. Searches were performed using generic and specially developed filters, relevant medical subject heading terms and free-text terms. Details of all literature searches are available from the NCC-WCH.

Searches were carried out for each topic of interest. The Cochrane Library (up to Issue 4, 2003) was searched to identify systematic reviews (with or without meta-analyses) of randomised controlled trials (RCTs) as well as individual RCTs. The electronic databases MEDLINE (Ovid version for the period January 1966 to December 2003), EMBASE (Ovid version for the period January 1980 to December 2003), the Cumulative Index to Nursing and Allied Health Literature (Ovid version for the period January 1982 to December 2003), PsycINFO (Ovid version for the period January 1974 to December 2003), and the Database of Abstracts of Reviews of Effects were also searched.

There was no systematic attempt to search the 'grey literature' (conferences, abstracts, theses and unpublished trials).

The National Guidelines Clearinghouse database, the Turning Research into Practice database and the Organising Medical Networked Information service on the Internet were searched for guidelines produced by other development groups. The reference lists in these guidelines were checked against our searches to identify any missing evidence.

A preliminary scrutiny of titles and abstracts was undertaken and full copies of all publications that addressed the guideline development group's clinical questions were obtained. Following a critical appraisal of each publication, studies not relevant to a particular clinical question were excluded. Studies that did not report relevant outcomes were also excluded. Evidence submitted by stakeholder organisations that was relevant to the guideline development group's clinical questions and was of equivalent or better quality than evidence identified in the literature searches was also included.

It was thought that there would not be a large body of economic evidence and that specific searches could miss some relevant studies. A general search was therefore designed to find all economic studies relating to children and young people with type 1 diabetes. Additional search terms relating to economic studies were added to a search string for identifying the clinical effectiveness evidence on children and young people with type 1 diabetes. A second search on topics relating to education and psychological interventions was also undertaken. The searches were undertaken using the same databases as the clinical effectiveness searches. Additional searches were undertaken of the Health Economic Evaluations Database and the National Health Service Economic Evaluations Database.

Abstracts and/or database reviews of papers that were identified by the economic searches were reviewed and excluded if they contained no economic data or if the focus of the paper explicitly excluded children and young people. Relevant references in the bibliographies of reviewed papers were also identified and reviewed.

3.1.2 Synthesis of clinical effectiveness evidence

Evidence relating to clinical effectiveness was reviewed using established guides[3–9] and classified using the established hierarchical system shown in Table 6. This system reflects the susceptibility to bias that is inherent in particular study designs

Table 6: Levels of evidence

Level	Source of evidence
Ia	Systematic review or meta-analysis of randomised controlled trials
Ib	At least 1 randomised controlled trial
IIa	At least 1 well-designed controlled study without randomisation
IIb	At least 1 well-designed quasi-experimental study, such as a cohort study
III	Well-designed non-experimental descriptive studies, such as comparative studies, correlation studies, case–control studies and case series
IV	Expert committee reports, opinions and/or clinical experience of respected authorities

The type of clinical question dictates the highest level of evidence that may be sought. For issues of therapy or treatment, the highest possible level of evidence is a systematic review or meta-analysis of RCTs (evidence level Ia) or an individual RCT (evidence level Ib). For issues of prognosis, the highest possible level of evidence is a cohort study (evidence level IIb).

For each clinical question, the highest available level of evidence was selected. Where appropriate, for example, if a systematic review, meta-analysis or RCT existed in relation to a question, studies of a weaker design were ignored. Where systematic reviews, meta-analyses and RCTs did not exist, other appropriate experimental or observational studies were sought. For diagnostic tests, test evaluation studies examining the performance of the test were used if the efficacy of the test was required, but where an evaluation of the effectiveness of the test in the clinical management of patients and the outcome of disease was required, evidence from RCTs or cohort studies was used.

Evidence was synthesised qualitatively by summarising the content of identified papers in evidence tables and agreeing brief statements that accurately reflected the evidence. Quantitative synthesis (meta-analysis) was performed where appropriate.

Summary results and data are presented in the guideline text. More detailed results and data are presented in the accompanying evidence tables. Where possible, dichotomous outcomes are presented as relative risks (RRs) with 95% confidence intervals (CIs), and continuous outcomes are presented as mean differences with 95% CIs or standard deviations (SDs) or standard errors (SEs) where CIs were not reported. Statistically significant RRs are also presented as numbers needed to treat (NNTs) where appropriate. Meta-analyses based on dichotomous outcomes are presented as pooled RRs with 95% CIs, and meta-analyses based on continuous outcomes are presented as weighted mean differences (WMDs) with 95% CIs. The results of meta-analyses that were performed specifically for this guideline are also presented as forest plots in Appendix J:.

3.1.3 Health economics

The purpose of the economic input to the guideline was to inform the guideline development group of potential economic issues that needed to be considered, to review the economic literature, and to carry out economic analyses agreed with the guideline development group where appropriate data were available.

Since the overall body of literature was expected to be small, the economic review considered all types of economic studies (cost benefit, cost effectiveness, cost utility, cost consequence and cost minimisation). The cost data were only considered if they were

generalisable to England and Wales, or if resource use was described in sufficient detail to be able to apply UK cost data.

It was agreed that economic models using data from the clinical literature review should be considered where guideline recommendations had major resource implications, or represented a change in policy, or where clinical effectiveness data from well conducted studies were available.

3.1.4 Young people's consultation day

A young people's consultation day was organised for this guideline in collaboration with the National Children's Bureau (NCB). The objective of the consultation day was to elicit the views of young people with type 1 diabetes and their carers in relation to topics considered in the guideline. A summary of the conclusions reached following the consultation day is presented in Appendix M:. Issues relating to specific topics are also discussed in relevant sections of the guideline.

3.1.5 Forming and grading recommendations

For each clinical question, recommendations were derived using, and explicitly linked to, the evidence that supported them. Where possible, the guideline development group worked on an informal consensus basis. Where necessary, formal consensus methods (such as modified Delphi and nominal group techniques) were used to agree recommendations and audit criteria.

Each recommendation was graded according to the level of evidence upon which it was based using the established system shown in Table 7. For issues of therapy or treatment, the best possible level of evidence (a systematic review or meta-analysis or an individual RCT) would equate to a grade A recommendation. For issues of prognosis, the best possible level of evidence (a cohort study) would equate to a grade B recommendation. However, this should not be interpreted as an inferior grade of recommendation because it represents the highest level of relevant evidence.

Table 7: Grading of recommendations

Grade	Basis for recommendation
A	Based directly based on level I evidence
B	Based directly on level II evidence or extrapolated from level I evidence
C	Based directly on level III evidence or extrapolated from level I or level II evidence
D	Based directly on level IV evidence or extrapolated from level I, level II or level III evidence
GPP	Good practice point based on the view of the Guideline Development Group
NICE TA	Recommendation taken from a NICE Technology Appraisal

3.1.6 External review

The guideline has been developed in accordance with the NICE guideline development process. This has included giving registered stakeholders the opportunity to comment on the scope of the guideline, the first draft of the full and summary guidelines and the second drafts of the full and summary guidelines. In addition the first and second drafts were reviewed by an independent Guideline Review Panel (GRP) established by NICE.

The comments made by the stakeholders and the GRP were collated and presented anonymously for consideration by the guideline development group. All comments were considered systematically by the guideline development group and the resulting actions and responses were recorded.

3.1.7 Outcome measures used in the guideline

For this guideline, the management of type 1 diabetes has been assessed against a number of outcome measures linked to physical and behavioural responses to care. Some of the outcome measures relate to responses that are regarded as beneficial (such as maintenance of glycaemic control), while others relate to responses that are regarded as undesirable (such as episodes of severe hypoglycaemia and diabetic ketoacidosis). Priority outcome measures, which were agreed by the guideline development group on the basis of their relevance to patients and professionals, are shown in Table 8.

Table 8: Priority outcome measures

Outcome category	Specific outcome measures
Glucose regulation	Glycaemic control: • glycated haemoglobin (HbA1 and HbA1c) • blood glucose concentration Diabetic ketoacidosis Severity of hypoglycaemia Hypoglycaemic awareness Frequency of hypoglycaemia
Lipid regulation	Triglycerides Low-density lipoprotein cholesterol High-density lipoprotein cholesterol
Endocrine function	Normal growth, height and weight Body mass index Sexual maturation
Cardiovascular function	Blood pressure
Ocular function	Retinopathy Juvenile cataract
Renal function	Urine protein excretion ('microalbuminuria')
Hospitalisation	Number of, duration of and reason for hospital admissions Emergency hospital admissions
Physical activity	Participation in physical activity
Psychological factors	Psychological wellbeing, including self-esteem Eating disorders Quality of life Diabetes knowledge
Psychosocial factors	School participation/absence Clinic attendance
Education	Knowledge

3.1.8 Terminology used in the guideline

The internationally agreed term 'type 1 diabetes'[11] is used in this guideline, rather than 'insulin-dependent diabetes mellitus'. Similarly, 'type 2 diabetes' is used in the guideline, rather than 'non-insulin-dependent diabetes mellitus'.

The guideline relates to the care of children (people younger than 11 years) and young people (those aged 11 years or over, but under 18 years). Where appropriate, the following terms are used to refer to specific age groups:

- neonates (0 weeks or older and younger than 4 weeks)
- infants (4 weeks or older and younger than 52 weeks)
- pre-school children (1 year or older and younger than 5 years)

- primary school children (5 years or older and younger than 11 years)
- young people (11 years or older and younger than 18 years)
- adults (18 years or older).

Where children are too young to make informed decisions, their treatment and care should be discussed in consultation with their parents (or legal guardians). Some aspects of care will also require discussion with, or provision of information for, other family members (such as siblings) and carers who are not part of the family (for example, childminders and school staff).

Methodology for 2015 update

This section was updated in 2015.

3.1.9 Introduction

This guideline was commissioned by NICE and developed in accordance with the process outlined in the 2009 and 2012 editions of The guidelines manual. Table 9 summarises the key stages of the process and which version was followed for each stage.

Table 9: Stages in the NICE guideline development process and versions of The guidelines manual followed at each stage

Stage	2009 edition	2012 edition
Scoping the guideline (determining what the guideline would and would not cover)	✓	
Preparing the work plan (agreeing timelines, milestones, guideline development group constitution, etc.)	✓	
Forming and running the guideline development group	✓	
Developing review questions	✓	
Identifying evidence		✓
Reviewing and synthesising evidence		✓
Incorporating health economics		✓
Making group decisions and reaching consensus		✓
Linking guidance to other NICE guidance		✓
Creating guideline recommendations		✓
Writing the guideline		✓
Stakeholder consultation on the draft guideline		✓
Finalising and publishing the guideline		✓
Declaration of interests		✓

Information about the clinical areas covered by the guideline (and those that are excluded) is available in the scope of the guideline (reproduced in Appendix B:). A list of registered stakeholder organisations is presented in Appendix C:.

All guideline development group members' potential and actual conflicts of interest were recorded on declaration forms provided by NICE (summarised in Appendix D:). (The guideline development group chair and members, and the expert advisers to the group, were recruited under NICE's April 2007 code of conduct on declaring and dealing with conflicts of interest.) The Chair of the diabetic ketoacidosis (DKA) subgroup was an author of some studies considered by the group, and so group discussions that included consideration of such studies were chaired by the NCC-WCH's clinical director. These occasions are documented in relevant sections of the guideline. No other interests declared by guideline

development group members constituted a material conflict of interest that would influence recommendations developed by the group.

Organisations with an interest in the diagnosis and management of diabetes in children and young people were encouraged to register as stakeholders for the guideline. Registered stakeholders were consulted throughout the guideline development process.

In accordance with NICE's equality scheme, ethnic and cultural considerations and factors relating to disabilities were considered by the guideline development group throughout the development process and specifically addressed in individual recommendations where relevant. Further information is available from: www.nice.org.uk/About/Who-we-are/Policies-and-procedures/NICE-equality-scheme

This is one of 5 NICE clinical guidelines that were developed in the same timescale to address diabetes care:

- Diabetes (type 1 and type 2) in children and young people (this guideline, which was developed by the National Collaborating Centre for Women's and Children's Health [NCC-WCH])
- Diabetes in pregnancy (developed by the NCC-WCH)
- Type 1 diabetes in adults (developed by the National Clinical Guideline Centre [NCGC])
- Type 2 diabetes in adults (developed by the Internal Clinical Guidelines Programme, Centre for Clinical Practice, NICE)
- Diabetic foot problems (developed by the Internal Clinical Guidelines Programme, Centre for Clinical Practice, NICE).

NICE set up a steering committee to oversee the production of the 5 clinical guidelines. The group, which included the chairs of the guideline development groups, together with staff from the 3 guidance-producing centres and NICE, identified and resolved gaps and overlaps across the different guidance topics to ensure that the final guidelines were complementary and consistent. The guidance-producing centres shared systematic reviews and draft guideline outputs to facilitate this.

3.1.10 Developing review questions and protocols and identifying evidence

The guideline development group for this guideline formulated review questions based on the scope (see Appendix B:) and prepared a protocol for each review question (see Appendix E:). These formed the starting point for systematic reviews of relevant evidence. Published evidence was identified by applying systematic search strategies (see Appendix F:) to the following databases: Medline (1946 onwards), Embase (1974 onwards), the Health Technology Assessment (HTA) database and 3 Cochrane databases (Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews and the Database of Abstracts of Reviews of Effects). Searches to identify economic studies were undertaken using the above databases and the NHS Economic Evaluation Database (NHS EED). The Cumulative Index to Nursing and Allied Health Literature (CINAHL; 1980 onwards) and PsycINFO (1806 onwards) were searched for selected topics only (these were review questions related to dietary advice and those related to psychological and/or behavioural interventions). Where possible, searches were limited to English-language only. Generic and specially developed search filters were used to identify particular study designs, such as RCTs. There was no systematic attempt to search grey literature (conference abstracts, theses or unpublished trials), nor was hand searching of journals not indexed on the databases undertaken.

Towards the end of the guideline development process, the searches were updated and re-executed to include evidence published and indexed in the databases by 26 August 2014.

3.1.11 Reviewing and synthesising evidence

The number of studies identified for each review question is summarised in Appendix G: Some studies were excluded from the guideline reviews because they did not meet inclusion criteria specified by the guideline development group (see Appendix H:). The characteristics of each included study were summarised in evidence tables for each review question (see Appendix I:).

Raw data, or odds ratios (ORs), relative risks (RRs) or hazard ratios, together with their 95% confidence intervals (CIs), from multivariate analyses were extracted from the articles where appropriate. Data for the outcomes defined in the review protocol are summarised in tables within the relevant evidence review. Full data for all the outcomes are presented in the evidence tables (see Appendix I:).

Evidence related to clinical effectiveness was synthesised and evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. Using this approach, the quality of the evidence identified for each outcome listed in the review protocol is assessed according to the factors listed below and an overall quality rating (very low, low, moderate or high) is assigned by combining the ratings for the individual factors.

- study design (as an indicator of intrinsic bias; this determines the initial quality rating)
- limitations in the design or execution of the study (including concealment of allocation, blinding, loss to follow-up; these can reduce the quality rating)
- inconsistency of effects across studies (this can reduce the quality rating)
- indirectness (the extent to which the available evidence fails to address the specific review question; this can reduce the quality rating)
- imprecision (this can reduce the quality rating)
- other considerations (including large magnitude of effect, evidence of a dose–response relationship, or confounding variables likely to have reduced the magnitude of an effect; these can increase the quality rating in observational studies provided no downgrading for other features has occurred).

GRADE findings are presented in full in Appendix K:, with abbreviated versions (summaries of findings without the individual components of the quality assessment) presented in this document.

The type of review question determines the highest level of evidence that may be sought to answer a question. For issues of therapy or treatment, this is a well conducted systematic review or meta-analysis of RCTs or an individual RCT. Where systematic reviews, meta-analyses or individual RCTs were not identified, other appropriate experimental or observational studies were sought.

For diagnostic questions, studies evaluating the performance of the test were sought, and sensitivity, specificity and likelihood ratios for positive and negative test results (LR+ and LR−, respectively) were calculated or quoted where possible (see Table 10). Where an evaluation of the effectiveness of the test in the clinical management of the condition was required, evidence from RCTs or cohort studies was considered optimal. NICE recommends using the Quality Assessment of Studies of Diagnostic Accuracy (QUADAS) methodology checklist to assess the quality of diagnostic studies (see the NICE guidelines manual).

It is necessary to predetermine values for minimally important differences (MIDs) for outcomes in order to make an assessment of imprecision. The MIDs were discussed and agreed with the guideline development group before the reviews commenced. For dichotomous outcomes the defaults of ±0.25 for RRs and ORs relative to no effect (RR=1 or OR=1) were used and imprecision was graded according to the following 3 ‘zones’ for effect estimates: less than 0.75; 0.75 to 1.25; greater than 1.25. If the CI for a particular effect estimate was wholly within 1 of the zones then the outcome would be graded as having no

serious imprecision; if the CI spanned 2 of the zones, the outcome would be graded as having 'serious imprecision'; and if the CI spanned all 3 zones, then the outcome would be graded as having 'very serious imprecision'.

Where outcomes were continuous variables the MID was agreed at the protocol stage with the guideline development group and used when judging whether observed differences between treatment groups were considered clinically important (see Section 3.1.15 for details of MIDs used in this uideline). As with dichotomous outcomes, zones for determining imprecision of effect estimates were defined and applied based on the value that would correspond to no effect (for example a mean difference of zero) and then added to or subtracted from the MID.

The body of evidence identified for each review question (or part of a review question) was presented in a GRADE evidence profile which summarised the quality of the evidence by outcome and the findings (pooled relative and absolute effect sizes, and associated CIs). Where possible, the body of evidence corresponding to each outcome specified in the review protocol was subjected to quantitative meta-analysis. In such cases, pooled effect sizes were presented as pooled RRs, pooled ORs or weighted mean differences (WMDs). By default, meta-analyses were conducted by fitting fixed effect models, but where statistically significant heterogeneity was identified random effects models were used. Where quantitative meta-analysis could not be undertaken (for example because of heterogeneity in the included studies) the effect sizes reported in the included studies were presented for each individual study. Forest plots for meta-analyses conducted for the guideline are presented in Appendix J:.

Table 10: '2×2' table for calculation of diagnostic test accuracy parameters

	Reference standard positive	Reference standard negative	Total
Index test result positive	a (true positive)	b (false positive)	a+b
Index test result negative	c (false negative)	d (true negative)	c+d
Total	a+c	b+d	a+b+c+d=N (total number of tests in study)

Note: Sensitivity=a/(a+c), specificity=d/(b+d), LR+ =sensitivity/(1–specificity), LR− =(1−sensitivity)/specificity

3.1.12 Assessing cost effectiveness

The aims of the health economic input to the guideline were to inform the guideline development group of potential economic issues related to diagnosis and management of type 1 and type 2 diabetes in children and young people, and to ensure that recommendations represented a cost-effective use of healthcare resources. Health economic evaluations aim to integrate data on benefits (ideally in terms of quality adjusted life years [QALYs]), harms and costs of different care options.

The guideline development group prioritised a number of review questions where it was thought that economic considerations would be particularly important in formulating recommendations. A single global systematic search for published economic evidence was undertaken to cover all clinical topics addressed in the guideline. For economic evaluations, no standard system of grading the quality of evidence exists and included papers were assessed using a quality assessment checklist based on good practice in economic evaluation. Reviews of the relevant published health economic literature are presented in Section 19 and summarised alongside the relevant clinical effectiveness reviews.

Health economic considerations were aided by original economic analysis undertaken as part of the development process. For this guideline the areas prioritised for economic analysis were:

- effectiveness of structured education programmes for children and young people with type 1 diabetes (see Section 5.4 and Section 19.2)
- comparative effectiveness of multiple daily injections of insulin and mixed insulin injections in children and young people with type 1 diabetes (see Section 6.1.2 and Section 19.3)
- dietary advice based on carbohydrate counting in children and young people with type 1 diabetes using multiple daily injections of insulin (see Section 6.4.3)
- frequency of capillary blood glucose (finger-prick) testing in children and young people with type 1 diabetes (see Section 6.9.4 and Section 19.4)
- comparative effectiveness of capillary blood glucose testing and continuous glucose monitoring in children and young people with type 1 diabetes (see Section 6.10.10)
- comparative effectiveness of continuous glucose monitoring performed intermittently and continuous glucose monitoring performed in real-time in children and young people with type 1 diabetes (see Section 6.10.11)
- comparative effectiveness of blood ketone monitoring and urine ketone monitoring for the prevention of DKA (see Section 6.13 and Section 19.5).

Original analysis was not undertaken for all these areas. For structured education programmes there was recently published economic evidence undertaken from an NHS perspective (Christie 2014). For continuous glucose monitoring the guideline development group's view was that the clinical evidence was not sufficiently robust to support a recommendation for routine use and therefore the group felt that modelling was not needed to aid recommendations. The health economic analyses that were undertaken are described in detail in Section 19.

3.1.13 Evidence to recommendations

For each review question recommendations for clinical care were derived using, and linked explicitly to, the evidence that supported them. In the first instance, informal consensus methods were used by the guideline development group to agree short clinical and, where appropriate, cost effectiveness evidence statements which were presented alongside the evidence profiles. Statements summarising the group's interpretation of the evidence and any extrapolation from the evidence used to form recommendations were also prepared to ensure transparency in the decision-making process. The criteria used in moving from evidence to recommendations were:

- relative value placed on the outcomes considered
- consideration of the clinical benefits and harms
- consideration of net health benefits and resource use
- quality of the evidence
- other considerations (including equalities issues).

In areas where no substantial clinical research evidence was identified the guideline development group considered other evidence-based guidelines and consensus statements or used their collective experience to identify good practice. The health economics justification in areas of the guideline where the use of NHS resources (interventions) was considered was based on group consensus in relation to the likely cost effectiveness implications of the recommendations. The group also identified areas where evidence to answer their review questions was lacking and used this information to formulate recommendations for future research.

Towards the end of the guideline development process, formal consensus methods were used to consider all the clinical care recommendations and research recommendations that had been drafted previously, including those brought forward from the 2004 guideline. The guideline development group identified 10 key priorities for implementation (key recommendations) and 5 high-priority research recommendations. The key priorities for implementation were those recommendations thought likely to have the biggest impact on the care of children and young people with type 1 or type 2 diabetes in the NHS as a whole; hese were selected using a variant of the nominal group technique (see the NICE guidelines manual). The priority research recommendations were selected in a similar way. Questions to be addressed through further research are listed in the relevant sections of the guideline. Further details, including a summary of why further research is important for topics covered by the scope of the 2015 update and summaries of changes made to research recommendations contained in the 2004 guideline, are presented in Appendix L:.

During the selection of key priorities for implementation and key recommendations all guideline development group members had an opportunity to nominate clinical recommendations and research recommendations as potential priorities. The interests declared by group members did not impact on the eventual selection of key priorities for implementation or key research recommendations because the only potential conflict of interest (due to the DKA sub-group chair's involvement in research related to when to start and stop intravenous insulin therapy for the management of DKA; see Section 17.3.1.1) was unrelated to any of the recommendations nominated as potential priorities.

3.1.14 Stakeholder involvement

Registered stakeholder organisations were invited to send representatives to a stakeholder scoping workshop and to comment on the draft scope and draft guideline for consultation. The guideline development group carefully considered and responded to all comments received from stakeholder organisations. The comments and responses were reviewed by NICE in accordance with the NICE guideline development process.

3.1.15 Specific considerations for this guideline

The guideline scope defines children and young people as those younger than 18 years. At the beginning of the development process the guideline development group agreed that for each review question the initial approach would be to include studies only if they reported results for people younger than 18 years. This approach was relaxed for a few review questions (for example intravenous osmotic agents for the management of cerebral oedema) where otherwise there would have been very little or no evidence for the group to consider (these exceptions are noted in the corresponding review protocols). Additionally, the NICE clinical guidelines addressing care for adults with type 1 or type 2 diabetes (Type 1 diabetes in adults and Type 2 diabetes in adults) were available where evidence specific to children and young people was lacking and extrapolation from adult evidence or recommendations was agreed by the guideline development group to be appropriate, although in most cases the group used informal consensus to formulate recommendations where evidence specific to children and young people was lacking.

Selected searches were date-limited to capture evidence published since the searches for the 2004 guideline were completed (December 2003). Where searches were date-limited this is indicated in the corresponding review protocol (see Appendix F:) and relevant studies considered in the 2004 guideline were retained and included in GRADE evidence profiles. Date-limited searches were limited to January 2003 onwards to ensure that relevant articles published in or after December 2003 were identified (because some databases do not allow date-limited searches to be specified by a particular month but only by a particular year).

The outcomes presented in GRADE profiles were identified as priorities by the guideline development group during review protocol development. For most review questions, the

group limited the number of outcomes to 7 from the outset, and all of these were regarded as being critical to the formulation of recommendations. For a few questions where prioritisation of outcomes was more difficult, the group initially identified more than 7 outcomes with a view to extracting data for those most frequently reported in the studies identified for inclusion: for these questions the body of evidence identified for consideration was subsequently found to be sufficiently small for all outcomes reported in the included studies and listed in the review protocols to be extracted for consideration by the group.

For review questions in which the level of glycated haemoglobin (HbA1c) was prioritised as an outcome, evidence was extracted and presented in evidence tables and GRADE profiles using Diabetes Control and Complications Trial (DCCT) units (percentages) to allow inclusion of historical evidence. The guideline development group was, however, aware that current practice is to use International Federation of Clinical Chemistry (IFCC) units (mmol/mol) and these units were used when specific HbA1c levels were included in recommendations.

3.1.15.1 Minimally important differences

For dichotomous outcomes the defaults of ±0.25 for RRs and odds ratios ORs relative to no effect (RR=1 or OR=1) were used to assess imprecision.

MIDs for continuous variables were agreed by the guideline development group in advance of considering relevant evidence where possible, and agreed MIDs are reflected in footnotes to the GRADE profiles. MIDs that were used across several review questions are presented in Table 11.

Table 11: Minimally important differences for continuous variables used as outcomes across review questions

Outcome	Minimally important difference
HbA1c	0.5 percentage points (5.5 mmol/mol)
Body mass index standard deviation score	0.5 for weight-loss interventions 0 for all other interventions

For reviews of diagnostic or predictive accuracy of tests the following terms and thresholds were used to define the usefulness of the index test:

Sensitivity and specificity:

- low: 74.9% or below
- moderate: 75% to 89.9%
- high: 90% or above

Positive likelihood ratio:

- not useful: less than 5
- moderately useful: 5 or more but less than 10
- very useful: 10 or more

Negative likelihood ratio:

- not useful: more than 0.5
- moderately useful: more than 0.1 up to (and including) 0.5
- very useful: 0.1 or below

For correlation coefficients the following terms were used to indicate the strength of the correlation:

- very low or no correlation: r-value of 0 to 0.19 (or 0 to −0.19)

- low correlation: r-value of 0.2 to 0.39 (or −0.2 to −0.39)
- moderate correlation: r-value of 0.4 to 0.59 (or −0.4 to −0.59)
- high correlation: r-value of 0.6 to 1.0 (or −0.6 to −1.0)

3.1.15.2 Methods for the review question considering the effectiveness of C-peptide and antibody tests to distinguish between type 1 and type 2 diabetes

The details above apply to systematic reviews conducted by the NCC-WCH as part of the development of this guideline. The systematic review for the review question related to the effectiveness of C-peptide and antibody tests to distinguish between type 1 and type 2 diabetes was conducted by the guidance-producing centre for the guideline on type 1 diabetes in adults (NCGC). The methods applicable to that review are described in the corresponding full guideline. Specific considerations that apply to quality assessment for the non-comparative observational studies included for this review question are noted below for completeness.

A customised quality assessment checklist (adapted from the NICE prognostic studies checklist) was used for assessing the quality of non-comparative observational studies (for example cross-sectional studies or case-series) in the review question related to diagnosis. The main criteria considered in assessing study quality were whether:

- the study design was prospective, cross-sectional or retrospective (retrospective studies are more likely to be at higher risk of bias)
- the study sample was representative of the population of interest with regard to key characteristics, sufficient to limit potential bias to the results
- the outcome of interest was measured adequately in study participants, sufficient to limit bias
- important potential confounders were 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 included for the review question related to diagnosis were graded as low quality due to the inherent high risk of bias associated with these study designs. The specific methodological limitations of these studies is summarised in Appendix K:. As GRADE is not currently designed for these types of studies, quality was determined on a study-by-study basis (rather than an outcome-by-outcome basis) for this review question.

3.1.16 Terminology used in the guideline

The 2004 guideline used the internationally agreed terms ‘type 1 diabetes’ and ‘type 2 diabetes’ rather than ‘insulin-dependent diabetes mellitus’ and ‘non-insulin-dependent diabetes mellitus’, respectively. This terminology has been retained in the 2015 update.

Similarly, the 2015 update relates to the care of children (people younger than 11 years) and young people (those aged 11 years or over, but under 18 years), as did the 2004 guideline. The following terminology used in the 2004 guideline has been retained in the 2015 update to refer to specific age groups:

- neonates (0 weeks or older and younger than 4 weeks)
- infants (4 weeks or older and younger than 52 weeks)
- pre-school children (1 year or older and younger than 5 years)
- primary school children (5 years or older and younger than 11 years)
- young people (11 years or older and younger than 18 years)
- adults (18 years or older).

4 Diagnosis of diabetes

4.1 Introduction

This section was updated in 2015.

For the 2015 update a specific review question on the effectiveness of C-peptide and antibody tests for distinguishing type 1 and type 2 diabetes was considered. The evidence identified in relation to this review question and the guideline development group's interpretation of the evidence are presented in Section 4.3. The 2004 guideline evidence reviews related to diagnosis are presented in Section 4.2, while the 2004 recommendations and the recommendations arising from the 2015 update are presented together in Section 4.3.8.

4.2 Clinical diagnosis of diabetes

The classic symptoms of diabetes are thirst, polydipsia (increased drinking), polyuria (increased urine output), recurrent infections and weight loss. The diagnostic criteria for diabetes are the same in children, young people and adults.[11] [evidence level IV]

Children and young people with diabetes nearly always present with symptoms such as those described above, as well as metabolic changes such as hyperglycaemia (excessive glucose in the blood), marked glycosuria (glucose in the urine) and ketonuria (excessive ketone bodies in the urine).[11] [evidence level IV] Studies have shown that at diagnosis around 25% of children and young people present with diabetic ketoacidosis and in children under the age of 4 years the proportion is higher.[12,13] [evidence level III] In children and young people with severe symptoms, the diagnosis can be confirmed by a random plasma glucose concentration ≥ 11.1 mmol/l.[11] [evidence level IV] An oral glucose tolerance test (OGTT) is not usually necessary or appropriate for children and young people who present with symptoms.

In the unusual situation where a child presents without definitive symptoms but with a plasma glucose concentration ≥ 11.1 mmol/l, the World Health Organization recommends that a fasting plasma glucose test and/or an OGTT may be required to confirm the diagnosis.[11] [evidence level IV] Fasting plasma glucose measurements should be obtained after more than 8 hours without caloric intake,[14] [evidence level IV] and a fasting plasma glucose concentration ≥ 7.0mmol/l can be used to confirm the diagnosis.[11] [evidence level IV] A suitable OGTT for children and young people involves oral administration of 1.75 g of glucose/kg body weight up to a maximum of 75 g of glucose, followed by measurement of glucose and insulin levels at 0, 1 and 2 hours. Confirmation of diagnosis by this method requires a plasma glucose concentration ≥ 11.1 mmol/l from a blood sample collected 2 hours after administering the glucose load.[11] [evidence level IV]

Impaired glucose regulation (a metabolic state intermediate between normal glucose homeostasis and diabetes) occurs in 2 forms:[11] [evidence level IV]

- impaired glucose tolerance (fasting plasma glucose concentration <7.0 mmol/l, and plasma glucose concentration ≥7.8 mmol/l but <11.1 mmol/l 2 hours after OGGT)
- impaired fasting glycaemia (fasting plasma glucose concentration ≥6.1 mmol/l but <7.0 mmol/l, and plasma glucose concentration <7.8 mmol/l 2 hours after OGGT).

Impaired glucose tolerance and impaired fasting glycaemia are risk categories for future diabetes and/or adult cardiovascular disease, rather than clinical entities in their own right.[11] [evidence level IV] Children and young people with impaired glucose regulation and/or asymptomatic presentation of mild hyperglycaemia may have non-type 1 diabetes (such as early-onset type 2 diabetes, other insulin resistance syndromes, maturity-onset diabetes in

the young and molecular/enzymatic abnormalities). Non-type 1 diabetes should be considered if the child is obese, or of Black or Asian origin, or if there is a strong family history of early-onset type 2 diabetes or other syndromes.

An international expert committee considered the World Health Organization's criteria for diagnosis and classification of type 1 diabetes.[16] [evidence level IV] The expert committee agreed with the criteria used by the World Health Organization except for concluding that OGTTs should be discouraged in clinical practice due to their inconvenience, greater cost and lower reproducibility compared with fasting plasma glucose or 2 hours post-glucose plasma glucose tests.

4.2.1 Record keeping and registers

At present there is no complete national register of children and young people with type 1 diabetes in the UK. The National Paediatric Diabetes Audit, which started in 1999 and was funded through the Diabetes Foundation, is a joint initiative between Diabetes UK, the Royal College of Paediatrics and Child Health and the British Society for Paediatric Endocrinology and Diabetes. This audit project has now moved to the National Clinical Audit Support Programme. The aim of the audit is to establish a national paediatric diabetes recording system to facilitate a national audit mechanism and develop a cycle of continuous quality improvement in paediatric diabetes care throughout the UK.[17]

A 1998 survey of consultant paediatricians who provide care for children and young people with diabetes aged under 16 years in the UK found that 34% of consultants reported using a computer database. 'Twinkle' was used in 19 centres, 'Novonet' was used in 5 centres and 'Diamond' was used in 4 centres. The majority of services used locally developed databases.[18] [evidence level III]

We identified no studies that investigated the clinical effectiveness of registers for children and young people with type 1 diabetes.

An RCT of different implementation strategies for using a diabetes register found that use of registers to produce letters to remind patients of clinic appointments showed no overall improvement in glycated haemoglobin level or attendance for testing of glycated haemoglobin compared with patients who did not receive letters.[19] [evidence level Ib]

A retrospective cohort study of adult patients with all types of diabetes investigated the effects of an electronic management system compared with traditional paper medical records (n=82).[20] [evidence level IIb] The study found the electronic management system was associated with an increased number of foot examinations/year (2.9 ±1.1 versus 1.8 ±1.4, $p<0.001$), an increased number of blood pressure readings/year (3.6 ±1.6 versus 2.7 ±1.6, $p<0.0035$) and an increase in the number of patients having 4 glycated haemoglobin tests in the last year (76.9 versus 51.2, $p=0.016$). However, there was no difference between the most recent glycated haemoglobin levels (9.7 ±1.7% versus 10.2 ±1.9%).

4.3 C-peptide and antibody tests for distinguishing type 1 and type 2 diabetes

4.3.1 This section was updated in 2015.Review question

What is the effectiveness of C-peptide and antibody tests to distinguish type 1 and type 2 diabetes?

4.3.2 Introduction

The evidence review for this part of the 2015 update (Section 4.3.3 to Section 4.3.6) was prepared by the guidance-producing centre for the guideline on type 1 diabetes in adults National Clinical Guideline Centre [NCGC]). In that guideline the review question was stated as 'In adults and young people with diabetes, what is the best marker (C-peptides plus or minus antibodies) to distinguish between a diagnosis of type 1 diabetes, type 2 diabetes and other forms of diabetes?' The evidence review prepared for this guideline is specific to populations relevant to children and young people with diabetes, and more specifically to young people with diabetes because it is unlikely that people younger than 11 years will present with type 2 diabetes (Barrett 2013; see Table 12). The evidence to recommendations section in this guideline and the recommendations themselves (Section 4.3.7 and Section 4.3.8) were prepared by the guideline development group for this guideline with support from the corresponding guidance-producing centre (NCC-WCH).

The diagnosis of type 1 diabetes is usually made on clinical grounds. Type 1 diabetes is characterised by severe insulin deficiency and clinically by ketosis, as circulating insulin concentrations are not even sufficient to suppress lipolysis and ketogenesis. The type 1 patient generally has a shorter prodromal illness than someone presenting with symptomatic type 2 diabetes and very often is losing weight through increased micturition (due to osmotic dieresis) and also loss of muscle and fat. Type 1 diabetes can present at any age, although incidence peaks in early childhood (age 6 months to 5 years) and again during puberty. Although most type 1 diabetes is autoimmune in aetiology (type 1a), a proportion of type 1 diabetes patients lack any evidence of known markers of such a process (type 1b).

The need to substantiate a diagnosis occurs when a clinical feature is atypical. Until recently, in adults this has most commonly been when the clinical picture is of type 2, but the patient lacks any of the typical risk factors for type 2 at presentation; for example they have no family history, are slim, are not of a high-risk ethnicity and are well exercised. Here, evidence of the autoimmune process that underlies most type 1 diabetes may be sought, as knowing a patient is undergoing a type 1 process is likely to influence choice of therapy.

Increasingly, however, there are other reasons to wish to substantiate or refute a diagnosis of type 1 diabetes more robustly. With the growing prevalence of obesity, type 1 diabetes may arise in an overweight or obese person and the clinician (and patient) may seek extra evidence for the underlying pathology, especially if the patient is considering surgical options for obesity, which may lead to remission of type 2 diabetes but not type 1 diabetes.

A growing knowledge of single-gene defects causing diabetes has also changed the clinical picture, and although this is of more relevance in the differential diagnosis of type 2 diabetes, there have been high-profile cases of people diagnosed with type 1 diabetes in the first 6 months of life later being found to have a single-gene defect of beta cell glucose sensing and getting better control of their condition with non-injectable therapies. Genetic testing is outside the scope of this guideline: instead we have sought evidence for the efficacy, and limitations, of seeking positive markers for the type 1 process, namely evidence of autoimmunity and evidence of marked endogenous insulin secretory deficiency.

Table 12: PICO characteristics of the review question applied to children and young people with diabetes

Characteristic	Comments
Population	Young people with all types of diabetes: • young people defined as age at least 11 years but younger than 18 years (articles related to recruitment of people aged less than 11 years will be included) • diabetes types are: ○ type 1 diabetes

Characteristic	Comments
	○ type 2 diabetes ○ latent autoimmune diabetes of adulthood (LADA) ○ maturity onset diabetes of the young (MODY)
Diagnostic test	C-peptide: • plasma C-peptide (stimulated) • urinary C-peptide • urinary C-peptide:creatinine ratio Antibody tests: • anti-islet cell antibody (ICA) • anti-glutamic acid decarboxylase 65 antibody or anti-glutamic acid decarboxylase antibody (GADA) • insulinoma-associated (IA-2) autoantibody • other (zinc transporter 8 (ZnT8), islet-specific glucose-6-phosphatase catalytic subunit (IGRP), anti-ZnT8, anti-IA-2/ICA512)
Outcomes	• Presence of marker (number or percentage of participants with marker) • Concentration (titre) of marker • Change in marker over time (number or percentage of participants with marker) • Change in concentration (titre) of marker over time
Study design	All study types

GADA anti-glutamic acid decarboxylase antibody, IA-2 insulinoma-associated autoantibody, ICA anti-islet cell antibody, IGRP islet-specific glucose-6-phosphatase catalytic subunit, LADA latent autoimmune diabetes of adulthood, MODY maturity onset diabetes of the young, PICO population intervention comparison outcomes, ZnT8 zinc transporter 8

4.3.3 Description of included studies

The NCGC searched for studies that showed the presence of diagnostic markers (C-peptide and/or antibodies) in young people with different types of diabetes (type 1 diabetes, type 2 diabetes, latent autoimmune diabetes of adulthood [LADA] and maturity onset diabetes of the young [MODY], with the aim of seeing which markers could be used to distinguish between the diabetes types and thus aid diagnosis.

Twenty-two studies were included in the review (Andersson 2013; Barker 2014; Besser 2011; Borg 2003; Brunova 2002; Laadhar 2007; Lu 2014; McDonald 2011; Oram 2014; Ota 2005; Rajalakshmi 2014; Samuelsson 2013; Scholin 2004a; Scholin 2004b; Scholin 2004c; Scholin 2011; Shivaprasad 2014; Tridgell 2011; Tung 2008; Vermeulen 2011; Wenzlau 2010; Zanone 2003). Six of the studies were specific to young people with diabetes (Andersson 2013; Barker 2014; Shivaprasad 2014; Tung 2008; Vermeulen 2011; Wenzlau 2010; Zanone 2003), while the remainder were conducted in mixed populations of young people and adults (see below).

Nearly all the included studies were cross-sectional observational studies and thus were not able to be combined in a meta-analysis or GRADE evidence profile. The study details and full results have, therefore, been summarised in tables below.

Results from studies have been categorised into the following age groups:

- young people (older than 11 years but younger than 18 years)
- mixed population of young people and adults (age 11 years or older).

Due to the large number of studies retrieved, the following exclusion criteria were applied in the review (including sample size cut-off):

- studies with mixed populations of the following and no subgroup analyses for young people and/or adults:

  - children and young people (younger than 18 years)
  - all ages (children, young people and adults)
  - young people and adults with sample size of less than 50 (as there are many studies in young people and adults separately already).
- studies in young people with a sample size of less than 50 (if more than 20 studies in young people are retrieved).
- studies in children (younger than 11 years).

Unlike the guideline on type 1 diabetes in adults, which focused its evidence review on studies that included only newly diagnosed patients (diagnosis made up to 1 year prior to the study), the guideline development group for this guideline agreed that this was not an appropriate approach for younger age groups. This was because in children and young people the diagnosis is considered from the other end of the spectrum: clinicians are usually faced with children and young people in whom a diagnosis of type 1 diabetes is the default, and who after 1 year or more do not have characteristics typical of straightforward type 1 diabetes. In such children and young people a question as to whether the diabetes is a monogenic form or type 2 diabetes arises. If these children and young people do not test positive for stimulated blood or urine C-peptide after more than 1 year then they do not have type 1 diabetes and genetic tests may be considered.

Therefore, evidence for all durations of disease has been included in this review. The data for these studies are summarised in Table 13.

Table 13: Summary of studies included in the review

Study	Sample size and population	Follow-up	Outcomes[a]
Young people studies			
Andersson 2013	n=427 T1D young people (subgroup)	NA	GADA, IA-2A, IAA
Barker 2014	n=995 T1D young people (subgroup)	1 and 5 years	C-peptide
Samuelsson 2013	n=979 T1D young people	NA	C-peptide
Shivaprasad 2014	n=88 T1D young people	NA	GAD65, IA-2, ZnT8
Tung 2008	n=118 T1D (n=20 young people)	NA	C-peptide
Vermeulen 2011	n=655 T1D (n=223 young people)	NA	GADA, IA-2A, IA-2βA, IAA, ZnT8, Combi.
Zanone 2003	n=91 T1D	NA	C-peptide, GAD, IA-2, ICA, Combi
Mixed population: young people and adult studies			
Borg 2003	n=285 T1D, n=81 T2D	1 year	GAD, IA-2, ICA, Combi
Besser 2011	n=72 T1D	NA	C-peptide Urinary C-peptide/ creatinine ratio
Brunova 2002	n=55 T1D, n=137 T2D	NA	C-peptide, GAD
Laadhar 2007	n=261 T1D	NA	C-peptide
Lu 2014	n=140 T2D	NA	C-peptide
McDonald 2011	n=98 T1D	NA	GAD, IA-2
Oram 2014	n=74 T1D	NA	C-peptide, UCPCR
Ota 2005	n=101 T1D	NA	C-peptide, GAD, IA-2, Combi
Rajalakshmi 2014	n=150 T1D, n=150 T2D	NA	C-peptide

Study	Sample size and population	Follow-up	Outcomes[a]
Scholin 2004A	n=100 T1D	12 months	C-peptide, GAD, IA-2
Scholin 2004B	n=362 T1D	NA	C-peptide, GAD, IA-2, ICA
Scholin 2004C	n=254 T1D, n=30 T2D	8 years	C-peptide, GAD, IA-2
Scholin 2011	n=78 T1D	3 years	C-peptide
Tridgell 2011	n=5020 T1D	NA	GAD, IA-2, Combi
Wenzlau 2010	n=506 T1D	2.5 to 12 years	C-peptide, GAD, IA-2, ZnT8

GAD anti-glutamic acid decarboxylase, GADA anti-glutamic acid decarboxylase antibody, IA-2 insulinoma-associated autoantibody, IA-2A insulinoma-associated autoantibody, IA-2βA insulininoma beta autoantibody, IAA insulin autoantibody, ICA anti-islet cell antibody, T1D type1 diabetes, T2D type 2 diabetes, ZnT8 zinc transporter 8
a. C-peptide was measured as fasting C-peptide in nearly all of the studies; 'combi' is an abbreviation for combination.

Due to the large number of studies retrieved from the literature search and included in the review, conference abstracts were excluded.

There were no data reported in any of the studies for the marker IGRP (islet-specific glucose-6-phosphatase catalytic subunit).

4.3.4 Evidence profile

As noted above, nearly all of the studies included in the evidence review were cross-sectional observational studies and thus were not able to be combined in a meta-analysis or GRADE evidence profile. The study details and full results are summarised in tabular form in this section (Table 14 to Table 23).

4.3.4.1 Young people

Table 14: Percentage of participants with diagnostic markers: studies in young people

Diabetes type	Diagnostic marker, % of participants who were antibody positive (Ab+)				
	C-peptide	ICA	GADA / GAD65+	IA-2 / ICA512	ZnT8
T1D	-	34%	44%	45%	-
	-	-	-	47% IA-2βA	68%
Median % (range)	-	19%	62%	73%	-
	-	-	65%	19%	32%
	-	26.5	62	46	50
T2D	-	-	-	-	-
LADA	-	-	-	-	-
MODY	-	-	-	-	-

GAD65+ glutamic acid decarboxylase autoantibody 65 positive, IA-2 insulinoma-associated autoantibody, ICA anti-islet cell antibody, ICA512 anti-islet cell antibody 512, LADA latent autoimmune diabetes of adulthood, MODY maturity onset diabetes of the young, T1D type1 diabetes, T2D type 2 diabetes, ZnT8 zinc transporter 8

Table 15: Titre of diagnostic markers: studies in young people

Diabetes type	Diagnostic marker, mean titre				
	Fasting C-peptide	ICA	GADA/GAD65+	IA-2/ICA512	ZnT8
T1D	0.11 ng/ml 0.28 nm 0.34 nm/litre	-	-	-	-
T2D	1.0 nmol/litre	-	-	-	-
LADA	-	-	-	-	-
MODY	-	-	-	-	-

GAD65+ glutamic acid decarboxylase autoantibody 65 positive, IA-2 insulinoma-associated autoantibody, ICA anti-islet cell antibody, ICA512, LADA latent autoimmune diabetes of adulthood, MODY maturity onset diabetes of the young, T1D type 1 diabetes, T2D type 2 diabetes, ZnT8 zinc transporter 8

Table 16: Percentage of participants with combinations of diagnostic markers: studies in young people

Diagnostic marker	Type of diabetes			
	T1D, %	T2D	LADA	MODY
Only GAD+	-	-	-	-
Only IA-2A+	-	-	-	-
Only ICA+	-	-	-	-
Only ZnT8+	-	-	-	-
GAD+ and/or ICA+	-	-	-	-
GAD+ and/or IA-2+	68	-	-	-
GAD+/IA-2+	21 9	-	-	-
GAD±ICA+	-	-	-	-
GAD±ICA-	-	-	-	-
GAD±ICA+	-	-	-	-
GAD+/ZnT8+	16	-	-	-
IA-2+/ICA+	-	-	-	-
IA-2+/ZnT8+	2	-	-	-
ICA+/ZnT8+	-	-	-	-
ICA−/ GAD+ and/or IA-2+	40	-	-	-
ICA+/GAD- and/or IA-2−	6	-	-	-
GAD+/IA-2+/ICA+	9	-	-	-
GAD+/IA-2+/ZnT8+	6	-	-	-
IA-2+/ GAD65−	-	-	-	-
GAD65+/IA-2+	-	-	-	-
GAD65+/IA-2−	-	-	-	-
≥1 positive (GADA+, IA-2A+, IAA+)	93	-	-	-
≥1 positive (GADA+, IA-2A+, ZnT8+)	94	-	-	-
≥2 positive (GADA+, IA-2A+ and/or IAA+)	6	-	-	-
≥2 positive (GADA+, IA-2A+ and/or ZnT8+)	73	-	-	-

GAD anti-glutamic acid decarboxylase, GAD65+ glutamic acid decarboxylase autoantibody 65 positive, IA-2 insulinoma-associated autoantibody, IA-2A insulinoma-associated autoantibody, IAA insulin autoantibody, ICA anti-islet cell antibody, ICA512 anti-islet cell antibody 512, LADA latent autoimmune diabetes of adulthood, MODY maturity onset diabetes of the young, T1D type 1 diabetes, T2D type 2 diabetes, ZnT8-zinc transporter 8

Vermeulen 2011 all age groups:

- The prevalence of both insulininoma beta autoantibody (IA-2βA) and zinc transporter 8 (ZnT8) increased with the number of conventional antibodies (Abs) present.
- The prevalence of both IA-2βA and ZnT8 decreased with age at diagnosis (particularly after age 20 years).
- When testing for IA-2βA in addition to insulin autoantibody (IAA), anti-glutamic acid decarboxylase antibody (GADA) and insulinoma-associated autoantibody (IA-2A), the percentage of participants who were positive for 2 or more Abs increased from 51% to 56% (statistically significant [SS] compared with testing without the additional Ab).
- When testing for ZnT8 in addition to IAA, GADA and IA-2A, the percentage of participants who were positive for 2 or more Abs increased from 51% to 63% (SS compared with testing without the additional Ab).
- When testing for both IA-2βA and ZnT8 in addition to IAA, GADA and IA-2A, the percentage of participants who were positive for 2 or more Abs increased from 51% to 65% (SS compared with testing without the additional Abs).
- In participants with the same number of conventional Abs (positive for either 1 or 2 Abs) the prevalences of IA-2βA and ZnT8 were highest when IA-2A was also present. Thus ZnT8 was preferentially (and IA-2βA almost exclusively) associated with IA-2A.
- ZnT8A testing increased the fraction of double antibody-positive individuals more than IA-2βA.
- Random C-peptide did not vary according to ZnT8 or IA-2βA status.
- The prevalence of both IA-2βA and ZnT8 increased with the number of conventional Abs present.
- Replacing IAA by IA-2βA as a complement of GADA and IA-2A screening resulted in lower diagnostic sensitivity.

Barker 2014 all age groups:

- The titre of fasting C-peptide decreased over time (0.28 nmol, 0.26 nmol and 0.093 nmol at baseline/diagnosis, 1 year and 5 years respectively).

4.3.4.2 Young people and adults

Table 17: Percentage of participants with diagnostic markers – studies in mixed population of young people and adults

Diabetes type	Diagnostic marker, % of participants who were antibody positive (Ab+)					
	Fasting C-peptide	UCPCR	ICA	GADA/ GAD65+	IA-2/ ICA512	ZnT8
T1D	-	-	59.8%	71.1%	56.7%	-
	-	-	54%	77%	46%	-
	-	-	-	59%	37%	-
	-	-	-	66%	47%	-
	-	-	-	24.5%	94.5%	-
	-	-	-	31%	-	-
	-	-	34%	-	-	-
	-	-	62%	-	-	-
	73%	-	-	-	-	-
	-	68%	-	-	-	-
Median % (range)	73%	68%	57% (34 to 62%)	63% (24.5 to 77%)	47% (37 to 94.5%)	-

Diabetes type	Diagnostic marker, % of participants who were antibody positive (Ab+)					
	Fasting C-peptide	UCPCR	ICA	GADA/ GAD65+	IA-2/ ICA512	ZnT8
T2D	-	-	15%	21%	15%	-
	-	-	-	6.6%	-	-
Median % (range)	-	-	15%	13.8% (6.6 to 21%)	15%	-

GAD65+ glutamic acid decarboxylase autoantibody 65 positive, GADA anti-glutamic acid decarboxylase antibody, IA-2 insulinoma-associated autoantibody, ICA anti-islet cell antibody, ICA512 anti-islet cell antibody 512, T1D type 1 diabetes, T2D type 2 diabetes, UCPCR urine C-peptide:creatinine ratio, ZnT8 zinc transporter 8

Table 18: Titre of diagnostic markers – studies in mixed population of young people and adults

Diabetes type	Diagnostic marker, mean titre				
	Fasting C-peptide	ICA	GADA/GAD65+	IA-2 / ICA512	ZnT8
T1D	0.27 nmol/litre	-	-	-	-
	0.295 nmol/litre	-	-	-	-
	0.29 pmol/ml				
T2D	Ketosis group: 476 pmol/litre Non-ketosis group: 348 pmol/litre	-	-	-	-
	0.79 pmol/ml	-	-	-	-

GAD65+ glutamic acid decarboxylase autoantibody 65 positive, GADA anti-glutamic acid decarboxylase antibody, IA-2 insulinoma-associated autoantibody, ICA anti-islet cell antibody, ICA512 anti-islet cell antibody 512, T1D type 1 diabetes, T2D type 2 diabetes, ZnT8 zinc transporter 8

Table 19: Percentage of participants with combinations of diagnostic markers – studies in mixed population of young people and adults

Diagnostic marker, %	Type of diabetes			
	T1D	T2D	LADA	MODY
Only GAD+	-	-	-	-
Only IA-2A+	-	-	-	-
Only ICA+	-	-	-	-
Only ZnT8+	-	-	-	-
GAD+ and/or ICA+	-	-	-	-
GAD+ and/or IA-2+	68% 82%	- -	- -	- -
Mean (%)	75%			
GAD+/IA-2+	21% 10% 27% 37.8%	17% - - -	- - - -	- - - -
Mean (%)	24.0%	17%		
GAD+/ICA+	21%	17%	-	-
GAD+/ICA−	-	-	-	-
GAD−/ICA+	-	-	-	-
GAD+ /ZnT8+	-	-	-	-
IA-2+/ICA+	3%	11%	-	-
IA-2+/ZnT8+	-	-	-	-

Diagnostic marker, %	Type of diabetes			
	T1D	T2D	LADA	MODY
CA+/ZnT8+	-	-	-	-
ICA−/GAD+ and/or IA-2+	40%	-	-	-
ICA+ /GAD− and/or IA-2−	6%	-	-	-
GAD+/IA-2+/ ICA+	9%	-	-	-
GAD−/IA-2−/ICA−	19.7%	-	-	-
GAD+/IA-2+/ZnT8+	-	-	-	-
IA-2+/GAD65−	10%	-	-	-
GAD65+/IA-2−	32%	-	-	-

GAD anti-glutamic acid decarboxylase, GAD65 glutamic acid decarboxylase autoantibody 65, IA-2 insulinoma-associated autoantibody, IA-2A insulinoma-associated autoantibody, ICA anti-islet cell antibody, LADA latent autoimmune diabetes of adulthood, MODY maturity onset diabetes of the young, T1D type 1 diabetes, T2D type 2 diabetes, ZnT8 zinc transporter 8

Table 20: Changes in markers with disease duration – studies in mixed population of young people and adults

Type of diabetes	Changes in markers with disease duration
T1D	• % ICA+ was higher in T1D with less than 1 year duration than in the whole population (47.7% versus. 33.7%) Disease duration 0 to 5, 6 to 13 and ≥14 years: • % GADA+ decreased with increasing disease duration: 70.5%, 65.3% and 42.5% • % IA-2A+ decreased with increasing disease duration: 53.4%, 42.7% and 26.2% • % GADA+ and/or IA-2A+ decreased with increasing disease duration: 82.2%, 73.8% and 53.4%

GADA anti-glutamic acid decarboxylase antibody, IA-2A insulinoma-associated autoantibody, ICA anti-islet cell antibody, T1D type1 diabetes

Table 21: Changes in markers over time – studies in mixed population of young people and adults

Type of diabetes	Changes in markers over time
T1D	Time intervals: baseline 3, 6, 9, 12, 15, 18, 24, 30 and 36 months • % fasting C-peptide generally decreased over time: 0.24, 0.26, 0.31, 0.27, 0.27, 0.19, 0.17, 0.16, 0.12, 0.19 Time intervals: baseline (at diagnosis) and 8 years follow-up • % ICA+ decreased over time: 64% to 24% • % IA-2+ decreased over time: 46% to 34% • % GADA+ decreased over time: 76% to 65% • % C-peptide ≥0.1 nmol/litre increased over time: 60% to 76% • % C-peptide <0.1 nmol/litre increased over time: 90% to 95%
New onset T1D (<6 weeks)	Time intervals: baseline, 2.5 years and 12 years follow-up • % C-peptide decreased over time: 100%, 85.7% and not given • % GADA+ decreased over time: 95.2%, 85.7% and 11.5% • % IA-2+ decreased over time: 90.5%, 90.5% and 4.9% • % ZnT8+ decreased over time: 85.7%, 76.2% and not given

Type of diabetes	Changes in markers over time
T1D (4 years duration)	Time intervals: baseline, 2.5 years and 12 years follow-up • % C-peptide decreased over time: 100%, 85.7% and not given • % GADA+ decreased over time: 95.2%, 85.7% and 11.5% • % IA-2+ decreased over time: 90.5%, 90.5% and 4.9% • % ZnT8+ decreased over time: 85.7%, 76.2% and not given
T2D	Time intervals: baseline (at Dx) and 8 years follow-up • % C-peptide ≥0.1 nmol/litre was similar over time: 21% to 20% • % C-peptide <0.1 nmol/litre was similar over time: 4% to 3%

GADA anti-glutamic acid decarboxylase antibody, IA-2 insulinoma-associated autoantibody, ICA anti-islet cell antibody, T1D type1 diabetes, T1D type 1 diabetes, T2D type 2 diabetes, ZnT8 zinc transporter 8

Table 22: Changes in markers with age of onset – studies in mixed population of young people and adults

Type of diabetes	Changes in markers with age of onset
T1D	Age groups 2 to 7, 8 to 13 and >14 years • % of participants who were GADA+ increased with age of onset: 35.7%, 47.6% and 58.9% • % of participants who were IA-2+ decreased with age of onset: 43.1%, 53.1% and 40.6%

GADA anti-glutamic acid decarboxylase antibody, IA-2 insulinoma-associated autoantibody, T1D type 1 diabetes

Table 23: Urinary C-peptide/creatinine ratio (UCPCR) and serum C-peptide (sCP) – studies in mixed population of young people and adults

Type of diabetes	Urinary C-peptide/creatinine ratio (UCPCR) and serum C-peptide (sCP)
T1D	• MMTT 120 min UCPCR was highly correlated to 90 min CP (r=0.97; p<0.0001) • UCPCR ≥0.53 nmol/mmol had 94% sensitivity/100% specificity for significant endogenous insulin secretion (90 min CP ≥0.2 nmol/litre) • The 120 min postprandial evening meal UCPCR was highly correlated to 90 min sCP (r=0.91; p<0.0001) • UCPCR ≥0.37 nmol/mmol had 84% sensitivity/97% specificity for sCP ≥0.2 nmol/litre

MMTT mixed meal tolerance, sCP serum C-peptide, T1D type 1 diabetes, UCPCR urinary C-peptide/creatinine ratio

UCPCR measured during a mixed meal tolerance test (MMTT) or after a home meal is highly correlated with MMTT sCP. UCPCR testing is a sensitive and specific method for detecting insulin secretion. UCPCR may be a practical alternative to serum C-peptide testing, avoiding the need for in participant investigation.

4.3.5 Evidence statements

Twenty-two observational studies (cross-sectional studies and case series; total 3741 participants) showed both the percentage of participants with positivity, as well as the actual titre of diagnostic markers (antibodies: GAD, IA-2A, ICA, IAA and ZnT8; C-peptide; UCPCR) in young people and in young people and adults with type 1 diabetes, type 2 diabetes, LADA and MODY.

No studies reported results for IGRP.

4.3.5.1 Antibody tests

The following results were reported in studies of young people (total 1652 participants).

4.3.5.1.1 GAD65 / GADA

Studies reviewed reported a median prevalence of 62% in young people with type 1 diabetes. No studies were found reporting data in young people with type 2 diabetes, LADA or MODY. No studies reported data on titres.

4.3.5.1.2 IA-2

Studies reviewed reported a median prevalence of 46% in young people with type 1 diabetes. No studies were found reporting data in young people with type 2 diabetes, LADA or MODY. No studies reported data on titres.

4.3.5.1.3 ICA

Studies reviewed reported a median prevalence of 26.5% in young people with type 1 diabetes. No studies were found reporting data in young people with type 2 diabetes, LADA or MODY. No studies reported data on titres.

4.3.5.1.4 ZnT8

Studies reviewed reported a median prevalence of 50% in young people with type 1 diabetes. No studies were found reporting data in young people with type 2 diabetes, LADA or MODY. No studies reported data on titres.

4.3.5.1.5 IGRP

No studies reported results for IGRP.

4.3.5.1.6 IAA

No studies reported results for IAA.

4.3.5.1.7 C-peptide

No studies reported results for C-peptide in terms of prevalence of markers. However, 4 studies reported results for titres in type 1 diabetes and type 2 diabetes. Each study used different units of measurement and so a median summary statistic could not be reported.

4.3.5.1.8 UCPCR

No studies reported results for UCPCR.

4.3.5.1.9 Combinations of markers

In terms of combinations of markers, the only results reported for combinations of markers were from single studies in young people with type 1 diabetes. The prevalence varied depending upon which markers were combined. However, overall the evidence showed that the percentage of participants who were positive increased when using of a combination of at least 2 autoimmune antibody tests.

4.3.5.1.10 Changes over time and with age

The evidence also showed that the prevalence of antibodies also decreased with older age at diagnosis and C-peptide titre decreased over time (from baseline to both 1 year and 5 years).

4.3.5.2 Antibody tests

The following results were reported in studies of mixed populations of young people and adults (total n=2089).

4.3.5.2.1 GAD 65 / GADA

Studies reviewed reported a median prevalence of 63% in young people and adults with type 1 diabetes and 13.8% in young people and adults with type 2 diabetes. No studies were found reporting data in young people and adults with LADA or MODY. No studies reported data on titres.

4.3.5.2.2 IA-2

Studies reviewed reported a median prevalence of 47% in young people and adults with type 1 diabetes and 15% in young people and adults with type 2 diabetes. No studies were found reporting data in young people and adults with LADA or MODY. No studies reported data on titres.

4.3.5.2.3 ICA

Studies reviewed reported a median prevalence of 26.5% in young people and adults with type 1 diabetes and 15% in young people and adults with type 2 diabetes. No studies were found reporting data in young people and adults with LADA or MODY. No studies reported data on titres.

4.3.5.2.4 ZnT8

No studies reported results for ZnT8.

4.3.5.2.5 IGRP

No studies reported results for IGRP.

4.3.5.2.6 IAA

No studies reported results for IAA.

4.3.5.2.7 C-peptide

One study reported results for C-peptide: the prevalence was 73% in young people and adults with type 1 diabetes. No studies were found reporting data in young people and adults with type 2 diabetes, LADA or MODY. Four studies reported results for titres in type 1 diabetes and type 2 diabetes. Each study used different units of measurement and so a median summary statistic could not be reported.

4.3.5.2.8 UCPCR

One study reported results for UCPCR: the prevalence was 68% in young people and adults with type 1 diabetes. No studies were found reporting data in young people and adults with type 2 diabetes, LADA or MODY. No studies reported data on titres.

4.3.5.2.9 Combinations of markers

In terms of combinations of markers, the prevalence varied depending upon which markers were combined and the evidence was inconclusive. The percentage of participants who were positive seemed to be lower when the markers were combined.

4.3.5.2.10 Changes over time and with age

The evidence also showed that the prevalence of antibodies in young people and adults with type 1 diabetes decreased over time (when measured at multiple time points up to 12 years), and with increasing duration of diabetes (when measured at multiple durations up to 14 years and older). There were mixed results in terms of age of onset. In young people and adults with type 2 diabetes, C-peptide positivity was similar over time (at baseline and 8 years follow-up).

In terms of UCPCR, the evidence from a single study in young people and adults with type 1 diabetes showed that UCPCR testing was a potential alternative to serum C-peptide testing, due to the 2 tests having highly correlated results.

4.3.6 Health economics profile

No relevant economic evaluations comparing the diagnostic markers C-peptide and/or antibodies for distinguishing between type 1, type 2 and other forms of diabetes were identified.

This review question was not prioritised for health economic analysis because the guideline development group felt that there was only a limited role for these tests in a small subset of the population of children and young people with diabetes.

4.3.6.1 Unit costs

In the absence of recent UK cost effectiveness analysis, relevant unit costs are provided here to aid consideration of cost effectiveness.

Table 24: Cost of diagnostic tests

Diagnostic test	Cost	Reference
Plasma C-peptide (stimulated) (2 hour MMTT)	£177	Mark Peakman, Kings College London (personal communication)
Plasma C-peptide	£35	Guideline development group expert opinion
Urinary C-peptide/Urinary C-peptide creatinine ratio	£10.50	Mark Peakman, Kings College London (personal communication)
GADA, IA-2, ICA512, ZnT8	£20 to 41	Mark Peakman, Kings College London (personal communication)
ICA (1)	£10.50	University of Birmingham Clinical Immunology Service – April 2010[b]
ICA (2)	£17	University College London Provider to Provider Tariff 12-13[c]

GADA anti-glutamic acid decarboxylase antibody, IA-2 insulinoma-associated autoantibody, ICA islet-cell antibodies, ICA512 anti-islet cell antibody 512, MMTT mixed-meal tolerance test, ZnT8 zinc transporter 8

4.3.7 Evidence to recommendations

This section was updated in 2015.

[b] 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: http://www.uhb.nhs.uk/pdf/laboratoryhandbookuob.pdf

[c] 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

4.3.7.1 Relative value placed on the outcomes considered

The guideline development group noted that the evidence review had been designed to identify diagnostic test accuracy of C-peptide and antibody tests (for example sensitivity and specificity). However, most of the included studies incorporated an antibody test as part of the gold standard and most the studies were not designed as diagnostic test accuracy studies (instead they were prevalence studies).

The group also noted that diagnosis of diabetes can be an ongoing process, particularly if atypical features are present. For this reason, the group was particularly interested in evidence for longer durations of diabetes (for example 2 years' duration) than was the case in the guideline for type 1 diabetes in adults. In particular, the guideline development group for this guideline wished to consider evidence from studies that used C-peptide tests at 2 years' duration, whereas such studies were excluded from the review for the adults' guideline.

The guideline development group for this guideline did not wish to consider studies related to diagnosis in children (less than 11 years) because their primary interest was in distinguishing between type 1 diabetes and type 2 diabetes, and type 2 diabetes rarely occurs before age 11 years.

4.3.7.2 Consideration of clinical benefits and harms

The guideline development group emphasised that in children and young people with diabetes the default diagnosis would be one of type 1 diabetes, and this would constitute safe practice because administration of insulin would be considered at the outset. Moreover, the group's view was that type 1 diabetes was a rational assumption because there is rarely any confusion between type 1 diabetes and type 2 diabetes in children and young people (approximately 95% of children and young people in the UK who have diabetes will have type 1 diabetes).

4.3.7.3 Consideration of health benefits and resource use

For some forms of monogenic diabetes, insulin therapy is unnecessary and pharmaceutical therapies are preferable. This can have a major impact for the child or young person and their family, particularly if other family members have the same form of diabetes.

The guideline development group noted that recognition of type 2 diabetes can lead to different approaches to management, such as weight reduction strategies and the use of oral drug therapy initially.

The group also noted that antibody testing is expensive; without clear evidence of a clinical benefit and noting that as there would be no impact on subsequent management, such testing would not be considered cost effective.

4.3.7.4 Quality of evidence

The evidence identified with regard to study populations that included adults with diabetes demonstrated that antibody testing is not effective in either young people or adults (the evidence showed clearly that antibody testing could not be used to confirm or refute the diagnosis of a particular form of diabetes).

Most of the included studies constituted observational prevalence studies and the quality of this evidence was generally low. Nonetheless, the guideline development group noted that findings were consistent across studies and that the studies had sufficiently large sample sizes to lend credibility to the results reported.

4.3.7.5 Other considerations

The guideline development group noted that genetic testing is the gold standard for identifying monogenic forms of diabetes and is the only method that can confirm a suspicion of monogenic diabetes.

The group noted that current practice was to use C-peptide and antibody tests as part of the work-up for diagnosis. However, the evidence included in the guideline review suggested that such tests are of no benefit in distinguishing between different types of diabetes and so use of the tests should be discontinued.

4.3.7.6 Key conclusions

Based on the considerations above, the guideline development group recommended that when diagnosing diabetes in a child or young person, type 1 diabetes should be assumed unless there are strong indications of type 2 diabetes, monogenic diabetes or mitochondrial diabetes. Characteristics indicative of type 2 diabetes are:

- having a strong family history of type 2 diabetes
- being obese at presentation
- being of black or Asian family origin
- having no insulin requirement, or having an insulin requirement of less than 0.5 units/kg body weight/day after the partial remission phase
- showing evidence of insulin resistance (for example acanthosis nigricans).

Characteristics indicative of forms of diabetes other than type 1 or type 2 (such as other insulin resistance syndromes, or monogenic diabetes [including maturity-onset diabetes in the young] and mitochondrial diabetes) are:

- having diabetes in the first year of life (this would, for example, cover neonatal diabetes)
- rarely or never develop ketone bodies in the blood (ketonaemia) during episodes of hyperglycaemia
- having associated features, such as optic atrophy, retinitis pigmentosa, deafness or another systemic illness or syndrome.

The guideline development group also recommended that C-peptide or diabetes-specific autoantibody titres should not be measured at initial presentation to distinguish type 1 diabetes from type 2 diabetes. However, the group agreed that healthcare professionals should consider measuring C-peptide after initial presentation if there is difficulty distinguishing type 1 diabetes from other types of diabetes, and that they should be aware that C-peptide concentrations have better discriminative value the longer the interval between initial presentation and the test. The group also recommended performing genetic testing if atypical disease behaviour, clinical characteristics or family history suggest monogenic diabetes.

4.3.8 Recommendations

The current recommendations can be found at https://www.nice.org.uk/guidance/ng18.

5 Education for children and young people with type 1 diabetes

5.1 Introduction

This section was updated in 2015.

The evidence reviews in the 2004 guideline related to education for children and young people with type 1 diabetes were wide ranging and generalised. The 2004 guideline noted that further research was needed to evaluate the effectiveness of age-specific structured education and this was recognised in the grading of the recommendation related to structured education in the 2004 guideline, which reflected a limited evidence base comprising expert committee reports, opinions and clinical experience of respected authorities.

For the 2015 update a review question with the specific objective of determining the effectiveness of structured education programmes in improving outcomes for children and young people with type 1 diabetes was considered by the guideline development group. The evidence identified in relation to this review question and the guideline development group's interpretation of the evidence are presented in Section 5.4. The 2004 guideline evidence reviews related to other, more generalised aspects of education are presented in Section 5.2 and Section 5.3, while the 2004 recommendations and the recommendations arising from the 2015 update are presented together in Section 5.7.

5.2 Education at diagnosis

A consensus guideline has highlighted education as an essential part of the package of care at diagnosis.[15] [evidence level III] The consensus guideline and Diabetes UK care recommendations suggested topics that could act as a template in which to develop an appropriate curriculum, with the proviso that the content and pace of education should be determined by the individual and the model of care utilised. Education for children and young people with newly diagnosed type 1 diabetes, their families and other carers should aim to cover the following topics:[15,71] [evidence level IV]

- explaining how the diagnosis has been made and reasons for symptoms, including a simple explanation of the uncertain cause of diabetes and that there is no cause for blame
- identifying and addressing fears, anxieties and preconceived ideas of diabetes and other questions that children, young people or family members may have
- risks associated with type 1 diabetes
- the need for immediate insulin and how insulin works
- practical skills in insulin injection
- what glucose is, normal blood glucose levels, glucose targets, practical skills in self-monitoring of blood glucose and reasons for monitoring
- basic dietetic advice and information about healthy eating
- the advantages of physical activity and strategies to prevent adverse events occurring during or after physical activity
- awareness of acute complications and how to deal with them, including hypoglycaemia, stressing that glucose or sucrose must always be available
- management of type 1 diabetes during intercurrent illness, including advice not to omit insulin
- aspects of self-confidence needed for self-management

- psychological adjustment to the diagnosis of type 1 diabetes
- everyday issues such as diabetes at home and school, identification cards or bracelets and providing contacts for further advice
- information about diabetes support groups and local services for people with diabetes, including contact telephone numbers
- details of emergency telephone contacts.

A UK health technology assessment has addressed aspects of education in children, young people and young adults with type 1 diabetes (age range 9 to 21 years).[72] [evidence level Ia–II] The health technology assessment identified 5 studies that examined education of children and young people with type 1 diabetes. Three of the studies[36,73,74] [evidence level IIa–IIb] which concerned education offered in relation to the place of initial management, were discussed in Section 5.2. The 2 remaining studies[27,75] [evidence level Ib–IIa] are summarised below, together with other studies that were identified in our searches. Further evidence relating to education is presented in Section 5.3.

The young people's consultation day organised for this guideline in collaboration with the NCB found that some young people with type 1 diabetes felt they were given too much information at the time of diagnosis. Young people with type 1 diabetes wanted information aimed at them rather than just at their parents, although they understood that their parents also needed to know how to manage type 1 diabetes.[38] [evidence level IV]

An RCT in children and young people with newly diagnosed type 1 diabetes investigated the use of additional educational support at diagnosis in the form of a booklet called Improving compliance with treatment for diabetes. The study showed that there was a general tendency for lower glycated haemoglobin levels in the group given the booklet but a significantly lower glycated haemoglobin level was only seen at 10 to 13 months after diagnosis ($p<0.01$, exact results not reported).[76] [evidence level Ib]

5.2.1 Techniques for initiating insulin therapy

We found no systematic reviews, RCTs or observational studies that evaluated education for the initiation of insulin therapy for children and young people with newly diagnosed type 1 diabetes.

5.2.2 Techniques for monitoring blood glucose levels

We found 1 RCT that investigated education at diagnosis for self-monitoring of blood glucose levels.[75] [evidence level Ib] The RCT was based on 36 children and young people with newly diagnosed type 1 diabetes. The intervention group received 7 sessions of training that related specifically to self-monitoring of blood glucose for the purposes of adjusting diet, exercise and insulin administration. The intervention group was compared with a control group that received non-specific training sessions and another control group that received standard care. The group that received training in self-monitoring of blood glucose levels had lower HbA1 levels at 1 year ($p<0.01$) and 2 years ($p<0.05$) compared with the group that received standard care, but not compared with the group that received non-specific training.[75] [evidence level Ib]

5.2.3 Avoiding and treating symptoms of hypoglycaemia

We found no studies that evaluated initial education for avoiding and treating hypoglycaemia in children and young people with newly diagnosed type 1 diabetes.

An RCT involving 332 children and young people with previously diagnosed type 1 diabetes (diagnosed 5 years earlier on average) investigated an education programme involving a video and brochure that reviewed skills for self-control and treatment with the aim of

preventing hypoglycaemia. The study found no difference in the incidence of severe hypoglycaemia between the intervention and control groups after 1 year.[77] [evidence level Ib]

A non-controlled intervention study involving 86 children and young people with previously diagnosed type 1 diabetes (diagnosed 4 years earlier on average), found no difference in the incidence of hypoglycaemia after the use of a video and brochure. However, HbA1c levels were lower after 1 year and 2 years than at baseline. In this study, 84% of respondents indicated that receiving a video for home use was valuable, and 84% of respondents anticipated using the videos in future.[78] [evidence level III]

5.2.4 Psychological support

We found 1 study with a non-randomised control group that investigated the effects of intensive psychosocial education/support in the month following diagnosis.[27] [evidence level IIa] This study was based on 223 children, young people and young adults with type 1 diabetes (age range 7 to 24 years) who were followed up for 3 to 15 years. The study reported better adherence to therapy ($p<0.001$), better family relations ($p<0.02$) and better sociability ($p<0.025$) in the intervention group, although there was no significant difference in school work between the intervention and control groups, and the significant differences that were reported were specific to higher socio-economic groups.[27] [evidence level IIa]

We found no studies that investigated education for parents and other carers, dietary management, exercise or protocols for the management of intercurrent illness ('sick-day rules') in relation to children and young people with newly diagnosed type 1 diabetes. General evidence relating to these topics is discussed in Sections 5.4, 6.4, 6.5, and 8.1 respectively.

5.3 General and ongoing education

5.3.1 Universal principles of education

Education is the keystone of diabetes care.[15] [evidence level III]

Diabetes UK suggests that patient education should be a planned life-long process, starting from the point of diagnosis and remaining an essential component of diabetes care. Patient education should be tailored to the individual needs of the child or young person and their family, taking into account the level of knowledge and understanding, and the aim should be to optimise:[71] [evidence level IV]

- knowledge of diabetes, the aims of diabetes management and the prevention of complications
- motivation and attitudes to self-care, with potential barriers to self-care needing to be assessed and addressed
- the ability to define and agree personal healthcare targets and to develop strategies for meeting them
- behaviours which interact with diabetes management
- empowerment in self-management and communicating effectively with healthcare professionals.

A UK health technology assessment has extensively addressed many aspects of education in young people with type 1 diabetes (age range 9 to 21 years).[72] [evidence level Ia–II] A descriptive analysis of 62 studies was undertaken, with most (68%) of the studies being conducted in the USA and none of the studies being UK-based. The studies took place in various settings, evaluated a variety of interventions, addressed various components of diabetes care and addressed the effects by a range of outcomes, including measures of metabolic control and psychological and behavioural outcomes.[72] [evidence level Ia–II]

Twenty-five RCTs were examined in more detail, with effect sizes being calculated for 14 studies. The mean (pooled) effect size was 0.37 for psychosocial outcomes and 0.33 for glycated haemoglobin with outliers (0.08 without outliers), indicating that these interventions have a small to medium beneficial effect on diabetes management outcomes.[72] [evidence level Ia]

A narrative review was performed on the 21 studies that investigated the educational intervention by comparing outcomes before and after the intervention, but without a control group. This included evaluations of interventions for poorly controlled patients and educational interventions. All studies reported beneficial effects.[72] [evidence level III]

The health technology assessment also examined the cost effectiveness of education and psychological support.[72] It identified no good-quality economic studies that looked specifically at educational interventions. The studies that were identified were not complete economic evaluations, and the diversity of the interventions and outcomes impeded cost-effectiveness comparisons. The health technology assessment concluded that there was a lack of evidence to address the resource implications of educational interventions, and that there was insufficient evidence to construct a useful economic model for decision making.

The health technology assessment identified studies published up to the year 2000. We found no economic studies that had been published subsequently.

The health technology assessment concluded the following.[72] [evidence level IV]

- Quantitative and narrative analysis of the evidence suggested that interventions were more likely to be effective if they demonstrated the relationship between the various aspects of diabetes management. The effectiveness of interventions should be evaluated by assessing outcomes that the intervention explicitly targets for change and at an appropriate point in time post-intervention to reflect the impact of the intervention.
- Although educational interventions have shown small to medium beneficial effects on various diabetes management outcomes, well-designed trials of such interventions are still needed in the UK as currently there are no completed RCTs of educational interventions for type 1 diabetes in children and young people in the UK setting. Interventions need to be evaluated by well-designed studies that should be adequately powered for patient-preference and they should report results in such a way as to enable effect sizes to be calculated.
- An important gap in the evidence is that there is no systematic understanding of whether interventions should be targeted (for example, modified for different disease stages or different problems associated with diabetes management).[72] [evidence level Ia–III]
- To reap economic returns, interventions need to show favourable effects on behaviour and metabolic control, but there is a lack of cost-effectiveness studies that fully address the resource implications of educational interventions for children and young people and long-term consequences.

The young people's consultation day organised for this guideline in collaboration with the NCB found that young people with type 1 diabetes and their parents wanted consistent, accessible, up-to-date information on many aspects of living with type 1 diabetes, including information on:[38] [evidence level IV]

- what happens when you have type 1 diabetes
- healthy eating
- what to expect at clinic visits
- types of insulin
- injecting insulin and injection sites
- hypoglycaemia and what to do if it occurs
- complications of diabetes

- how to drink alcohol safely
- travelling abroad and leisure activities
- becoming more independent
- leaving home
- future careers and the implications of type 1 diabetes
- new products and research.

Parents felt that education should be delivered through one-to-one or group education sessions with a specialist nurse, whereas young people with type 1 diabetes were more positive about accessing information through leaflets, CD-ROMs, videos and websites.[38] [evidence level IV]

A consensus guideline recommends the following universal principles for education.[15] [evidence level IV]

- Every person with diabetes has a right to comprehensive expert practical education.
- Children and young people, their parents and other care providers should all have easy access to and be included in the educational process.
- Diabetes education should be delivered by healthcare professionals with a clear understanding of the special and changing needs of young people and their families as they grow through the different stages of life.
- Educators (doctors, nurses, dietitians and other healthcare professionals) should have access to continuing specialised training in diabetes education and educational methods.
- The priorities for healthcare professionals in diabetes education may not match those of children and young people and their families. Thus, diabetes education should be based on a thorough assessment of the child's or parent's attitudes, beliefs, learning style, ability and readiness to learn, existing knowledge and goals.
- Diabetes education needs to be adaptable and personalised so that it is appropriate to each individual's age, stage of diabetes, maturity and lifestyle, and so that it is culturally sensitive and delivered at a pace to suit the individual's needs.
- Diabetes education needs to be continuous and repeated for it to be effective.
- Diabetes education is the interface between research and clinical practice. It should be planned, documented, monitored and evaluated regularly by the diabetes care team.
- Research into diabetes educational methods is important in improving clinical practice.

5.3.2 Content of education programmes

We identified no RCTs that evaluated the content of education programmes. There are, however, many discussion papers that suggest appropriate topics for such programmes.

A consensus guideline and Diabetes UK care recommendations suggested topics that could act as a template in which to develop an appropriate curriculum, with the proviso that the content and pace of education be determined by the individual and the model of care utilised.[15,71] [evidence level IV]

Topics that should be covered at diagnosis are discussed in Section 5.2.

In the months following initial diagnosis, and at timely intervals thereafter, further education is required to build and reinforce the topics covered initially and to cover additional essential elements for living with diabetes. Education should aim to cover the following:[15,71] [evidence level IV]

- ensuring the optimal and appropriate use of therapy, including insulin secretion, action and physiology, insulin injections, types, absorption, action profiles, variability and adjustments

- basic knowledge of diabetes pathophysiology, epidemiology, classification and metabolism
- the effective management of nutrition and physical activity, including adjustments to treatment (matching insulin, food and exercise)
- monitoring, recording and acting appropriately to self-monitored blood glucose and glycated haemoglobin and the targets of control
- the detection, management and prevention of acute complications of therapy such as hypoglycaemia
- the management of type 1 diabetes during periods of intercurrent illness, to prevent hypoglycaemia and ketoacidosis
- knowledge of late complications, including the prevention, detection and treatment of complications and the need for regular assessment
- preparation of young people with type 1 diabetes so that they can make appropriate responses to unpredicted and new problems
- dealing with psychological aspects of living with diabetes
- accessing healthcare professionals when needed
- lifestyle and life events, if appropriate (including stress, holidays, travel, smoking, alcohol and recreational drugs, school, college and employment).

Diabetes UK care recommendations suggested that it would be ideal if an individualised plan could be prepared and completed by both patients and the 'educator'.[71] [evidence level IV]

5.3.3 Education according to age group

A consensus guideline and Diabetes UK care recommendations have suggested particular educational aims that are specific to different age groups.[15,71] [evidence level IV]

Educational aims for infants and pre-school children through their parents may involve the following:

- acknowledging that infants and pre-school children have total dependence on parents and care providers for injections, food and monitoring
- advising parents on the care of children with unpredictable and erratic eating and activity levels
- informing parents that hypoglycaemia is more common and possibly more severe in infants and pre-school children. Priority should be given to prevention, recognition and management of hypoglycaemia.

Educational aims for primary school children may involve:

- assisting children in learning to help with, and developing skills for, injecting insulin and self-monitoring of blood glucose
- assisting children in recognising hypoglycaemic symptoms and understanding self-management
- advising children and parents on adapting diabetes care and treatment to school programmes, school meals, exercise and sport
- advising parents on the gradual development of the child's independence and progressive handover of responsibility
- providing appropriate information for the child that does not frighten them about the possible implications of the condition in later life
- assisting the development of communication, problem-solving skills and family support.

Healthcare professionals should be aware that young people (adolescents) can become rebellious and begin to resent having to adhere to their self-care regimen. Management of

diabetes at this time can be difficult and once problems are established they can be difficult to rectify.[71] [evidence level IV] Educational aims for young people may involve the following:

- the promotion of independence and responsible self-management appropriate to the young person's level of maturity and understanding
- teaching of technical skills for developing independence in insulin administration and self-monitoring of blood glucose and strategies for dealing with dietary indiscretion, illness, hypoglycaemia, sports, etc.
- interventions that incorporate group coping skills training (including conflict resolution and bargaining techniques) that will assist in situations of conflict with parents or peers; young people should be advised that parent and peer support can be valuable
- the need for open non-judgemental information about living with diabetes, including information on minimising harm from experimentation with smoking, recreational drugs and alcohol
- the need for healthcare professionals to look out for the development of unhealthy eating habits
- the setting of achievable blood glucose targets to retain motivation
- caring for each patient's individual needs, personal priorities and social roles in their care
- providing advice and information on transition to adult care.

Knowledge about type 1 diabetes does not necessarily correlate with good glycaemic control. Successful education not only instils knowledge, but empowers and motivates children and young people to use the knowledge and assists in the development of practical skills to solve problems and improve self-management of diabetes.

5.3.4 Mode of education and resources

A UK health technology assessment conducted a descriptive analysis of 62 studies and found these studies took place in various settings and evaluated a variety of interventions. However, there was no discussion of the clinical evaluation of the mode of education and the resources used. The educational interventions in the studies included education during holidays and camps, videos, computer-assisted learning, booklets, workshops and group sessions.[72] [evidence level Ia–III]

A non-controlled study that looked at introducing an online chat-line found an improvement in glycaemic control between the start of the study and 6 months later (HbA1c 8.9% at the start of the study versus 7.8% at 6 months, no CIs given, $p<0.0001$). The number of times the children and young people decided to change their treatment in the previous 3 months was also increased from baseline (32.5% versus 83.7%), which could indicate the capacity to self-manage was improved.[79] [evidence level IIb]

5.3.5 Translation and literacy

We found 2 studies that examined the effects of literacy and language on patients with type 1 diabetes.[80,81]

A survey conducted in Birmingham showed that white young people and adults with diabetes had significantly higher levels of diabetes knowledge than Asian, Black African and Black Caribbean young people and adults with diabetes (n=161, age range 16 to 84 years, $p<0.001$). The survey also showed that white adults with diabetes had significantly higher levels of formal education, and that there was a significant association between level of education and diabetes knowledge scores ($p<0.0001$).[80] [evidence level III]

Another study examined the level of self-monitoring of blood glucose in adults with type 1 diabetes (n=44,181). This study found no significant difference in self-monitoring of blood glucose of patients who had difficulty understanding English. There was a significantly

decreased rate of self-monitoring blood glucose in patients with Asian/Pacific islander ethnicity compared with white ethnicity; however, there was no significant difference in the rate of self-monitoring of blood glucose between white, African American, Hispanic and American Indian ethnic groups.[81] [evidence level III]

We found 1 article that considered poor literacy in parents of children and young people with type 1 diabetes.[82] [evidence level IV] This suggested that individualised patient teaching plans based on the level of logic, language and experience of the family, combined with understanding, creativity and patience, can increase levels of adherence. Continued assessment, support, and reinforcement of required skills are needed to increase self-reliance and autonomy for the family and to improve healthcare for the child or young person.[82] [evidence level IV]

5.4 Structured education

This section was updated in 2015.

5.4.1 Review question

What is the effectiveness of structured education programmes in improving clinical and patient outcomes in children and young people with type 1 diabetes?

5.4.2 Introduction

The objective of this review question is to determine the effectiveness of structured education programmes in improving outcomes for children and young people with type 1 diabetes. Structured education programmes are intended to deliver information to the child or young person, and/or their family, with the intention of improving outcomes. The programmes use a process which includes:

- a structured and agreed written curriculum
- use of trained educators
- quality assurance
- audit.

The outcomes prioritised for inclusion in the review were:

- HbA1c (minimum follow-up 6 months after completion of primary intervention)
- severe hypoglycaemic episodes
- diabetic ketoacidosis (DKA; number of episodes)
- adherence to diabetes management (including self-management)
- adherence to education intervention
- health-related quality of life
- satisfaction of children, young people and families with the intervention
- risk-taking behaviours (for example smoking).

Studies included in the general evidence reviews related to education in the 2004 guideline (Section 5.2 and Section 5.3) have been considered for inclusion in the 2015 update review, but only systematic reviews and randomised controlled trials (RCTs) were eligible for inclusion here.

5.4.3 Description of included studies

Eight RCTs were identified for inclusion in this review, 3 of which were conducted in the UK (Christie 2014; Murphy 2007; Murphy 2012) and 5 in the USA (Delamater 1990; Grey 2013;

Howe 2005; Katz 2014; Svoren 2003). Details of the interventions evaluated in each study are summarised in Table 25.

Two of the UK studies were undertaken by the same study group and assessed the effectiveness of a family-centred group education programme: the first of these was a single-site trial (Murphy 2007) and this was followed by a larger-scale multisite trial (Murphy 2012). The programme was intended to promote increased sharing of diabetes responsibilities within families and improve glycaemic control. Small groups of young people and their parents were given training on self-management and family communication. In the first study (Murphy 2007) participants were randomised at diagnosis to receive structured education immediately in the first year or to receive structured education in the second year. By using the results at 12 months it was possible to compare an intervention group receiving structured education with controls who had yet to receive the intervention. At baseline, the mean HbA1c (glycated haemoglobin) was 9.1% in both groups and the mean age was 12.6 years in the structured education group and 13.1 years in the control group. In the second study (Murphy 2012) participants were randomised to structured education or conventional care. The mean HbA1c at baseline was 9.2% in the intervention group and 9.4% in the control group. The mean age was 13.1 years in the intervention group and 13.2 years in the control group. All participants had been diagnosed with type 1 diabetes for at least 1 year prior to enrolment.

The remaining UK study (Christie 2014) was a health technology assessment (HTA) report from the Child and Adult Structured Competencies Approach to Diabetes Education (CASCADE) cluster RCT. This study assessed the feasibility of providing a clinic-based structured educational group programme incorporating psychological approaches to improve long-term glycaemic control, health-related quality of life and psychosocial functioning in young people. The trial involved 362 participants with a mean age of 13.1±2.1 years in the structured programme group and 13.2±2.1 years in the control group. The mean HbA1c at baseline in the structured programme group was 9.9±1.5% and 10.0±1.5% in the control group. The structured education programme was a taught intervention designed to develop confidence in managing different aspects of diabetes, and consisted of 4 group education sessions delivered to groups of 3 to 4 families with children and young people with type 1 diabetes over 4 months. Participants were followed up and assessed at 12 months and 24 months from baseline.

The first of the US studies (Delamater 1990) was an RCT designed to evaluate the effects of a training programme related to self-management in children and young people (age range 3 to 16 years at study entry) in the first 2 years after diagnosis with type 1 diabetes. There were 36 participants and 3 treatment arms: conventional treatment, in which participants followed standard hospital procedures after discharge from hospital following the initial diagnosis (including regular outpatient contact with the healthcare team and telephone contact as needed); supportive self-care, in which participants and their parents attended sessions at frequent intervals in the first 4 months after diagnosis and then at 6 months and 12 months post-diagnosis (this group had appointments with a therapist and encouragement in self-management of blood glucose and served as an ‘attention’ control group); self-management training, in which participants had 7 sessions during the 4 months following initial diagnosis (according to the same schedule as the self-care group) and then at 6 months and 12 months post-diagnosis (the goal of the training programme was to develop and reinforce problem-solving strategies and integrate data from self-monitoring of blood glucose into everyday life).

The second US study (Grey 2013) was a multisite RCT designed to evaluate the effectiveness of 2 Internet-based education programmes (TeenCope and Managing Diabetes) in improving outcomes for young people with type 1 diabetes during adolescence. The trial involved 320 participants with a mean age of 12.3 years (range 11 to 14 years), about 37% of whom were from minority ethnic groups. TeenCope was based on social cognitive theory and a new Internet-based version of Coping Skills Training (CST), and

Managing Diabetes was a diabetes education and problem-solving programme which was developed to serve as the control arm of the trial. Each programme consisted of 5 sessions with content tailored to young people with type 1 diabetes. The sessions were undertaken once per week for 5 weeks and outcomes were assessed at 6 months' and 12 months' follow-up. At baseline, the participants had a mean HbA1c of 8.46±1.42% and the average mean duration of diabetes was 6.1±3.5 years.

The third US study (Howe 2005) compared 3 nursing interventions and their impact on glycaemic control in children and young people with type 1 diabetes. The participants were aged 1 to 16 years (mean age 12.4±3.3 years) and had had a diagnosis of type 1 diabetes for a minimum of 1 year and 2 consecutive HbA1c measurements of 8.5% or higher (mean baseline HbA1c 10.2±1.4%). The study compared standard care (control) with a single education session, and with telephone case management in addition to the education session. The education session aimed to provide families with basic diabetes management skills. The second education group additionally received regular telephone calls from the study coordinator to review and discuss diabetes-related factors.

The fourth US study (Katz 2014) designed a 3-arm, 2-year clinical study of children and young people with type 1 diabetes to assess the effectiveness of 'standard care', 'care ambassador plus' (CA+) and 'care ambassador ultra' (CA Ultra) in improving glycaemic control. The study included a total of 153 children and young people aged 8 to 16 years (median 12.9 years) who had been diagnosed with type 1 diabetes for at least 6 months. The standard care group received usual care coordinated by a 'care ambassador', who was a research assistant trained in care coordination but had no medical training. The CA+ group received a monthly outreach by the care ambassador via phone or email, in addition to the quarterly diabetes care and care coordination given to the standard care group. The CA Ultra group, in addition to monthly outreach and quarterly diabetes and care coordination, received a psycho-educational intervention conducted at quarterly study visits. At baseline the participants had a mean baseline HbA1c of 8.4±1.4%. Outcomes at 1-year and 2-year follow-up from baseline were reported.

The fifth US study (Svoren 2003) also compared 3 treatment methods based on a care ambassador framework: standard care; care ambassador alone; and care ambassador with psycho-educational modules. A care ambassador was allocated to each participant in the 2 intervention groups to monitor clinic attendance, provide families with telephone or written outreach and assist them with appointment scheduling. Psycho-educational modules comprised written teaching modules that addressed a number of issues related to diabetes care, covering topics such as understanding HbA1c, factors affecting blood glucose, the 'blame and shame' cycle, teamwork and communication, blood glucose monitoring and carbohydrate counting. The participants were aged 7 to 16 years (mean age 11.9 ±2.5 years) and diagnosed with type 1 diabetes more than 6 months before enrolment. The mean HbA1c at baseline was 8.7±1.2%.

Of the priority outcomes defined by the guideline development group, evidence was identified for mean HbA1c (Christie 2014; Delamater 1990; Grey 2013; Howe 2005; Katz 2014), change in HbA1c (Murphy 2007), episodes of severe hypoglycaemia or diabetic ketoacidosis (DKA) (Christie 2014; Murphy 2012), adherence to diabetes treatment (Howe 2005; Svoren 2003), children's and young people's health-related quality of life (Christie 2014; Katz 2014; Murphy 2012), children's and young people's satisfaction with treatment (Grey 2013) and adherence to the educational intervention (Grey 2013; Murphy 2012). No outcomes related to risk-taking behaviours were reported.

Table 25: Summary of structured education interventions and comparators

Study	Intervention	Session duration	Number of sessions	Frequency	Provider	Details of intervention
Christie 2014	CASCADE	120 minutes	4	Monthly	Paediatric diabetes specialist nurse and trained staff	A curriculum consisting of modules based on 8 competency levels to assess skills and knowledge of families/groups about managing diabetes. The teaching plan consisted of session activities, objectives, time guides and resources including key information essential for the educator, learning objectives for family and brief descriptions of each activity. Discussions included everyone in the group and participants were encouraged to share ideas and thoughts and develop own solutions to goals by evaluating past decisions and think about possibilities for the future. Young people and parents completed homework tasks including a post-module quiz.
Delamater 1990	Self-management	Not reported	9	At 1, 2, 5, 7, 9, 12, and 16 weeks after discharge following initial diagnosis and again at 6 and 12 months	Therapist, physicians nurse educator and dietitian	Participants and parents participated in sessions focusing on self-monitoring of blood glucose (SMBG) (including reinforcement of accurate monitoring and recording, and using results to understand blood glucose fluctuations). The goal of the training programme was to develop and reinforce problem-solving strategies and integrate data from SMBG into daily life and decisions regarding self-management.
	Supportive self-care	Not reported	9	At 1, 2, 5, 7, 9, 12, and 16 weeks after discharge following initial diagnosis and again at 6 and 12 months	Therapist, physicians nurse educator and dietitian	Participants and parents participated in sessions focusing on psychological adjustment issues, coping with the insulin regimen and family involvement in self-care. Self-management of blood glucose was encouraged.
	Conventional treatment	Not reported	Not reported	At 1 and 3 months after discharge following initial diagnosis and again at 6, 9 and 12 months	Physician, nurse educator and dietitian	Participants followed standard hospital procedures after discharge following the initial diagnosis. This comprised regular outpatient contact with the healthcare team and telephone contact as needed. Participants were prescribed 2 daily insulin injections and 2 to 4 daily blood glucose measurements.
Grey 2013	TeenCope	30 minutes	5	Weekly	Research staff and the study group	An Internet-based coping skills training programme. The intervention used a 'graphic novel video format' featuring a cast of characters with type 1 diabetes from a range of ethnic backgrounds to model common problematic social situations (such as parent conflict) and different coping skills to solve problems. Content included communication skills, social problem solving, stress management, positive self-talk and conflict resolution. A monitored discussion board allowed participants to communicate with young people from other participating sites.

Study	Intervention	Session duration	Number of sessions	Frequency	Provider	Details of intervention
	Managing Diabetes	30 minutes	5	Weekly	Research staff and the study group	Designed as a diabetes education and problem-solving programme to be delivered via the Internet. Used visuals and an interactive interface that allowed young people to learn about healthy eating, physical activity, glucose control, sick days and diabetes technology. Interactivity consisted of active links to more detailed information, polling about diabetes care issues and problem-solving exercises with tailored feedback to participants. Content was based on standards of care for diabetes management in young people with an emphasis on decision-making for optimal outcomes.
Howe 2005	Education and telephone case management (in addition to standard care)	Not reported	1	Single education session	Masters-prepared nurse	In addition to standard care and education session described below, participants received weekly telephone calls from the study coordinator (5 to 15 minutes per call) for 3 months or until the first clinic visit and then bimonthly calls for 3 months.
	Education only (in addition to standard care)	Unknown	1	Single education session	Masters-prepared nurse	The programme included a review of blood glucose testing, record keeping, insulin administration (including use of sliding scales), exercise management, sick-day management and carbohydrate counting. The programme did not include advanced problem-solving skills. Families were also given customised written guidance.
	Standard care	Unknown	NA	NA	Usual carer	Participants received standard care at a paediatric diabetes centre comprising 30-minute clinic visits with a nurse practitioner and endocrinologist (frequency at parents' discretion).
Katz 2014	Care ambassador ultra	30 minutes	NA	Quarterly	Care ambassador and senior study staff	Participants received a psycho-educational intervention conducted at quarterly study visits. The psycho-educational intervention consisted of a 30-minute session with participants and their parent or carer on the day of a regularly scheduled quarterly clinical visit. The psycho-educational materials related to family management of diabetes. The care ambassador facilitated problem-solving exercises and role-playing of realistic expectations for family teamwork. Senior study staff monitored the study's compliance to protocol by review of taped intervention sessions. Session topics included: family teamwork and communication; avoiding perfectionism and setting realistic goals; blood glucose monitoring and HbA1c; avoiding diabetes-related family conflict; weight gain and hypoglycaemia awareness; decreasing feelings of burnout and isolation; review sessions; a research and technology update.

Study	Intervention	Session duration	Number of sessions	Frequency	Provider	Details of intervention
	Care ambassador plus	Not reported	NA	Monthly	Care ambassador and usual care	Participants received monthly outreach by the care ambassador via telephone or email, in addition to quarterly diabetes care and care coordination given to the standard care group.
	Standard care	Unknown	NA	Quarterly	Usual care	Participants received usual paediatric diabetes subspecialty care including basic care coordination by the care ambassador to assist in scheduling quarterly clinic visits.
Murphy 2007	Family-centred group education and outpatient visits	1 hour	4	Quarterly	Different members of the multidisciplinary diabetes team	Session 1: food enjoyment with carbohydrate counting. Session 2: blood glucose testing and insulin dose adjustment. Session 3: teamwork and communication. Session 4: interdependence (sharing responsibility and letting go) Written information was provided at the end of each session.
	Waiting list	Not reported	4	Quarterly	Usual carer	Outpatient visits every 3 months during year 1 (this group received education in year 2).
Murphy 2012	Family-centred group education	1.5 hours	6	Monthly	Multidisciplinary health professionals	Family communication, carbohydrate counting, food portions, blood glucose monitoring, family problem-solving, shared decision-making, managing diabetes at school, physical activity, dealing with conflicts, family role reversal, teenage issues, communicating with health professionals and interdependence.
	Conventional clinical care	Unknown	4	Every 3 months	Usual carer	Outpatient visits every 3 months.
Svoren 2003	Care ambassador plus psycho-education	20 to 40 minutes per visit	Maximum 8 (coincided with routine medical visits individualised to participants)	Quarterly (expected but not necessarily achieved)	Written teaching modules were created by the study authors	Care ambassadors provided brief written materials and encouraged active family discussion as reinforcement. Written psycho-educational teaching modules addressed: HbA1c; factors affecting blood glucose; responding to blood glucose and avoiding the 'blame and shame' cycle; how diabetes affects the whole family and communication; myths and realities about blood glucose monitoring; carbohydrate counting and incorporating occasional sweets into a healthy diet; new trends in diabetes treatment and research in development; reviewing tools for diabetes management (HbA1c, blood glucose monitoring, understanding blood glucose, carbohydrate counting and family communication).
	Care ambassador only	5 to 10 minutes per clinic visit and 10 to 15 minutes between clinic visits	Maximum 8 (coincided with routine medical visits individualised to participants)	Quarterly (expected but not necessarily achieved)	Care ambassadors were college graduates with no formal medical education but trained by research and medical staff	Care ambassadors monitored participants' clinic attendance and provided telephone or written outreach to families after missed or cancelled appointments. They encouraged participants and their families to seek medical advice from the healthcare team in a timely manner.

CASCADE Child and Adult Structured Competencies Approach to Diabetes Education, HbA1c glycated haemoglobin, SMBG self-monitoring of blood glucose

5.4.4 Evidence profile

The evidence profile for this review question (structured education for type 1 diabetes) is presented in Table 26.

Table 26: Evidence profile for effectiveness of structured education programmes in children and young people with type 1 diabetes

Number of studies	Number of children and young people		Effect		Quality
	Structured education	Control	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Mean HbA1c at 6 months from baseline (education only versus standard care)					
1 (Howe 2005)	21	28	NA	MD 0.2 lower (1.21 lower to 0.81 higher)	Very low
Mean HbA1c at 6 months from baseline (education plus telephone case management versus standard care)					
1 (Howe 2005)	26	28	NA	MD 0.4 lower (1.28 lower to 0.48 higher)	Low
Mean HbA1c at 6 months from baseline (TeenCope versus Managing Diabetes)					
1 (Grey 2013)	167	153	NA	MD 0.02 higher (0.31 lower to 0.35 higher)	Moderate
Mean HbA1c at 12 months from baseline (TeenCope versus Managing Diabetes)					
1 (Grey 2013)	167	153	NA	MD 0.18 lower (0.49 lower to 0.13 higher)	Moderate
Mean HbA1c at 12 months from baseline (family-centred group education versus conventional clinical care)					
1 (Murphy 2012)	158	147	NA	MD 0.2 lower (0.55 lower to 0.15 higher)	Low
HbA1c change over 12 months from baseline (family-centred group education versus waiting list)					
1 (Murphy 2007)	33	34	NA	MD 0.01 lower (0.17 lower to 0.15 higher)	Moderate
Mean HbA1c at 12 months from baseline (care ambassador plus versus standard care)					
1 (Katz 2014)	52	51	NA	MD 0.1 lower (0.45 lower to 0.25 higher)	Moderate
Mean HbA1c at 12 months from baseline (care ambassador ultra versus standard care)					
1 (Katz 2014)	50	51	NA	MD 0.1 higher (0.26 lower to 0.46 higher)	Moderate
Mean HbA1c at 12 months from baseline (CASCADE versus control)					
1 (Christie 2014)	143	155	NA	MD 0.1 (0.28 lower to 0.50 higher)	Low
Mean HbA1c at 12 months post-diagnosis (supportive self-care versus conventional treatment)					
1 (Delamater 1990)	9	12	NA	MD 0.4 lower (not reported)[b]	Very low
Mean HbA1c at 24 months from baseline (care ambassador plus versus standard care)					
1 (Katz 2014)	52	51	NA	MD 0.2 lower (0.59 lower to 0.19 higher)	Low
Mean HbA1c at 24 months from baseline (care ambassador ultra versus standard care)					
1 (Katz 2014)	50	51	NA	MD 0 (0.39 lower to 0.39 higher)	Moderate
Average mean HbA1c at 24 months from baseline (care ambassador plus versus standard care)					
1 (Katz 2014)	52	51	NA	MD 0.1 lower (0.41 lower to 0.21 higher)	Moderate
Average mean HbA1c at 24 months from baseline (care ambassador ultra versus standard care)					
1 (Katz 2014)	50	51	NA	MD 0 (0.36 lower to 0.36 higher)	Moderate
Mean HbA1c at 24 months from baseline (CASCADE versus control)					
1 (Christie 2014)	135	149	NA	MD 0.03 (0.36 lower to 0.41 higher)	Moderate

Number of studies	Number of children and young people		Effect		Quality
	Structured education	Control	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Mean HbA1c at 24 months post-diagnosis (supportive self-care versus conventional treatment)					
1 (Delamater 1990)	9	12	NA	MD 0.9 lower (not reported)[b]	Very low
Mean number of severe hypoglycaemic episodes (per participant), over 12 months from baseline (Family-centred group education versus. Conventional clinical care)					
1 (Murphy 2012)	158	147	NA	MD 0.05 lower (0.21 lower to 0.11 higher)	Moderate
Severe hypoglycaemic episodes (1 or more episodes versus no episodes, parent- or adult-reported) over 12 months from baseline (CASCADE versus control)					
1 (Christie. 2014)	143	155	OR 0.76[a] (0.32 lower to 2.59 higher)	NA	Very low
Mean number of severe hypoglycaemic episodes (per participant), over 24 months from baseline (care ambassador plus psycho-education versus care ambassador only)					
1 (Svoren 2003)	97	94	NA	MD 0.17 higher (0.18 lower to 0.52 higher)	Low
Severe hypoglycaemic episodes (1 or more episodes versus no episodes, parent- or adult-reported) over 24 months from baseline (CASCADE versus control)					
1 (Christie 2014)	137	140	OR 0.92[a] (0.32 lower to 2.59 higher)	NA	Very low
Mean number of episodes of diabetic ketoacidosis (per participant), over 12 months from baseline (family-centred group education versus conventional clinical care)					
1 (Murphy 2012)	158	147	NA	MD 0.01 higher (0.09 lower to 0.11 higher)	Moderate
Adherence to diabetes treatment (percentage of positive adherence) at 6 months from baseline (education versus standard care)					
1 (Howe 2005)	21	28	NA	MD 4.9 higher (10.39 lower to 20.19 higher)	Very low
Children and young people's quality of life (DQOLY-SF), impact, at 6 months from baseline, higher score indicates better quality of life (family-centred group education versus conventional clinical care)					
1 (Murphy 2012)	158	147	NA	MD 0.7 higher (3.28 lower to 4.68 higher)	Very low
Children and young people's quality of life (DQOLY-SF), worry, at 6 months from baseline, higher score indicates better quality of life (family-centred group education versus conventional clinical care)					
1 (Murphy 2012)	158	147	NA	MD 3 lower (5.51 lower to 0.49 higher)	Low
Children and young people's quality of life (DQOLY-SF), parental involvement, at 6 months from baseline, higher score indicates better quality of life (family-centred group education versus conventional clinical care)					
1 (Murphy 2012)	158	147	NA	MD 0.3 lower (1.04 lower to 0.44 higher)	Low
Children and young people's quality of life (PedsQL) at 6 months from baseline (TeenCope versus Managing Diabetes)					
1 (Grey 2013)	167	153	NA	MD 4.63 higher (2.18 lower to 7.08 higher)	Very low
Children and young people's quality of life (PedsQL) at 12 months from baseline (TeenCope versus Managing Diabetes)					
1 (Grey 2013)	167	153	NA	MD 3.62 higher (0.98 lower to 6.26 higher)	Very low
Children and young people's quality of life (PedsQL) at 12 months from baseline, parent-reported (care ambassador plus versus standard care)					
1 (Katz 2014)	52	51	NA	MD 2.7 higher (1.93 lower to 7.33 higher)	Very low

Number of studies	Number of children and young people		Effect		Quality
	Structured education	Control	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Children and young people's quality of life (PedsQL) at 12 months from baseline, child- or young person-reported (care ambassador plus versus standard care)					
1 (Katz 2014)	52	51	NA	MD 0.1 lower (3.07 lower to 2.87 higher)	Very low
Children and young people's quality of life (PedsQL) at 12 months from baseline, parent-reported (care ambassador ultra versus standard care)					
1 (Katz 2014)	50	51	NA	MD 4.6 higher (0.06 lower to 9.26 higher)	Low
Children and young people's quality of life (PedsQL) at 12 months from baseline, child- or young person-reported (care ambassador ultra versus standard care)					
1 (Katz 2014)	50	51	NA	MD 0.8 lower (3.78 lower to 2.18 higher)	Very low
Children and young person's quality of life, PedsQL: general module, at 12 months from baseline, young person-reported (CASCADE versus control)					
1 (Christie 2014)	148	159	NA	MD 1.09 lower (3.15 lower to 0.03 higher)	Low
Children and young people's quality of life, PedsQL: diabetes module, at 12 months from baseline, young person-reported (CASCADE versus control)					
1 (Christie 2014)	148	159	NA	MD 0.62 higher (2.35 lower to 3.04 higher)	Very low
Children and young people's quality of life at 24 months from baseline, PedsQL: parent-reported (care ambassador plus versus standard care)					
1 (Katz 2014)	52	51	NA	MD 3.3 lower (7.74 lower to 1.14 higher)	Very low
Children and young people's quality of life at 24 months from baseline, PedsQL: child- or young person-reported (care ambassador plus versus standard care)					
1 (Katz 2014)	52	51	NA	MD 2.1 lower (5.46 lower to 1.26 higher)	Very low
Children and young people's quality of life at 24 months from baseline, PedsQL: parent-reported (care ambassador ultra versus standard care)					
1 (Katz 2014)	50	51	NA	MD 0.2 higher (4.22 lower to 4.62 higher)	Very low
Children and young person's quality of life at 24 months from baseline, PedsQL: child- or young person-reported (care ambassador ultra versus standard care)					
1 (Katz 2014)	50	51	NA	MD 2.1 lower (5.44 lower to 1.24 higher)	Very low
Children and young people's quality of life, PedsQL: general module, at 24 months from baseline, young person-reported (CASCADE versus control)					
1 (Christie 2014)	144	151	NA	MD 0.33 lower (2.53 lower to 1.97 higher)	Very low
Children and young person's quality of life, PedsQL: diabetes module, at 24 months from baseline, young person-reported (CASCADE versus control)					
1 (Christie 2014)	144	151	NA	MD 0.02 lower (3.19 lower to 2.72 higher)	Very low
Children and young people's satisfaction with treatment or intervention, follow-up time not reported (TeenCope versus Managing Diabetes)					
1 (Grey 2013)	167	153	NA	MD 0.08 lower (0.22 lower to 0.06 higher)	Moderate

CASCADE Child and Adult Structured Competencies Approach to Diabetes Education, DQOLY-SF Diabetes Quality of Life for Youth--Short Form; MD mean difference, NA not applicable, OR odds ratio, RCT randomised controlled trial, SD standard deviation
a. Adjusted for baseline and accounting for clustering within clinics
b. Unable to assess precision using data reported in the article, 12 months HbA1 self-management mean (SD)

5.4.5 Evidence statements

Overall, the evidence obtained from the included studies did not consistently demonstrate that structured education was more effective than comparators not involving structured education in reducing HbA1c or episodes of severe hypoglycaemia or DKA, nor in improving adherence to diabetes management, health-related quality of life, adherence to the

educational intervention or satisfaction among children and young people or their parents and carers. Further details related to this evidence are presented below.

None of the studies reported comparative data on risk-taking behaviours.

Mean HbA1c

At 6 months from baseline

The evidence from 1 study (total 49 participants) comparing structured education with standard care did not demonstrate that either intervention was more effective than the other at 6 months' follow-up. The quality of the evidence for this finding was very low.

The evidence from 1 study (total 54 participants) comparing structured education plus telephone case management with standard care did not demonstrate that either intervention was more effective than the other at 6 months' follow-up. The quality of the evidence for this finding was low.

The evidence from 1 study (total 320 participants) comparing the programmes TeenCope and Managing Diabetes did not demonstrate that either intervention was more effective than the other at 6 months' follow-up. The quality of the evidence for this finding was moderate.

At 12 months from baseline

The evidence from 1 study (total 320 participants) comparing the programmes TeenCope and Managing Diabetes did not show that either intervention was more effective than the other at 12 months' follow-up. The quality of the evidence for this finding was moderate.

The evidence from 1 study (total 305 participants) comparing family-centred group education and conventional clinical care did not demonstrate that either intervention was more effective than the other at 12 months' follow-up. The quality of the evidence for this finding was low.

The evidence from 1 study (total 69 participants) comparing family-centred group education with waiting list did not demonstrate that either intervention was more effective than the other at 12 months' follow-up. The quality of the evidence for this finding was moderate.

The evidence from 1 study (total 103 participants) comparing the programme care ambassador plus with standard care did not demonstrate that either intervention was more effective than the other at 12 months' follow-up. The quality of the evidence for this finding was moderate.

The evidence from 1 study (total 103 participants) comparing the programme care ambassador ultra with standard care did not demonstrate that either intervention was more effective than the other at 12 months' follow-up. The quality of the evidence for this finding was low.

The evidence from 1 study (total 298 participants) comparing the programme CASCADE with usual care did not demonstrate that either intervention was more effective than the other at 12 months' follow-up. The quality of the evidence for this finding was low.

The evidence from 1 study (total 21 participants) comparing a self-management training programme (conventional treatment) with supportive self-care and conventional treatment demonstrated that self-management was more effective than conventional treatment at 12 months' follow-up. The quality of the evidence for this finding was very low.

At 24 months from baseline

The evidence from 1 study (total 103 participants) comparing the programme care ambassador plus with standard care did not demonstrate that either intervention was more

effective than the other at 24 months' follow-up. The quality of the evidence for this finding was low.

The evidence from 1 study (total 101 participants) comparing the programme care ambassador ultra with standard care did not demonstrate that either intervention was more effective than the other at 24 months' follow-up. The quality of the evidence for this finding was moderate.

The evidence from 1 study (total 284 participants) comparing the programme CASCADE with usual care did not demonstrate that either intervention was more effective than the other at 24 months' follow-up. The quality of the evidence for this finding was moderate.

The evidence from 1 study (total 21 participants) comparing a self-management training programme (conventional treatment) with supportive self-care and conventional treatment demonstrated that self-management was more effective than conventional treatment at 24 months' follow-up. The quality of the evidence for this finding was very low.

Change over 12 months from baseline

The evidence from 1 study (total 305 participants) comparing family-centred group education with conventional clinical care did not demonstrate that either intervention was more effective than the other over 12 months' follow-up. The quality of the evidence for this finding was moderate.

Severe hypoglycaemia

Mean number of severe hypoglycaemic episodes over 12 months

The evidence from 1 study (total 305 participants) comparing family-centred group education with conventional clinical care did not demonstrate that either intervention was more effective than the other over 12 months' follow-up. The quality of the evidence for this finding was moderate.

The evidence from 1 study comparing the programme CASCADE with usual care (total 298 participants) demonstrated a reduced risk of severe hypoglycaemic episodes (as reported by the parent or another adult) over 12 months' follow-up. The quality of the evidence for this finding was very low.

Mean number of severe hypoglycaemic episodes over 24 months

The evidence from 1 study (total 191 participants) comparing the programme care ambassador with psycho-education and care ambassador only did not demonstrate that either intervention was more effective than the other at 24 months' follow-up. The quality of the evidence for this finding was low.

The evidence from 1 study (total 277 participants) comparing the programme CASCADE with usual care did not demonstrate that either intervention was more effective than the other (in terms of parent- or adult-reported episodes) over 24 months' follow-up. The quality of the evidence for this finding was very low.

Diabetic ketoacidosis

Mean number of episodes of diabetic ketoacidosis over 12 months

The evidence from 1 study (total 305 participants) comparing family-centred group education with conventional clinical care did not demonstrate that either intervention was more effective than the other over 12 months' follow-up. The quality of the evidence for this finding was moderate.

Adherence to diabetes management

Percentage of positive adherence at 6 months from baseline

The evidence from 1 study (total 49 participants) comparing structured education with usual care did not demonstrate that either intervention was more effective than the other at 6 months' follow-up. The quality of the evidence for this finding was very low.

Children and young people's quality of life

At 6 months from baseline

The evidence from 1 study (total 305 participants) comparing family-centred group education with conventional clinical care did not demonstrate that either intervention was more effective than the other in terms of the impact domain of quality of life (DQOLY-SF, impact) at 6 months' follow-up. The quality of the evidence for this finding was very low.

The evidence from 1 study (total 305 participants) comparing family-centred group education with conventional clinical care did not demonstrate that either intervention was more effective than the other in terms of the worry domain of quality of life (DQOLY-SF, worry) at 6 months' follow-up. The quality of the evidence for this finding was low.

The evidence from 1 study (total 305 participants) comparing family-centred group education with conventional clinical care did not demonstrate that either intervention was more effective than the other in terms of the parental involvement domain of quality of life (DQOLY-SF, parental involvement) at 6 months' follow-up. The quality of the evidence for this finding was low.

The evidence from 1 study (total 320 participants) comparing the programmes TeenCope and Managing Diabetes did not demonstrate that either intervention was more effective than the other at improving health-related quality of life using the PedsQL at 6 months' follow-up. The quality of the evidence for this finding was very low.

At 12 months from baseline

The evidence from 1 study (total 320 participants) comparing the programmes TeenCope and Managing Diabetes did not demonstrate that either intervention was more effective than the other at improving health-related quality of life using the PedsQL at 12 months' follow-up. The quality of the evidence for this finding was very low.

The evidence from 1 study (total 320 participants) comparing the programme care ambassador plus with standard care did not demonstrate that either intervention was more effective than the other in terms of parent-reported quality of life using the PedsQL at 12 months' follow-up. The quality of the evidence for this finding was very low.

The evidence from 1 study (total 103 participants) comparing the programme care ambassador plus with standard care did not demonstrate that either intervention was more effective than the other in terms of child- or young person-reported quality of life using the PedsQL at 12 months' follow-up. The quality of the evidence for this finding was very low.

The evidence from 1 study (total 101 participants) comparing the programme care ambassador ultra with standard care did not demonstrate that either intervention was more effective than the other in terms of parent-reported quality of life using the PedsQL at 12 months' follow-up. The quality of the evidence for this finding was low.

The evidence from 1 study (total 101 participants) comparing the programme care ambassador ultra with standard care did not demonstrate that either intervention was more effective than the other in terms of child- or young person-reported quality of life using the PedsQL at 12 months' follow-up. The quality of the evidence for this finding was very low.

The evidence from 1 study (total 307 participants) comparing the programme CASCADE with usual care did not demonstrate that either intervention was more effective than the other in terms of the general quality of life module using the PedsQL at 12 months' follow-up. The quality of the evidence for this finding was low.

The evidence from 1 study (total 307 participants) comparing the programme CASCADE with usual care did not demonstrate that either intervention was more effective than the other in terms of the diabetes-specific quality of life module using the PedsQL at 12 months' follow-up. The quality of the evidence for this finding was very low.

At 24 months from baseline

The evidence from 1 study (total 103 participants) comparing the programme care ambassador plus with standard care did not demonstrate that either intervention was more effective than the other in terms of parent-reported quality of life using the PedsQL at 24 months' follow-up. The quality of the evidence for this finding was very low.

The evidence from 1 study (total 103 participants) comparing the programme care ambassador plus with standard care did not demonstrate that either intervention was more effective than the other in terms of child- or young person-reported quality of life using the PedsQL at 24 months' follow-up. The quality of the evidence for this finding was very low.

The evidence from 1 study (total 101 participants) comparing the programme care ambassador ultra with standard care did not demonstrate that either intervention was more effective than the other in terms of parent-reported quality of life using the PedsQL at 24 months' follow-up. The quality of the evidence for this finding was very low.

The evidence from 1 study (total 101 participants) comparing the programme care ambassador ultra with standard care did not demonstrate that either intervention was more effective than the other in terms of child- or young person-reported quality of life using the PedsQL at 24 months' follow-up. The quality of the evidence for this finding was very low.

The evidence from 1 study (total 295 participants) comparing the programme CASCADE with usual care did not demonstrate that either intervention was more effective than the other in terms of the PedsQL general quality of life module at 24 months' follow-up. The quality of the evidence for this finding was very low.

The evidence from 1 study (total 295 participants) comparing the programme CASCADE with usual care did not demonstrate that either intervention was more effective than the other in terms of the PedsQL diabetes-specific quality of life module at 24 months' follow-up. The quality of the evidence for this finding was very low.

Children and young people's satisfaction with treatment

The evidence from 1 study (total 320 participants) comparing the programmes TeenCope and Managing Diabetes did not demonstrate that either intervention was more effective than the other in terms of the child's or young person's satisfaction with the educational intervention. The duration of follow-up was not reported. The quality of the evidence for this finding was moderate.

5.4.6 Health economics profile

This question was prioritised for health economic analysis.

A systematic search found 1 recent UK economic evaluation (Christie 2014), also included in the clinical review, which considered the cost effectiveness of a structured psychoeducational programme compared with current NHS practice for children and young people with type 1 diabetes. The study used HbA1c data collected as part of the Child and Adolescent Structured Competencies Approach to Diabetes Education (CASCADE) study to

model long-term costs and effects. This study, which is reported in more detail in Section 19.2, did not find the structured education programme to be cost effective.

The clinical review undertaken for this guideline did not find published evidence demonstrating the clinical effectiveness of structured education. As there was a recently published economic evaluation in a UK setting and a lack of evidence of clinical benefit, it was not thought that an original analysis would aid guideline development group decision-making.

5.4.7 Health economics evidence statement

One directly applicable cost-utility analysis with minor limitations failed to demonstrate the cost effectiveness of structured education in children and young people with type 1 diabetes.

5.4.8 Evidence to recommendations

5.4.8.1 Relative value placed on the outcomes considered

The guideline development group agreed that HbA1c value was the highest priority outcome for this review question because, in their view, if the use of a particular structured education programme resulted in a reduction in HbA1c by near to or greater than 0.5 percentage points (or 5.5 mmol/mol) then this would represent an important clinical benefit to a child or young person with type 1 diabetes. This decision was underpinned by the group's knowledge of research in adults with type 1 diabetes (The Diabetes Control and Complications Trial Research Group 1993) which showed that a 1 percentage point decease in HbA1c halved the risk of diabetes-related complications, including retinopathy and nephropathy. The group considered that this result could be meaningfully extrapolated to cover the population of children and young people with type 1 diabetes of relevance in this question.

The guideline development group considered that severe hypoglycaemic episodes and episodes of DKA were important outcomes for consideration in determining the effectiveness of structured education.

The group also prioritised adherence to diabetes management because this is often a specified aim of education programmes and one mechanism by which glycaemic control can be improved.

Adherence to the educational intervention was itself prioritised as an outcome because non-adherence would make the intervention less cost effective.

Measures of health-related quality of life, the satisfaction of children, young people and families with treatment and incidence of risk-taking behaviours were also identified as important outcomes.

5.4.8.2 Consideration of clinical benefits and harms

The guideline development group acknowledged that the evidence related to structured education programmes did not provide objective support for such interventions in terms of any of the prioritised outcomes, apart from the very low quality evidence from 1 study that compared the programme CASCADE with usual care and found a reduced risk of severe hypoglycaemic episodes at 12 months' follow-up. Nevertheless, the group emphasised that some education is essential for children and young people with type 1 diabetes and their families to enable them to manage this life-long condition.

The group also noted that contact with families of children and young people with type 1 diabetes supports the perception that each family would wish to receive an individualised approach to education to reflect their needs and from this the group concluded that every child or young person with type 1 diabetes, and their family, differ in their educational needs

and learning styles. The group therefore believed that while any structured education curriculum needed to cover key points, the timing and approach to delivery should be individualised.

Reflecting on education in the broadest context, the guideline development group noted that the person delivering the structured education will have a big impact on the effectiveness of the intervention and that this would not necessarily be captured in a clinical trial. The group acknowledged that it would be hard to capture the qualities of an 'inspirational teacher' in a recommendation, but was of the view that healthcare professionals could seek to acquire teaching expertise and skills that would make them effective in delivering education.

The group noted that the educational needs and receptivity of children, young people and their families would change over time, and that delivery of education programmes needed to be a continual process. The group felt that 'anticipatory guidance' that would identify possible challenges in advance (for example the child or young person being offered sweets at Christmas, or exposure to alcohol) and providing advice proactively was particularly important to this concept of continuing education.

5.4.8.3 Consideration of health benefits and resource use

Structured education has been shown to be effective in adults with type 1 diabetes. In the dose adjustment for normal eating trial (DAFNE Study Group 2002) structured education led to reduced HbA1c and improved dietary freedom without increasing the risk of severe hypoglycaemia. It is, however, an expensive intervention and the evidence identified in the guideline review did not demonstrate a benefit in terms of the guideline development group's prioritised outcomes in children and young people. The guideline development group noted that no studies were identified for inclusion that specifically evaluated the effectiveness of structured education programmes delivered at the time of diagnosis, and the group felt that the effectiveness of structured education programmes might be influenced by the timing of first delivery. The group was aware of a cluster RCT, Kids In Control OF Food (KICk-OFF) that was in progress at the time the guideline was being developed and which might have a bearing on future recommendations with regard to cost effectiveness of structured education for children and young people with type 1 diabetes (Price 2013).

In their experience, and as noted above, the guideline development group considered that education might be more effective when delivered by motivational teachers with relevant expertise, but no evidence was identified to support this view. Furthermore, the group reiterated the view that some education about the condition is essential for children and young people with type 1 diabetes and their families to enable them to manage this life-long condition and revised the 2004 recommendation accordingly.

5.4.8.4 Quality of evidence

The guideline development group noted that there was no high-quality evidence included in the review for this question. The group expressed some scepticism as to the generalisability of structured education delivered in a trial setting compared with the reality of delivering such education in routine clinical practice. For example, the group highlighted the quality of teachers delivering education programmes and the level of engagement of participants as being important factors in the effectiveness of such programmes. The group also noted that several of the studies included in the guideline review involved fewer than 100 participants and there were very few studies overall. The evidence from 1 study comparing a self-management training programme with supportive self-care and conventional treatment demonstrated that self-management was more effective than conventional treatment at 12 months' and 24 months' follow-up, but the quality of the evidence for these outcomes was very low and the findings were not replicated across the other 7 studies included in the guideline review, several of which contributed low or moderate evidence for similar outcomes.

The health-related quality of life evidence included in the guideline review was obtained using the PedsQL and DQOL-SF measurement scales. The evidence was found to be of very low quality.

5.4.8.5 Other considerations

The guideline development group considered that it was appropriate to retain the existing recommendation from the 2004 guideline regarding the need to take special care when delivering information (or education) to groups of children and young people with type 1 diabetes and families who might otherwise be disadvantaged. Such groups would include:

- people with special needs, such as those associated with physical and sensory disabilities
- people with difficulties in speaking or reading English.

5.4.8.6 Key conclusions

The guideline development group concluded that a strong recommendation to offer children and young people with type 1 diabetes and their family members or carers a continuing programme of education from diagnosis was warranted. The group specified the core topics to be included in the education programme and areas in which the programme should be tailored to individual circumstances.

5.4.8.6.1 Core topics

The core topics selected by the group reflect the recommendations on management of type 1 diabetes in the guideline. These are:

- insulin therapy
- blood glucose monitoring
- diet, physical activity and intercurrent illness
- managing intercurrent illness
- detecting and managing hypoglycaemia, hyperglycaemia and ketosis.

Insulin therapy

The guideline development group recognised this as fundamentally important and a challenge for children and young people with type 1 diabetes and their families (for example in self-injection, the need to adjust dosages and to understand, where appropriate, special insulin delivery systems, including CSII [insulin pump therapy] can be challenging). To manage their insulin effectively it is necessary for the child or young person and their family members or carers (as appropriate) to understand how insulin affects their blood glucose.

Blood glucose monitoring

The group considered that as this essential process is managed by the child or young person with type 1 diabetes and their family members or carers (as appropriate) it was important that they should have a full understanding of the approach to monitoring that will ensure optimal blood glucose control.

Diet, physical activity and intercurrent illness

All of these factors affect blood glucose control and it is important that children and young people with type 1 diabetes and their family members or carers (as appropriate) have a thorough understanding of their effects.

Managing intercurrent illness

It is essential that children and young people with type 1 diabetes and their family members or carers (as appropriate) are aware that such illnesses can affect blood glucose control and can even precipitate DKA.

Detecting and managing hypoglycaemia, hyperglycaemia and ketosis

It is important that children and young people with type 1 diabetes and their family members or carers (as appropriate) have a clear understanding of the approach to monitoring blood glucose and ketone levels, including during intercurrent illness, and they should know what to do if difficulties arise.

5.4.8.6.2 Individualised care

The nature and content of the education programme needs to be individualised to take account of the personal preferences of the child or young person with type 1 diabetes and their family members or carers (as appropriate). The delivery of the programme needs to be done in a sensitive manner, taking into account the emotional wellbeing of the child or young person and their age and maturity. Cultural considerations (for example with regard to dietary practices), existing knowledge, current and future social circumstances and life goals should also be taken into account.

The group also included a recommendation to encourage children and young people with type 1 diabetes and their family members or carers (as appropriate) to discuss any concerns and raise any questions they have with the diabetes team.

Recommendations related to education for children and young people with type 1 diabetes are presented in Section 5.7.

5.5 Long-distance travel

A survey of advice on insulin treatment, time zones and air travel given in British diabetic clinics found variation in advice and many regimen changes were reported as being excessively complicated.[471] [evidence level III] The authors of the survey recommended that patients discussed their travel arrangements individually with their diabetes care team, with full flight details, in particular the local departure and arrival times and the duration of the flight.

A small non-controlled study investigated patients using a ‘westward-increase, eastward-decrease’ insulin system (n=27, age unknown).[472] [evidence level IIb] Self-monitored blood glucose profiles were only slightly higher during travel than when at home, overall daily insulin doses changed little, and there were no significant problems with hypoglycaemia.

5.6 Immunisation

5.6.1 Influenza

An 8-year cohort study investigated deaths in people diagnosed with diabetes under the age of 30 years who were taking insulin (n=1210, total 145 deaths).[474] [evidence level III] The study found no increased risk of death from pneumonia or influenza in these people (standardised mortality ratio 7.6, 95% CI 0.9 to 27.4).

A case–control study investigated the effect of an influenza epidemic on ketoacidosis, pneumonia and death in patients with diabetes mellitus compared with patients with duodenal ulcer in 1976 to 1979.[475] [evidence level III] The study found that patients with diabetes mellitus were more likely to be hospitalised with influenza than patients with

duodenal ulcer in 1976 and 1978, years of influenza epidemic (RR for hospitalisation 5.7 in 1976, RR 6.2 in 1978; there were no supporting data to give 95% CIs). There was no increase in the number of patients with diabetes mellitus who were hospitalised with influenza in 1977 and 1979, years of no influenza epidemic (RR for hospitalisation 1.1 in 1977, RR 1.0 in 1979). RRs of pneumonia and death were increased in patients with diabetes mellitus compared with patients with duodenal ulcers in all years (pneumonia 25.6 in 1976, 20.3 in 1977, 25.6 in 1978, 15.8 in 1979; death 42.4 in 1976, 30.9 in 1977, 91.8 in 1978, 31.8 in 1979).

A cohort study followed up a group of children and young people with type 1 diabetes who were offered influenza immunisation (n=63, age not reported).[476] [evidence level III] Sixty-three percent of children and young people had the immunisation. There were no cases of influenza symptoms lasting 3 or more days in children and young people who had the immunisation (0/40), whereas 26% of children and young people who did not have the immunisation had influenza symptoms lasting 3 or more days (6/23). However, 10% of children and young people who had the immunisation had influenza symptoms lasting 1 to 3 days (4/40); none of the children and young people who did not have the immunisation had influenza symptoms lasting 1 to 3 days, and overall there was no association between having had the influenza immunisation and any influenza symptoms lasting more than 1 day (4/40 versus 6/23, OR 0.31, 95% CI 0.08 to 1.19). A case–control study of children, young people and adults with diabetes investigated influenza immunisation rates in hospitalised patients compared with patients with diabetes not hospitalised during 2 influenza epidemics.[477] [evidence level III] The study found that people admitted to hospital with pneumonia, bronchitis, influenza, diabetic ketoacidosis, coma and diabetes (n=37) and then discharged during the influenza epidemics of 1989 to 1990 and 1993 were less likely to have been immunised for influenza than people on the diabetes register who had not been admitted to hospital (n=77) (estimated reduction in hospital admissions after immunisation against influenza 79%, 95% CI 19 to 95%, after adjustment for potential confounders).

A survey of influenza and pneumococcal immunisation history in children, young people and adults with type 1 diabetes found a low rate of immunisation coverage (n=113).[478] [evidence level III] Forty-four per cent had received the influenza immunisation in a previous year and 36% had received the pneumococcal immunisation.

The guideline development group for the 2004 guideline was aware of guidance from the Department of Health regarding annual influenza immunisation for children and young people with diabetes.[473] That guidance has been superseded by the Department of Health's 'Green Book'. The recommendations related to influenza immunisation have been updated accordingly and the summary of the guidance considered in the 2004 guideline has been moved to Appendix N: to avoid presentation of outdated guidance.

5.6.2 Pneumococcal infection

We found no studies that investigated the incidence of pneumococcal infection or immunisation against pneumococcal infection in children and young people with type 1 diabetes.

The guideline development group for the 2004 guideline was aware of guidance from the Department of Health regarding immunisation against pneumococcal infection for children and young people with diabetes.[479] That guidance has been superseded by the Department of Health's 'Green Book'. The recommendations related to immunisation against pneumococcal infection have been updated accordingly and the summary of the guidance considered in the 2004 guideline has been moved to Appendix N: to avoid presentation of outdated guidance.

Recommendations related to immunisations for children and young people with type 1 diabetes are presented in Section 5.7, and those for children and young people with type 2 diabetes are presented in Section 11.

5.7 Recommendations

The current recommendations can be found at https://www.nice.org.uk/guidance/ng18

5.8 Research recommendations

1. **What is the clinical and cost effectiveness of a programme of structured education from diagnosis for children and young people with type 1 diabetes?**

2. **What is the impact of training in teaching skills for healthcare professionals on the effectiveness of education for children and young people with type 1 diabetes?**

3. **What is the effectiveness of education programmes in which young people with type 1 diabetes provide training for their peers?**

6 Management of type 1 diabetes – insulin, oral drug therapy, dietary advice and exercise

6.1 Insulin treatment for type 1 diabetes

6.1.1 Introduction

This section was updated in 2015.

The evidence reviews in the 2004 guideline related to insulin treatment for type 1 diabetes covered:

- insulin regimens (including intensive versus conventional insulin regimens)
- insulin preparations
- methods of delivering insulin.

Intensive insulin regimens include either multiple daily injections of insulin or continuous subcutaneous insulin infusion (insulin pump therapy). For the 2015 update a specific review question on the effectiveness of multiple daily injection (MDI) regimens compared with mixed daily insulin injections was considered. The evidence identified in relation to this review question and the guideline development group's interpretation of the evidence are presented in Section 6.1.2.6.8. The 2004 guideline evidence reviews that related to insulin regimens have been modified to reflect the 2015 update scope (so that topics are not duplicated in 2004 and 2015 text), while retaining general discussion of topics such as intensive versus conventional insulin regimens, special insulin regimens in neonates, infants and pre-school children, maximum insulin dosage and the effectiveness of insulin pump therapy (see Section 6.1.2.1 to Section 6.1.2.5). The 2004 recommendations related to insulin regimens and the recommendations arising from the 2015 update are presented together in Section 6.1.5. The sections of the 2004 guideline that related to insulin preparations and methods of delivering insulin were not covered by the 2015 update scope and have been retained as Section 6.1.3 and Section 6.1.4, respectively.

6.1.2 Insulin regimens

The aims of insulin therapy are to provide sufficient insulin to cover basal requirements throughout a 24-hour period, and to deliver higher boluses of insulin that are synchronised with the hyperglycaemic effects of meals.[15] The choice of insulin regimen may depend on factors such as age, duration of diabetes, lifestyle, targets of metabolic control, and individual patient/family preferences.

All insulin therapy is delivered as part of a 'package of care' that includes:

- initial and continuing education
- specific paediatric dietary management
- specific practical instruction on the use of insulin delivery systems and blood glucose monitoring
- initial and continuing support for living with diabetes
- initial and continuing emotional and behavioural support
- medical, nursing and dietetic support and technical advice on paediatric diabetes.

With the use of frequent insulin injections, the intensity of the package of care and the commitment from patients and carers are required to be substantial if the package is to be successful (particularly if adjustment of insulin dose is considered at each injection).

A 2001 audit recorded the number of insulin injections used by 2090 of 15 437 children and young people aged 0 to 16 years in England known to have diabetes; 7.7% of the children and young people received 4 or more injections/day, 4.3% received 3 injections/day, 86% received 2 injections/day, 1.7% received 1 injection/day, and 0.3% received no injections/day (these may have been children or young people who do not have type 1 diabetes).[1] The average number of injections/day increased with the age of the child.[1] [evidence level III]

Historically, 'conventional therapy' has been taken to mean 2 to 3 injections/day of pre-mixed or self-titrated, the dose being adjusted occasionally in response to general health, growth and overall glycaemic control. 'Intensive insulin therapy' has been described as multiple daily injections (usually 4 or more) using a basal–bolus regimen, or CSII using an insulin pump. Multiple daily injection regimens involve pre-carbohydrate injections of short- or rapid-acting insulin, together with separate daily injection(s) of intermediate- or long-acting insulin (these different types of insulin preparation are discussed in Section 6.1.4).

The Diabetes Control and Complications Trial (DCCT) used the following definitions.[83–85]

- Conventional therapy consisted of 1 or 2 daily injections of insulin, including mixed short- and intermediate-acting insulin, daily self-monitoring of urine or blood glucose, and education about diet and exercise. Conventional therapy did not usually include daily adjustments in the insulin dosage. The goals of conventional therapy included: the absence of symptoms attributable to glycosuria or hyperglycaemia; the absence of ketonuria; the maintenance of normal growth, development and ideal body weight; and freedom from severe or frequent hypoglycaemia.
- Intensive therapy consisted of the administration of insulin 3 or more times/day by injection or an external pump. The dosage was adjusted according to the results of self-monitoring of blood glucose performed at least 4 times/day, dietary intake and anticipated exercise. The goals of intensive therapy included preprandial blood glucose concentrations between 3.9 and 6.7 mmol/l, postprandial concentrations of less than 10 mmol/l, a weekly 3 a.m. measurement greater than 3.6 mmol/l and monthly HbA1c measurements less than 6.05%.

A consensus guideline used the following definitions:[15]

- two injections daily: a mixture of short- and intermediate-acting insulin (before breakfast and before the main evening meal)
- three injections daily: a mixture of short- and intermediate-acting insulin before breakfast; short-acting insulin alone before an afternoon snack or main evening meal; intermediate-acting insulin before bed; or variations of this
- basal–bolus regimen: short-acting insulin 20 to 30 minutes before main meals (for example, breakfast, lunch and the main evening meal) and intermediate- or long-acting insulin at bedtime or rapid-acting insulin analogue immediately before main meals and intermediate-or long-acting insulin at bedtime
- CSII regimen (insulin pump therapy): fixed or variable basal dose and bolus dose with meals, using only short- or rapid-acting insulin.

A systematic review defined intensive therapy as 'a method of intensifying diabetes management with the goal of improving metabolic control over that achieved by conventional therapy'.[86] Intensive therapy could be achieved through multiple daily injections (3 or 4 doses/day) or CSII, whereas conventional therapy was defined as '1 or 2 insulin injections/day'.

All of the studies that we identified examined the impact of different insulin regimens on glycaemic control. Long-term studies related the change in glycaemic control to clinical

outcomes and quality of life. From our original literature search we focused on the following questions when considering insulin regimens.

- How many times a day should insulin be given?
- At what time of day should insulin be given?
- When should different types of insulin be given?

The young people's consultation day organised for this guideline in collaboration with the NCB found that young people with type 1 diabetes wanted insulin regimens that were flexible and allowed for a measure of spontaneity, and they wanted to be informed about the types of insulin that were available and to be given up-to-date information on insulin delivery devices and blood-glucose-testing monitors. Parents requested annual updates from staff on the availability of new products. Some young people with type 1 diabetes said they may find 4 injections/day too many, but they wanted to be involved in the discussion about how best to fit diabetes treatment into their chosen lifestyle while maintaining optimal metabolic control.[38] [evidence level IV]

6.1.2.1 Intensive versus conventional insulin regimens

Evidence derived from studies that compared intensive and conventional insulin regimens is presented below according to outcomes.

6.1.2.1.1 Glucose control

A systematic review (search date 1991, 7 small RCTs all involving mainly adult participants with type 1 diabetes, n=266) found that intensive treatment reduced HbA1c compared with standard treatment (reduction 1.4%, 95% CI −1.8 to −1.1%).[87] [evidence level Ia]

Ten further RCTs that were not included in the systematic review examined glycaemic control in participants receiving intensive treatment compared with standard treatment.[88–97] [evidence level Ib] Three of these studies involved children or young people.[91,96,97] Three of the RCTs involving adults found no significant differences in glycaemic control.[88–90] However, 6 RCTs, including the 3 involving children or young people, found improvements in glycaemic control in participants receiving intensive therapy.[91–96] One of these RCTs reported on a subgroup of young people (n=209, age range 13 to 17 years) involved in the DCCT trial for a mean of 7.4 years; this RCT found a reduction in HbA1c levels in the young people receiving intensive therapy (reduction of 1.7 ±0.18%).[91] [evidence level Ib] A second RCT involved children and young people, and compared a 3-dose regimen of short-acting insulin before breakfast and lunch with a mixture of short-acting and intermediate-acting insulin before the evening meal (n=186 children and young people). This study found a significant decrease in glycated haemoglobin in the children receiving the 3-dose regimen (9.3 ±0.2% versus 9.8 ±0.3%).[97] [evidence level Ib] The third RCT, which involved young people with newly diagnosed type 1 diabetes (n=26), found a decrease in glycated haemoglobin in young people who received intensive treatment (7.2 ±0.7% versus 10.8 ±1.2%, p<0.01).[96] [evidence level Ib]

6.1.2.1.2 Hypoglycaemia

A 1997 systematic review of 14 RCTs (n=2067) compared the adverse effects of intensive and standard treatments in adults with type 1 diabetes.98 The review found an increased risk of 1 or more episodes of severe hypoglycaemia among those who received intensive treatment (combined OR 2.99, 95% CI 2.45 to 3.64).[98] [evidence level Ia]

An RCT that was not included in the above systematic review followed young people (n=209) over a mean of 7.4 years. This RCT found that intensively treated young people had a greater risk of hypoglycaemia than adults (severe hypoglycaemia requiring assistance: RR 2.96, 95% CI 1.90 to 4.62; hypoglycaemia resulting in coma or seizure: RR 2.93, 95% CI 1.75 to 4.90).[91] [evidence level Ib] However, 6 further RCTs that were not included in the

systematic review, 2 of which involved children or young people, found no significant differences between intensive and standard treatments in the risk of hypoglycaemia.[88–90,95–97] [evidence level Ib]

6.1.2.1.3 Diabetic ketoacidosis

A 1997 systematic review of 14 RCTs (n=2067) compared the adverse effects of intensive and standard treatments in adults with type 1 diabetes.[98] The review found an increased risk of ketoacidosis among adults who received intensive treatment (combined OR 1.74, 95% CI 1.27 to 2.38).[98] [evidence level Ia] However, a subgroup of young people (n=209, age range 13 to 17 years) involved in the DCCT trial followed over a mean of 7.4 years found no difference in the risk of diabetic ketoacidosis between intensive and standard treatments.[91] [evidence level Ib]

6.1.2.1.4 Death from all causes

A 1997 systematic review of 14 RCTs (n=2067) compared adverse effects of intensive and standard treatments in adults with type 1 diabetes.[98] There was no significant difference in mortality between the intensive and standard treatments (combined OR 1.40, 95% CI 0.65 to 3.01).[98] [evidence level Ia]

6.1.2.1.5 Retinopathy

A systematic review (search date 1991, 6 small RCTs involving mainly adults with type 1 diabetes, n=271) found that after 2 years or more the risk of retinopathy progression was lower with intensive treatment than with conventional treatment (OR 0.49, 95% CI 0.28 to 0.85).[87] [evidence level Ia]

The DCCT, an RCT with 1441 people aged between 13 and 39 years with type 1 diabetes, found a decreased risk of developing retinopathy in patients treated intensively compared with those treated conventionally. This effect was seen in patients who had no retinopathy or nephropathy at the start of the study (risk reduction 76%, 95% CI 62 to 85%), and in patients who had minimal background retinopathy at the start of the study (risk reduction 54%, 95% CI 39 to 66%). [evidence level Ib] The difference continued for at least 4 years (3-step progression from no retinopathy: RR 0.39, 95% CI 0.19 to 0.79, NNT 9.9).[99] [evidence level Ib]

The DCCT showed that the risk of macular oedema did not differ significantly between intensive and conventional treatment in patients who had minimal background retinopathy at the start of the study. However, the risk of severe non-proliferative or proliferative retinopathy was decreased with intensive treatment in patients who had no retinopathy or nephropathy at the start of the study (risk reduction 45%, 95% CI 14 to 67%), and in patients who had minimal background retinopathy at the start of the study (risk reduction 56%, 95% CI 26 to 74%).[83] [evidence level Ib]

Two further small RCTs that were not included in the systematic review compared the incidence of retinopathy in adult patients treated with intensive and standard treatments (n=65 and n=49). These RCTs found no significant differences between intensive and standard treatment groups.[92,93] [evidence level Ib]

6.1.2.1.6 Nephropathy

A systematic review (search date 1991, 7 small RCTs of type 1 diabetes, n=266) found intensive treatment reduced the risk of nephropathy compared with standard treatment (OR 0.34, 95% CI 0.20 to 0.58).[87] [evidence level Ia]

The DCCT found that intensive treatment decreased the risk of developing nephropathy compared with conventional treatment in patients who had no retinopathy or nephropathy at the start of the study (risk reduction 69%, 95% CI 24 to 87%) and in patients who had

minimal background retinopathy at the start of the study (risk reduction 60%, 95% CI 38 to 74%, n=1441 young people and adults).[83] [evidence level Ib]

The DCCT also showed that intensive treatment decreased the risk of developing urinary albumin excretion ≥ 40 mg/24 hours in patients who had no retinopathy or nephropathy at the start of the study (risk reduction 34%, 95% CI 2 to 56%) and in patients who had minimal background retinopathy at the start of the study (risk reduction 39%, 95% CI 21 to 52%).[83] [evidence level Ib] This continued for at least 4 years (microalbuminuria excretion ≥ 40 mg/24 hours: RR 0.47, 95% CI 0.31 to 0.71, NNT 17.1).[99] [evidence level Ib] Intensive treatment also decreased the risk of developing urinary albumin excretion ≥ 300 mg/24 hours in patients who had minimal background retinopathy at the start of the study (risk reduction 56%, 95% CI 18 to 76%). However, there was no significant change in patients who had no retinopathy or nephropathy at the start of the study.[83] [evidence level Ib]

Three further small RCTs involving adults that were not included in the systematic review compared the incidence of nephropathy in patients treated with intensive and standard treatments (n=65, n=49 and n=70). Two of the RCTs found no significant differences between intensive and standard treatments.[93,94] [evidence level Ib] The third RCT found a decreased deterioration of creatinine clearance, and a lower plasma creatinine level in patients treated intensively (creatinine clearance: 1.7 ±30.1 ml/min versus −17.3 ±33.5 ml/min, p=0.022; plasma creatinine: 2.7 ±26.4 µmol/l versus 17.4 ±16.4 µmol/l, p=0.009).[92] [evidence level Ib]

6.1.2.1.7 Macrovascular events

A systematic review (search date 1996, 6 RCTs of mainly adults with type 1 diabetes, n=1732) examined the occurrence of macrovascular events, including cardiovascular disease, cerebrovascular disease, peripheral vascular disease and macrovascular death. The review found that the number of macrovascular events after 2 or more years of intensive treatment was lower than for conventionally treated patients (OR 0.55, 95% CI 0.35 to 0.88).[86] [evidence level Ia] However, intensive treatment did not have a significant effect on the number of patients developing macrovascular disease (OR 0.72, 95% CI 0.44 to 1.17) or macrovascular mortality (OR 0.91, 95% CI 0.31 to 2.65).[86] [evidence level Ia]

6.1.2.1.8 Weight gain

Six RCTs compared weight changes with intensive and standard treatments in patients with type 1 diabetes.

One RCT involving adults with type 1 diabetes examined changes in body mass index after 5 years of treatment (n=96).100 This RCT found a 5.8% increase in body mass index with intensive treatment (22.5 ±0.3 kg/m2 at entry to 23.8 ±0.3 kg/m2), but no increase with conventional treatment (22.8 ±0.3kg/m2 at entry to 22.8 ±0.3 kg/m2).[100] [evidence level Ib]

The DCCT compared the risk of reaching 120% of ideal body weight after 5 years of intensive and standard treatment in patients with type 1 diabetes (n=1441 young people and adults).[101] The risk was greater with intensive treatment (12.7 cases/100 person years with intensive treatment versus 9.3 cases/100 person years with standard treatment). After 5 years, the mean weight gain of patients receiving intensive therapy was 4.6 kg more than that of patients receiving standard treatment (no CIs reported).[83] [evidence level Ib] In a subgroup of young people (n=209) involved in the DCCT trial followed for a mean of 7.4 years (n=209), those who received intensive therapy were more likely to be overweight than those who received standard therapy (RR 2.11, 95% CI 1.31 to 3.40).[91] [evidence level Ib]

Four further RCTs that recorded weight changes found no significant differences between intensive and standard therapies.[89,90,93,95] [evidence level Ib]

6.1.2.1.9 Neuropsychological impairment

Three RCTs compared neuropsychological impairment between intensive and standard treatments in patients with type 1 diabetes.

The DCCT looked at neuropsychological ratings based on Wechsler intelligence scales for young people and adults after 2 years (n=517) and 5 years (n=245) of treatment. There was no significant difference between treatments in terms of the number of patients whose neuropsychological assessments became slightly or significantly worse at 2 or 5 years.[102] [evidence level Ib]

A second RCT involving adults compared auditory and visual reaction times, digit span, perceptual maze tests, and Necker cube tests after 3 years of intensive and standard treatments (n=97). This RCT found no significant differences between intensive and conventional treatments.[103] [evidence level Ib]

The third RCT compared memory and reaction times after 2.2 years of intensive and standard treatment in children and young people (n=25). Intensive treatment increased error rates in memory recall (p=0.05, error rates not reported) and reaction times (p<0.01, reaction times not reported). However, there were no significant differences between treatments in terms of task accuracy, word recognition or paragraph recognition.[104] [evidence level Ib]

6.1.2.1.10 Quality of life

Two RCTs compared quality of life with intensive and standard treatments in patients with type 1 diabetes.

The DCCT found no significant differences between intensive and standard treatments in terms of quality of life or psychiatric symptoms after a mean of 6.5 years (n=1441 young people and adults).[105] [evidence level Ib] However, intensively treated patients had more hypoglycaemic episodes than conventionally treated patients, and this led to a lower quality of life with intensive treatment.[105] [evidence level IIb]

The second RCT involved adults (n=169) and found that 6 months of intensive treatment improved patients' perceptions of the impact of diabetes on freedom to eat as they wished (−1.8 ±2.3 versus −4.0 ±2.8, p<0.0001), impact of diabetes on quality of life (−1.6 ±1.6 versus −1.9 ±1.4, p<0.01), total wellbeing (24.3 ±5.7 versus 21.4±5.5, p<0.01) and total satisfaction (31.6 ±3.9 versus 22.8 ±6.0, p<0.0001), but reduced perceived frequency of hyperglycaemia (2.90 ±1.4 versus 4.03 ±1.3, p<0.0001). There were no differences between intensive and standard therapies in terms of perceived frequency of hypoglycaemia (2.2 ±1.3 versus 2.4 ±1.3, p=0.31) or quality of life (1.3 ±0.9 versus 1.0 ±1.1, p=0.095).[95] [evidence level Ib]

Two further RCTs in adults investigated a range of quality of life issues. One RCT found that intensive treatment decreased anxiety compared with conventional treatment (36.0 ±2.5 versus 39.5 ±2.7, p<0.05).[106] [evidence level Ib] Another RCT (n=19) found that patients preferred intensive to standard treatment (79% versus 16%).[90] [evidence level Ib]

6.1.2.1.11 Cost effectiveness

The DCCT included an economic analysis that examined the cost effectiveness of alternative approaches to the management of type 1 diabetes. An economic simulation model was constructed to estimate the lifetime costs and outcomes of conventional and intensive insulin therapy. Quality-of-life scores assigned to specific health states were not based on primary research into the social valuations for different health states (as would be normally be expected in health economic evaluation).

The simulations showed that the mean annual cost of intensive therapy using multiple daily injections was around $4,000 and for CSII was $5,800. The figure for CSII is approximately 3 times the mean annual cost of conventional therapy ($1,700). The model estimated that the

cost of the adverse effects of intensive therapy was 3 times the cost of the adverse effects of conventional therapy, but these costs accounted for only about 5% of the total costs of therapy in both groups. The expected lifetime cost/patient was around $100,000 for intensive therapy and $66,000 for conventional therapy at 1996 prices. The analysis concluded that intensive therapy cost $28,661/year of life gained.

No study has estimated the cost effectiveness of alternative forms of treatment for children and young people in the UK setting. The DCCT model included patients aged 13 to 39 years, and so the costs and benefits associated with children and young people cannot be estimated from this model. Also, the cost of initiation of intensive therapy was around $2,900. More than 85% of this cost was attributable to hospitalisation to initiate intensive therapy, but this level of hospitalisation might not be expected in UK healthcare settings outside a research environment. Further research based on the experience of children and young people accessing conventional and intensive forms of treatment in England and Wales is required.

6.1.2.2 Other insulin regimens

Fourteen RCTs have evaluated special insulin regimens (excluding comparisons between intensive and conventional regimens).

6.1.2.2.1 Two doses of intermediate-acting insulin/day

Two RCTs have investigated a regimen consisting of 2 doses of intermediate-acting insulin in addition to short-acting insulin before the 3 main meals in comparison with a regimen consisting of intermediate-acting insulin with short-acting insulin before bedtime and short-acting insulin before breakfast and lunch. The first RCT involved people over 16 years and gave the additional intermediate-acting insulin dose before lunch (n=104). This RCT found no difference in HbA1c, although mild hypoglycaemia increased in the group that received 2 injections of intermediate-acting insulin (average 24-hour mean difference −0.93%, range −13.7 to 15.4%, p=0.002).[107] [evidence level Ib] The second RCT added the intermediate-acting insulin before breakfast (n=43 adults). This study found no differences in glycated haemoglobin or mean daily blood glucose.[108] [evidence level Ib]

6.1.2.2.2 Timing of intermediate-acting insulin

Two RCTs have compared a regimen involving 4 daily insulin injections (short-acting insulin before each meal and intermediate-acting insulin before bedtime) with a regimen where intermediate-acting insulin was given at the same time as one of the short-acting doses. In one RCT, intermediate-acting insulin was given before breakfast with short-acting insulin, whereas short-acting insulin was given alone before the other 2 meals (n=10 young people). This RCT found no significant difference in glycated haemoglobin with timing of intermediate-acting insulin, although there were differences in blood glucose concentration at some time periods during the day.[109] [evidence level Ib] In the second RCT, intermediate-acting insulin was given with short-acting insulin before the evening meal, whereas short-acting insulin was given alone before other main meals (n=22 adults). This RCT found a significant increase in the number of hypoglycaemic episodes in the group that received intermediate-acting insulin before the evening meal (OR 3.1, 95% CI 2.0 to 5.0), and in blood glucose concentration.[110] [evidence level Ib]

6.1.2.2.3 One dose of mixed insulin/day compared with 2 doses of mixed insulin/day

A small RCT involving young people aged 12 to 17 years compared 2 daily injections of mixed short- and intermediate-acting insulin with 1 daily injection (n=10). There was a decrease in HbA1c in young people treated with 2 injections (9.7 ±0.4% versus 10.4 ±0.5%, p=0.003). However, there was an increase in mean glucose level (11.7 ±1.3 mmol/l versus 110.4 ±1.3 mmol/l, p=0.04) and in triglycerides (7.6 ±1.4 mmol/l versus 10.2 ±2.7 mmol/l, p=0.04) in young people who received 2 injections.[111] [evidence level Ib]

6.1.2.2.4 Three insulin injections/day compared with 2 injections/day

An RCT compared a 3-dose regimen of intermediate-acting and short-acting insulin before breakfast, short-acting insulin before the evening meal, and intermediate-acting insulin before bedtime with a 2-dose regimen of mixed intermediate-acting and short-acting insulin (n=18 children and young people). There was no difference in HbA1c between the 2 groups, but patients found the 3-dose regimen more convenient (72% versus 11%).[112] [evidence level Ib]

Extra daily dose of intermediate-acting insulin and no dose of short-acting insulin daily, compared with short-acting insulin before each meal and intermediate-acting insulin before bedtime

An RCT investigated a 3-dose regimen consisting of a mixed dose of intermediate-acting and short-acting insulin at breakfast, no insulin before lunch, short-acting insulin before the evening meal and intermediate-acting insulin at bedtime and compared this with a 4-dose regimen of short-acting insulin before each meal and intermediate-acting insulin before bedtime (n=18 adults). There was a decrease in HbA1c in patients who received 4 insulin injections/day, but no decrease in patients who received 3 injections/day.[113] [evidence level Ib]

6.1.2.2.5 Computer-assisted (3 to 4 insulin injections/day) compared with conventional (2 to 3 insulin injections/day)

An RCT (n=12, age not reported) examined a computer-assisted daily intensive regimen (3–4 daily insulin injections) compared with a conventional insulin regimen (2 to 3 daily insulin injections). There was a greater decrease in glucose level (9.10 ±2.96 mmol/l to 6.22 ±0.65 mmol/l versus 8.86 ±1.83 mmol/l to 6.91 ±0.90 mmol/l, $p<0.05$), and a greater decrease in HbA1 (10.2 ±1.5% to 8.6 ±0.8% versus 9.8 ±1.3% to 9.1 ±1.0%, $p<0.05$) in the group that received the computer-assisted insulin regimen.[114] [evidence level IIb]

Another RCT investigated 2 different 2-dose insulin regimens, short-acting and intermediate-acting insulin before breakfast and intermediate-acting at bedtime, compared with short-acting and intermediate-acting insulin before breakfast and intermediate-acting insulin (and in some children and young people short-acting insulin as well) before the evening meal (n=16 children and young people). There was no difference in glycated haemoglobin between the groups, but mild hypoglycaemia was increased in the group that received intermediate-acting insulin before bedtime (7.25 ±2.9 mmol/l versus 5.25 ±2.4 mmol/l, $p<0.04$).[115] [evidence level Ib]

6.1.2.3 Special insulin regimens in neonates, infants and pre-school children

A non-randomised controlled trial (n=19) examined the management of type 1 diabetes in children under the age of 5 years. One group of children with newly diagnosed type 1 diabetes was treated with an ‘intensive’ programme. A second group of children initially received less intensive treatment and was then transferred to the intensive treatment package after an average of 14.9 months. The intensive programme promoted frequent home blood-glucose monitoring and emphasised parental adjustment of insulin in response to glucose measurements and anticipated diet and exercise. The first group of children (those receiving the intensive programme) had significantly fewer episodes of severe hypoglycaemia than the second group of children during their period of less intensive treatment (0.4 episodes of severe hypoglycaemia/child/18 months in the first group versus 3.3 episodes/child/18 months in the second group, $p<0.01$; 1 hospitalisation in intensively treated children versus 11 with less intensively treated children, $p<0.01$). There was no overall difference in the level of HbA1 between the 2 groups. However, the first group had significantly lower HbA1 levels than the second group at equivalent durations of illness. With ‘before–after’ analysis the second group of children had significantly fewer severe hypoglycaemic episodes and fewer hospitalisations due to hypoglycaemia during the period

of intensive therapy than the period of less intensive therapy (episodes of severe hypoglycaemia/child/18 months: 1.7 with intensive treatment versus 3.3 with less intensive treatment, p<0.01; hospitalisations: 2 with intensive treatment versus 11 with less intensive treatment, p<0.01).[116] [evidence level IIb–III]

No further evidence was identified in relation to special insulin regimens in neonates, infants or pre-school children.

6.1.2.4 Maximum insulin dosage

No specific studies have assessed the maximum insulin dosage that can be administered. Descriptive studies in young people without diabetes suggest an increasing resistance to insulin during adolescence. A multicentre cross-sectional study in 18 countries found the average insulin dosage/kg body weight for children aged 2–9 to be 0.654 units/kg/day. The highest mean dosage was 0.98 ±0.03 units/kg/day which was recorded at 14 years for females and at 17 years for males (prepubertal females 95% CI 0.5 to 1.2 units/kg/day; prepubertal males 95% CI 0.4 to 1.0 units/kg/day; pubertal females 95% CI 0.7 to 1.7 units/kg/day; pubertal males 95% CI 0.6 to 1.5 units/kg/day; n=2873).[117] [evidence level III] A cross-sectional survey in adults found a higher mean insulin dosage in males than females (0.76 ±0.25 units/kg/day for males versus 0.61 ±0.20 units/kg/day for females, p<0.001); this study also found a positive correlation between body weight and insulin dosage (n=198).[118] [evidence level III] A crossover RCT investigated an increased insulin dosage of 1.4 units/kg/day compared with a normal insulin of 1 unit/kg/day in young people who had poor glycaemic control (n=10).[119] [evidence level 1b] Increased insulin dosage was associated with improved glycaemic control (HbA1 13.5%, SE 0.7% versus 15.9%, SE 0.7%, p<0.001) and lower mean daily blood glucose (10.6%, SE 1.1% versus 12.5%, SE 1.0%, p<0.01).

A 2001 audit of the care of children and young people with diabetes in the UK recorded an average insulin dosage of 0.97 units/kg/day (n=2099).[120] [evidence level III]

A daily dose of insulin over 1 unit/kg/day may be appropriate in some individuals. Ineffectiveness of high daily doses of insulin (>1.2 units/kg/day) may be related to ineffective action in clearing peripheral blood glucose levels at these higher doses, while inducing increased appetite, or it may reflect non-adherence to insulin therapy (see Section 9.6).

6.1.2.5 Continuous subcutaneous insulin infusion (insulin pump therapy)

A NICE Technology Appraisal (NICE TA 151) has provided guidance on the use of continuous subcutaneous insulin infusion for the treatment of diabetes mellitus[d]. The guideline development group for the 2004 guideline was aware of a previous version of the NICE TA guidance on the use of continuous subcutaneous insulin infusion (insulin pump therapy).[121] The recommendations related to insulin pump therapy have been updated to refer to the current NICE TA guidance and the summary of the guidance considered in the 2004 guideline has been moved to Appendix N: to avoid presentation of outdated guidance

CSII devices are external pumps comprising a programmable pump and an insulin storage reservoir to which the patient is continuously connected.[121] Insulin is administered to the patient via a needle or cannula inserted under the skin. The pump delivers insulin continuously at a constant or variable basal rate with an additional boost dose delivered at meal times. Currently available insulin pumps are smaller and more reliable than earlier models.[121]

We identified 2 RCTs published after the NICE TA[121] that compared CSII therapy with multiple daily injection therapy in young people with type 1 diabetes. In 1 of the studies there was no significant improvement in HbA1c (8.15 ±1.3% versus 8.57 ±0.44%, n=12), fructosamine (384 ±77 µmol/l versus 399 ±55 µmol/l), frequency of symptomatic

[d] www.nice.org.uk/guidance/ta151

hypoglycaemia (0.13 events/patient year versus 0.61 events/patient year), frequency of hyperglycaemic events (0.58 ±1.7 mean/patient/6 months versus 0.2 ±0.4 mean/patient/6 months), or body mass index standard deviation score for age at 6 months (0.23 ±0.45 versus 0.25 ±0.44) for patients on CSII therapy compared with multiple daily injection therapy.[126] [evidence level Ib] The study found higher satisfaction with treatment and quality of life with CSII therapy compared with multiple daily injection therapy (treatment satisfaction: 32 ±6.5 versus 21.8 ±3.7, p<0.05; quality of life satisfaction: 82.7 ±13 versus 76.4 ±14.3, p<0.05). The second study in young people and young adults (aged 12 to 35 years, n=19) found no significant difference in HbA1c (6.3 ±0.5% versus 6.2 ±0.3%), frequency of severe hypoglycaemic events (numbers not reported) or body weight (numbers not reported) after 2 years' treatment with CSII therapy compared with multiple daily injection therapy.[127] [evidence level Ib]

Two case series were published after the NICE TA[121] had been published. One study followed 51 children and young people 12 months before and after introducing CSII. This study found that HbA1c was lower after transfer to CSII and was still lower at 12 months after transfer (12 months before CSII 8.4 ±0.2% versus 12 months after transfer to CSII 7.9 ±0.1%, p<0.01).[130] [evidence level III] The second case series of 9 infants who were treated with multiple daily insulin injections before transferring to CSII found that HbA1c and episodes of hypoglycaemia were lower after transfer to CSII (mean HbA1c 9.5 ±0.4% before CSII treatment versus 7.9 ±0.3% after initiation of CSII; mean 0.52 episodes of hypoglycaemia/month before CSII treatment versus 0.09 episodes/month after initiation of CSII).[131] [evidence level III]

In a small RCT involving children with type 1 diabetes (n=10, age range 7 to 10 years), 1 treatment group received night-time CSII therapy and daytime insulin delivered by pump or injection; the comparison group received 3 daytime insulin injections only (multiple daily injection therapy). The duration of treatment was 4 weeks in both treatment groups. The percentage of blood glucose levels within targets was higher in the CSII treatment group (44 ±6.7% with CSII versus 37 ±6.7% with multiple daily injections, p=0.04) and fructosamine levels were lower (345 ±36.6 µmol/l with CSII versus 390 ±36.6 µmol/l with multiple daily injections, p=0.03).[132] [evidence level Ib] The NICE TA concluded that nighttime use of CSII may be a useful treatment option for children unable to use 24-hour CSII, but that further research was needed.

Healthcare professionals may find it useful to refer to the recommendations in Section 5 (education) when offering information about insulin regimens.

6.1.2.6 Multiple daily injections for type 1 diabetes

This section was updated in 2015.

6.1.2.6.1 Review question

What is the effectiveness of multiple daily injections of insulin when compared with mixed insulin injections in improving glycaemic control in children and young people with type 1 diabetes?

6.1.2.6.2 Introduction

The objective of this review question is to determine the effectiveness of multiple daily injections in the management of type 1 diabetes in children and young people. The review was not limited by study design as no systematic reviews or randomised controlled trials (RCTs) of multiple daily injections in children and young people with type 1 diabetes were identified that met the inclusion criteria. The guideline development group defined a mixed insulin regimen as any regimen using less than 4 injections of insulin per day and a multiple daily injections (MDI) regimen as any regimen using 4 or more injections of insulin per day (also known as a basal-bolus regimen).

The guideline development group noted that an MDI regimen implied matching insulin to food and was not the same as a twice-daily or three times per day injection regimen with corrections, although children and young people using such regimens might well have more than 4 injections per day. Cases where it was not clear which category an insulin regimen would fall into were discussed with the group.

In subsequent text the term 'fewer than 4 injections per day' will be used rather than mixed insulin as this more accurately reflects the broader description of the comparator agreed by the guideline development group for the review protocol.

The outcomes prioritised for inclusion in the review were:

- HbA1c (glycated haemoglobin; minimum follow-up 6 months)
- severe hypoglycaemic episodes
- diabetic ketoacidosis (DKA; number of episodes)
- adherence to diabetes management (including self-management)
- changes in body mass index (BMI) standard deviation score (SDS)
- health-related quality of life
- satisfaction of children, young people and families with the intervention.

6.1.2.6.3 Description of included studies

Thirteen studies were identified for inclusion in this review question (Abid 2011; Adhikari 2009; Alemzadeh 2003; Alexander 2001; Al-Fifi 2003; Bin-Abbas 2006; Bin-Abbas 2007; de Beaufort 2007; Dorchy 1997; Karaguzel 2005; Lievre 2005; Mahommad 2012; Vanelli 2005). Three studies were retrospective cohort studies (Abid 2011; Adhikari 2009; Al-Fifi 2003), 4 were interrupted time series (Alemzadeh 2003; Bin-Abbas 2006; Bin-Abbas 2007; Karaguzel 2005) and 6 were cross-sectional surveys (Alexander 2001; de Beaufort 2007; Dorchy 1997; Lievre 2005; Mahommad 2012; Vanelli 2005). Two retrospective cohort studies included cohorts of children who switched insulin regimens after at least 1 year on a single regimen; these cohorts have been treated as interrupted time series (Abid 2011; Adhikari 2009). All studies included children and young people with type 1 diabetes only.

Two studies involved children and young people newly diagnosed with type 1 diabetes (Abid 2011; Adhikari 2009), 8 studies involved children and young people with type 1 diabetes for at least 1 year (Alemzadeh 2003; Al-Fifi 2003; Bin-Abbas 2006; Bin-Abbas 2007; de Beaufort 2007; Lievre 2005; Mahommad 2012; Vanelli 2005) and 3 studies involved children and young people with diabetes of any duration (Alexander 2001; Dorchy 1997; Karaguzel 2005). The treatment switch cohorts in the retrospective cohort studies involved children and young people with type 1 diabetes for at least 1 year (Abid 2011; Adhikari 2009).

Four studies included participants of any age less than 18 years (Abid 2011; Dorchy 1997; Mahommad 2012; Vanelli 2005), 2 studies included participants of any age less than 16 years (Alemzadeh 2003; Alexander 2001) and 2 studies included young people aged 11–18 years (Al-Fifi 2003; de Beaufort 2007). The age range of participants in the remaining studies varied: more than 6 years (mean age 10.7±2.8 years; Adhikari 2009); 7–11 years (Bin-Abbas 2007); 7–17 years (Karaguzel 2005); 8–14 years (Bin-Abbas 2006); and 10–16 years (Lievre 2005).

The number of participants ranged from 81 to 459 in the retrospective cohort studies (Abid 2011; Adhikari 2009; Al-Fifi 2003), from 10 to 44 in the interrupted time series (Alemzadeh 2003; Bin-Abbas 2006; Bin-Abbas 2007; Karaguzel 2005), from 36 to 198 in the treatment-switch cohorts in the retrospective cohort studies (Abid 2011; Adhikari 2009) and from 144 to 3560 in the cross-sectional surveys (Alexander 2001; de Beaufort 2007; Dorchy 1997; Lievre 2005; Mahommad 2012; Vanelli 2005).

The ethnicity of participants was 100% white in 1 study (Alemzadeh 2003), 68% white in 1 study (Adhikari 2009) and 100% Saudi in 2 studies (Bin-Abbas 2006; Bin-Abbas 2007), but

was not reported in the remaining studies (Abid 2011; Alexander 2001; Al-Fifi 2003; de Beaufort 2007; Dorchy 1997; Karaguzel 2005; Lievre 2005; Mahommad 2012; Vanelli 2005).

Six studies compared 2 injections per day with multiple daily injections (Abid 2011; Al-Fifi 2003; Bin-Abbas 2006; Bin-Abbas 2007; Dorchy 1997; Karaguzel 2005), 1 study compared 3 injections per day with multiple daily injections (Adhikari 2009) and 6 studies compared different regimens of 1–3 injections per day with multiple daily injections (Alemzadeh 2003; Alexander 2001; de Beaufort 2007; Lievre 2005; Mahommad 2012; Vanelli 2005).

The guideline development group priority outcomes reported in the studies were: HbA1c change or HbA1c during study period (for cross-sectional surveys), severe hypoglycaemic episodes, episodes of diabetic ketoacidosis (DKA) and change in body mass index standard deviation score (BMI SDS). Long-term outcomes were thought to be more important than short-term outcomes. For this reason, outcomes reported at multiple lengths of follow-up are presented in reverse chronological order in the GRADE profiles and evidence statements, with the longer-term outcomes reported first. Some outcomes were not reported in sufficient detail to be included in GRADE tables: quality of life was reported in 1 study (Al-Fifi 2003) as 'improved' under multiple daily injections, severe hypoglycaemic episodes had 'no significant relationship' or 'no correlation' to insulin regimen in 2 studies (de Beaufort ; Vanelli 2005) and DKA had 'no significant relationship' to insulin regimen in 1 study (de Beaufort 2007). Two other priority outcomes – adherence to treatment and satisfaction with treatment – were not reported in any studies.

6.1.2.6.4 Evidence profile

The evidence profiles for this review question (multiple daily injections compared with mixed insulin) are presented in Table 27 and Table 28.

Table 27: Evidence profile for effectiveness of multiple daily injections in improving glycaemic control in children and young people newly diagnosed with type 1 diabetes compared with mixed insulin injections

Number of studies	Number of children and young people		Effect		Quality
	Multiple daily injections	Fewer than 4 injections per day	Relative (95% confidence interval)	Absolute (95% confidence interval)	
HbA1c (%) change from baseline after 1 year					
1 (Abid 2011)	29 (changed from 9.1 at baseline to 7.9 at 1 year)	88 (changed from 11.4 at baseline to 9.1 at 1 year)	NA	MD 1.2 lower CI NC	Very low
1 (Adhikari 2009)	212 (changed from 11.4 ±1.9 at baseline to 7.5 ±1.6 at 1 year)	247 (changed from 11.6 ±1.8 at baseline to 8.2 ±1.8 at 1 year)	NA	MD 0.7 lower (1.01 lower to 0.39 lower)	Very low
HbA1c (%) change from baseline after 9 months					
1 (Adhikari 2009)	212 (changed from 11.4 ±1.9 at baseline to 7.2 ±1.7 at 9 months)	247 (changed from 11.6 ±1.8 at baseline to 7.9 ±1.4 at 9 months)	NA	MD 0.7 lower (0.98 lower to 0.42 lower)	Very low
HbA1c (%) change from baseline after 6 months					
1 (Adhikari 2009)	212 (changed from 11.4 ±1.9 at baseline to 6.6 ±1.4 at 6 months)	247 (changed from 11.6 ±1.8 at baseline to 7.3 ±1.4 at 6 months)	NA	MD 0.7 lower (1.96 lower to 0.44 lower)	Very low
BMI standard deviation score (SDS) change from baseline after 1 year					
1 (Abid 2011)	29 (changed from 0.28 at baseline to 0.56 at 1 year)	88 (changed from 0.41 at baseline to 0.9 at 1 year)	NA	MD 0.34 lower CI NC	Very low

Abbreviations: BMI body mass index, CI confidence interval, HbA1c glycated haemoglobin, MD mean difference, NA not applicable, NC not calculable

Table 28: Evidence profile for effectiveness of multiple daily injections in improving glycaemic control in children and young people with type 1 diabetes of at least 1 year's duration when compared with mixed insulin injections

Number of studies	Number of children and young people		Effect		Quality
	Multiple daily injections	Fewer than 4 injections per day	Relative (95% confidence interval)	Absolute (95% confidence interval)	
HbA1c (%) change from baseline after 2 years					
1 (Al-Fifi 2003)	24 (changed from 9.34 ±1.55 at baseline to 9.49 ±1.55 at 2 years)	57 (changed from 9.37 ±1.8 at baseline to 9.59 ±1.59 at 2 years)	NA	MD 0.1 lower (0.86 lower to 0.66 higher)	Very low
HbA1c (%) change from baseline after 1 year					
1 (Al-Fifi 2003)	24 (changed from 9.34 ±1.55 at baseline to 9.2 ±1.7 at 1 year)	57 (changed from 9.37 ±1.8 at baseline to 9.46 ±1.61 at 1 year)	NA	MD 0.26 lower (1.05 lower to 0.53 higher)	Very low
1 (Abid 2011)	36 (9.2 at 1 year)	36 (8.9 at treatment switch)	NA	MD 0.3 higher CI NC	Very low
1 (Adhikari 2009)	118 (8.5 ±1.6 at 1 year)	198 (8.4 ±1.5 at treatment switch)	NA	MD 0.1 higher (0.25 lower to 0.45 higher)	Very low
1 (Alemzadeh 2003)	44 (8.1 ±1.0 at 1 year)	44 (9.2 ±1.1 at treatment switch)	NA	MD 1.1 lower (1.55 lower to 0.65 lower)	Very low
1 (Karaguzel 2005)	25 (8.2 ±1.5 at 1 year)	25 (9.3 ±2.5 at treatment switch)	NA	MD 1.1 lower (2.27 lower to 0.07 higher)	Very low
HbA1c (%) change from baseline after 9 months					
1 (Adhikari 2009)	129 (8.5 ±1.6 at 9 months)	198 (8.4 ±1.5 at treatment switch)	NA	MD 0.1 higher (0.24 lower to 0.44 higher)	Very low
HbA1c (%) change from baseline after 6 months					
1 (Adhikari 2009)	142 (8.3 ±1.4 at 6 months)	198 (8.4 ±1.5 at treatment switch)	NA	MD 0.1 lower (0.42 lower to 0.22 higher)	Very low
1 (Bin-Abbas 2007)	10 (8.4 ±0.7 at endpoint)	10 (8.6 ±1.2 at treatment switch)	NA	MD 0.2 lower (1.12 lower to 0.72 higher)	Very low
1 (Bin-Abbas 2006	10 (8.6 ±0.5 at endpoint)	10 (10.6 ±1.2 at treatment switch)	NA	MD 2.0 lower (2.86 lower to 1.14 lower)	Very low
1 (Karaguzel 2005)	25 (8.3 ±1.6 at 6 months)	25 (9.3 ±2.5 at treatment switch)	NA	MD 1.0 lower (2.19 lower to 0.19 higher)	Very low
HbA1c (%) during study period (cross-sectional observational data)					
1 (Alexander 2001)	30 (9.79 ±1.77)	1573 (9.04 ±1.53)	NA	MD 0.75 higher (0.20 higher to 1.30 higher)	Very low
1 (de Beaufort 2007)	926 (8.2 ±0.0)	524 (8.2 ±0.1)	NA	MD 0.0 (0.01 lower to 0.01 higher)	Low
1 (Dorchy 1997)	15 (6.6 ±1.1)	129 (6.6 ±1.2)	NA	MD 0.0 (0.64 lower to 0.64 higher)	Very low
1 (Vanelli 2005)	1911 (8.7 ±0.2)	1608 (8.3 ±0.1)	NA	MD 0.4 higher (0.39 higher to 0.41 higher)	Low

Proportion achieving ADA age-specific HbA1c target 24 (cross-sectional observational data)					
1 (Mohammad 2012)	31/42 -73.80%	192/373 -51.50%	RR 1.43 (1.17 to 1.76)	211 more per 1000 (from 88 more to 391 more)	Very low
Number of severe hypoglycaemic episodes (ISPAD 2000 grades 2-3 or ISPAD 2009 'severe')					
1 (Al-Fifi 2003)	4/24 -16.70%	16/57 -28.10%	RR 0.59 (0.22 to 1.59)	115 fewer per 1000 (from 219 fewer to 166 more)	Very low
1 (Alemzadeh 2003)	7/44 -15.90%	17/44 -38.60%	RR 0.41 (0.19 to 0.89)	228 fewer per 1000 (from 43 fewer to 313 fewer)	Very low
Number of episodes of DKA					
1 (Al-Fifi 2003)	6/24 -25%	17/57 -29.80%	RR 0.84 (0.38 to 1.86)	48 fewer per 1000 (from 185 fewer to 256 more)	Very low
1 (Alemzadeh 2003)	0/44 0%	2/44 -4.50%	RR 0.2 (0.01 to 4.05)[a]	36 fewer per 1000 (from 45 fewer to 139 more)	Very low
1 (Bin Abbas 2007)	0/10 0%	0/10 0%	NC	NC	Very low
1 (Bin Abbas 2006)	0/10 0%	0/10 0%	NC	NC	Very low

ADA American Diabetes Association, CI confidence interval, DKA diabetic ketoacidosis, HbA1c glycated haemoglobin, ISPAD International Society for Paediatric and Adolescent Diabetes, MD mean difference, NA not applicable, NC not calculable, RR relative risk as RR calculated by adding 0.5 to events in each arm
a. RR calculated by adding 0.5 to events in each arm

6.1.2.6.5 Evidence statements

Children and young people with newly diagnosed type 1 diabetes

Two studies (total 576 participants) showed a reduction in HbA1c from baseline at 1 year with both multiple daily injections and fewer than 4 injections per day. One of these studies also showed a reduction in HbA1c from baseline at 9 months and 6 months with both multiple daily injections and fewer than 4 injections per day. The reduction from baseline was greater in those children and young people using multiple daily injections.

One study showed BMI SDS (total 117 participants) increased with both multiple daily injections and fewer than 4 injections per day. The increase in BMI SDS was smaller in those children and young people using multiple daily injections.

The quality of the evidence was very low for all reported outcomes.

The studies did not report any outcomes related to the number of episodes of severe hypoglycaemia or DKA, adherence to treatment, health-related quality of life or satisfaction with treatment.

Children and young people with type 1 diabetes of 1 year or more duration

There was variability in the evidence for the effectiveness of multiple daily injections in children and young people who had had type 1 diabetes for 1 year or more.

HbA1c at 2 years

One study (total 81 participants) showed little change in HbA1c when compared with baseline with either multiple daily injections or with fewer than 4 injections per day, and therefore this evidence did not indicate that either regimen was more effective than the other. The quality of the evidence was very low.

HbA1c at 1 year

One study (total 81 participants) showed little change in HbA1c when compared with baseline with either multiple daily injections or with fewer than 4 injections per day, and therefore this evidence did not indicate that either regimen was more effective than the other. The quality of the evidence was very low.

Four studies (total 526 participants) showed that switching from fewer than 4 injections per day to multiple daily injections was associated with a similar or reduced HbA1c. The quality of the evidence was very low.

HbA1c at 9 months

One study (total 327 participants) showed that switching from fewer than 4 injections per day to multiple daily injections was not associated with a reduction in HbA1c. The quality of the evidence was very low.

HbA1c at 6 months

Four studies (total 430 participants) showed that switching from fewer than 4 injections per day to multiple daily injections was associated with a similar or reduced HbA1c. The quality of the evidence was very low.

HbA1c during study period

Four studies (total 6716 participants) showed variable evidence for HbA1c with multiple daily injections when compared with fewer than 4 injections per day. This evidence showed that multiple daily injections were associated with higher or similar HbA1c levels. The quality of the evidence was very low to low.

Proportion achieving ADA age-specific HbA1c targets

One study (total 415 participants) showed a greater proportion of participants achieved American Diabetes Association (ADA) age-specific HbA1c targets when using multiple daily injections compared with fewer than 4 injections per day. The quality of the evidence was very low.

Hypoglycaemic episodes

Two studies (total 169 participants) showed variable evidence for the impact of multiple daily injections and fewer than 4 injections per day on hypoglycaemic episodes. This evidence showed that multiple daily injections were associated with either similar or fewer episodes. The quality of the evidence was very low in both cases.

DKA episodes

One study (total 88 participants) showed a similar proportion of DKA episodes with both multiple daily injections and fewer than 4 injections per day and therefore this evidence did not indicate that either regimen was associated with fewer DKA episodes than the other. The quality of the evidence was very low.

Three studies (total 121 participants) showed that switching from fewer than 4 injections per day to multiple daily injections was not associated with a change in the number of DKA episodes. The quality of the evidence was very low.

The studies did not report data for the following outcomes in a form that could be incorporated into GRADE tables: adherence to treatment; changes in BMI SDS; health-related quality of life; and satisfaction with treatment.

6.1.2.6.6 Health economics profile

This question was prioritised for health economic analysis.

A systematic literature search did not find any published evidence on the cost effectiveness of multiple daily injections in improving glycaemic control in children and young people with type 1 diabetes when compared with mixed insulin injections.

Therefore an original health economic model was developed using the IMS CORE Diabetes Model. Data from 1 of the studies included in the clinical review (Adhikari 2009) were used to estimate the reduction of HbA1c as a result of multiple daily injections and (mixed) injections 3 times per day at 12 months from the time of diagnosis. It was assumed that the differential in HbA1c between the different approaches would be maintained throughout the child or young person's life.

The IMS CORE Diabetes Model simulates a person with type 1 diabetes from the point of diagnosis to the end of life. By simulating many such people the model is able to estimate lifelong costs and effects arising from diabetes complications. By performing repeated simulations the model is able to quantify the uncertainty in model outcomes associated with model inputs.

The results from the model suggested that multiple daily injections was £3,550 cheaper than injections 3 times per day, despite higher treatment costs. The results also suggested that multiple daily injections produced a longer life expectancy and an incremental quality adjusted life years (QALYs) gain of 0.605, suggesting that MDI was cost effective relative to injections 3 times per day. The model is described in detail in Section 19.3.

6.1.2.6.7 Evidence statement

Original health economic analysis conducted for the guideline indicates treatment with multiple daily injections dominates treatment with injections 3 times per day when treatment is started in children and young people with newly diagnosed type 1 diabetes. The analysis was assessed as partially applicable with potentially serious limitations.

6.1.2.6.8 Evidence to recommendations

Relative value placed on the outcomes considered

The guideline development group agreed that HbA1c value was the highest priority outcome because, in their view, if the use of a particular insulin regimen resulted in a reduction in HbA1c by near to or greater than 0.5 percentage points (or 5.5 mmol/mol) then this would represent an important clinical benefit to a child or young person with type 1 diabetes. This decision was underpinned by the group's knowledge of research in adults with type 1 diabetes (The Diabetes Control and Complications Trial Research Group 1993) which showed that a 1 percentage point decease in HbA1c halved the risk of diabetes-related complications, including retinopathy and nephropathy. The guideline development group considered that this result could be meaningfully extrapolated to cover the population of children and young people with type 1 diabetes of relevance in this question.

Severe hypoglycaemic episodes were also prioritised because these were considered to be potential harms associated with the more intensive insulin strategy of multiple daily injections. Episodes of DKA were prioritised because these might be associated with less effective insulin therapy regimens. Changes in BMI SDS were also prioritised: multiple daily injection regimens allow increased flexibility in terms of meal frequency and size, and the group considered that this might have an effect on BMI. Furthermore, the 2004 guideline had recommended that children and young people using multiple daily injection regimens should be informed that they may experience an initial increase in the risk of hypoglycaemia and short-term weight gain, and the group considered that if there was further evidence on these effects, this would be important to consider.

The guideline development group also prioritised adherence to treatment, health-related quality of life and children and young people's and families' satisfaction with treatment as important outcomes.

Consideration of clinical benefits and harms

This review question updated the corresponding section of the 2004 guideline and the guideline development group undertook detailed discussion of the 2004 recommendations and the evidence available to support them in the light of new evidence identified for the 2015 guideline update. These discussions are documented here, alongside new issues that were considered because of the newly identified evidence.

The studies included in the review compared the effectiveness of multiple daily injection regimens with that of regimens based on fewer than 4 injections per day. The guideline development group noted that there was some evidence that, when used from diagnosis, multiple daily injection regimens were more effective in improving glycaemic control. Two studies showed that multiple daily injections were associated with a larger reduction in HbA1c from baseline at 1 year, 9 months and 6 months than with regimens based on fewer than 4 injections per day. The reduction in HbA1c resulting from multiple daily injection treatment exceeded the group's a priori definition of a minimally important difference (MID), namely 0.5 percentage points (or 5.5 mmol/mol).

The group noted that there was no evidence that multiple daily injection regimens were more effective than regimens based on fewer than 4 injections per day in children and young people who began using multiple daily injection regimens 1 year after diagnosis.

In the 2004 guideline evidence was identified that intensive insulin therapy (meaning 3 or more injections per day or continuous subcutaneous insulin infusion [CSII] using an insulin pump) was associated with an increased risk of severe hypoglycaemia compared with 1 or 2 injections of insulin per day. The guideline development group for the 2015 update noted that the studies included in the update review did not show that children and young people using multiple daily injection regimens experienced more hypoglycaemic episodes than those using regimens based on fewer than 4 injections per day. The group did not consider that there was sufficient evidence for the previous recommendation that children and young people should be informed that they may experience an initial increase in the risk of hypoglycaemia or that concern about the possibility of hypoglycaemia should influence the decision to use multiple daily injection therapy. The group therefore deleted the previous recommendation. The 2015 guideline update provides recommendations on the recognition and management of hypoglycaemia that apply to all children and young people with type 1 diabetes.

The guideline development group also noted that the included studies did not demonstrate evidence for an altered risk of DKA with multiple daily injections compared with fewer than 4 injections per day.

In the 2004 guideline evidence was sought regarding the influence of intensive insulin therapy (meaning 3 or more injections per day or continuous subcutaneous insulin infusion using an insulin pump) on BMI compared with 1 or 2 daily injections of insulin. Some supportive evidence was identified in adult studies: 1 RCT reported that participants receiving intensive therapy were more likely to be overweight, while other RCTs found no significant effect. The guideline development group for the 2015 guideline update noted that the studies included in the update review demonstrated no evidence for a greater risk of increase in BMI SDS with multiple daily injections compared with fewer than 4 injections per day. The 2004 recommendation that children and young people using multiple daily injections should be informed that they may experience a greater risk of short-term weight gain was therefore deleted. The group did not think that concerns about changes in BMI should influence the decision to use multiple daily injection therapy.

The guideline development group's view was that all the available evidence was rendered somewhat equivocal by the very low to low quality rating, but nevertheless they considered it credible, being consistent with their clinical experience and understanding. They considered that multiple daily injection regimens more closely mimic normal physiological processes in healthy people, in that insulin supply is led by food consumption rather than vice versa. They also noted that multiple daily injection regimens can enable healthier patterns of food consumption compared with regimens based on fewer than 4 injections per day because the need to match meal size to a fixed insulin dose could lead children and young people to eat more or less than is appropriate for their needs. In short, multiple daily injection regimens allow for appetite-led (rather than insulin-led) eating. The guideline development group also felt that, regardless of whether the use of multiple daily injection regimens improved the quality of the child or young person's diet, the additional control and flexibility it offers the child or young person over what they eat can encourage adherence.

The guideline development group believed that multiple daily injection regimens were more likely to be effective if used from diagnosis because, in their experience, some children and young people might view being asked to change to regimens of more frequent injections as an indication that they were doing badly. They might also experience the change as an unwelcome reminder of their condition and younger children might even perceive the change as a punishment. This, along with the difficulty of changing behaviour, means that children and young people who are used to regimens based on fewer than 4 injections per day may find it difficult to adhere to multiple daily injection regimens, whereas those who have never switched treatments appear to cope more readily. Moreover the group felt that by learning the use of multiple daily injection regimens from diagnosis, children and young people would gain confidence in self-management and that this would have long-lasting benefits.

The group noted that that increasing the number of injections (and by association blood tests) can be impracticable in very young children and that some children and young people find the process of injecting and testing distressing and/or socially awkward, and for this reason the group felt that personal and family circumstances were relevant to the choice of insulin regimen.

Consideration of health benefits and resource use

The guideline development group noted that the use of multiple daily injection regimens was current practice in most age groups and therefore recommending its use in all children and young people from diagnosis would be unlikely to be associated with a significant uplift in resources.

Based on their experience, the group believed that, compared with using regimens based on fewer than 4 injections per day, multiple daily injection regimens might require a greater level of initial support in terms of the frequency with which children and young people and their parents and carers would need to contact the diabetes team for advice, as they learned how to calculate and adjust the insulin dose. On the other hand, they felt that the need for this additional support decreased over time and that multiple daily injection regimens led to better self-management in the long term. Therefore long-term clinical benefits associated with improved glycaemic control would mean that the use of multiple daily injection regimens was likely to be cost effective, and may perhaps offer savings in downstream costs, a view supported by the health economic model developed for the guideline (see Section 19.3).

Quality of evidence

The guideline development group was aware that most of the available evidence was of very low quality and that some of the older studies included in the guideline review would have used insulin regimens that are not in keeping with current practice (for example using older insulin preparations). Nevertheless, the quality considerations did not prevent the group making recommendations related to use of multiple daily injections.

Other considerations

The guideline development group acknowledged that there may be an implementation issue related to the use of multiple daily injections in schools, but they felt strongly that this should not be a barrier to access to such regimens.

Key conclusions

In light of all their considerations the guideline development group concluded that multiple daily injection regimens were likely to be a useful element in diabetes management and should be offered from diagnosis. The group also noted that the guideline on type 1 diabetes in adults had included a recommendation to provide suitable containers for collecting used needles and other sharps and to arrange for the suitable disposal of these containers; that recommendation was mirrored in this guideline because this was seen by the guideline development group as an important practical and safety aspect of self-management.

The group recommended that children and young people with type 1 diabetes should be provided with rapid-acting insulin analogues for use during intercurrent illness or episodes of hyperglycaemia so that any necessary dosage adjustments can be made.

The group considered that if a child or young person with type 1 diabetes does not have optimal blood glucose control then appropriate additional support (such as increased contact frequency with the diabetes team) should be offered and, if necessary, an alternative insulin regimen should be offered. These considerations were also reflected in their recommendations. For example, consideration could be given to changing to multiple daily injections or CSII (insulin pump therapy) or mixed insulin injecting 1, 2 or 3 times per day, depending on individual circumstances.

6.1.3 Insulin preparations

People with type 1 diabetes are dependent on insulin for survival. Many different types of insulin are available. A summary of the onset of action, overall effect and maximum effect times for subcutaneous injection of different insulin types in adults is given below. The period over which any particular type of insulin operates varies considerably between patients, and must be assessed on an individual basis.

6.1.3.1 Short-acting insulins

Soluble (regular) insulin is normally given by subcutaneous injection but can also be given by CSII and, in special cases, by intramuscular or intravenous injection or intravenous infusion. When administered by subcutaneous injection, soluble insulin has an onset of action of between 30 and 60 minutes, a peak action between 2 and 4 hours, and a duration of action of up to 8 hours.[133] It is usual for soluble insulin to be injected subcutaneously [15–30] minutes before meals.133 When injected intravenously soluble insulin has a half-life of about 5 minutes and the effect normally disappears within 30 minutes.[133]

Rapid-acting insulin analogues are recombinant human insulins, with faster onset and shorter durations of action than soluble insulin.[133] Rapid-acting insulin analogues are usually given by subcutaneous injection, but can also be given by CSII, and in special circumstances can be given by intramuscular or intravenous injection, or intravenous infusion.[133] There are currently 2 rapid-acting insulin analogues available: insulin aspart and insulin lispro.

When administered by subcutaneous injection in adults, insulin aspart has an onset of action of between 10 and 20 minutes, a peak action between 1 and 3 hours, and a duration of action of 3 to 5 hours. However, the pharmacodynamic profile differs for children and young people.[134] When administered by subcutaneous injection in adults, insulin lispro has an onset of action of approximately 15 minutes and a duration of action of 2 to 5 hours; the

pharmacodynamic profile of insulin lispro in children and young people is similar to that in adults.[134] Rapid-acting insulin analogues can be given shortly before or shortly after meals.[133]

Short-acting soluble insulin and rapid-acting insulin analogues are the only insulin preparations that can be given by intravenous injection, and the only insulins that can be used in CSII using insulin pumps.[134]

6.1.3.2 Intermediate- and long-acting insulins

When given by subcutaneous injection, intermediate- and long-acting insulins have an onset of action of approximately 1 to 2 hours, maximal effects between 4 and 12 hours, and a duration of action of 16 to 35 hours.[133] Several types exist (insulin zinc suspension, crystalline insulin zinc suspension, protamine zinc insulin and isophane insulin, which is sometimes referred to as neural protamine hagedorn), with varying durations of action as specified by the manufacturers. However, as for short-acting insulins, there may be considerable variation from patient to patient.

Protamine zinc insulin binds with short-acting soluble insulin and rapid-acting insulin analogues (aspart and lispro) when mixed in the same syringe, and so these forms of insulin should not be mixed.

Insulin analogues with extra-long action have been manufactured recently. The only long-acting insulin analogue that is licensed currently is insulin glargine, which should be administered by subcutaneous injection. Although absorption changes over time, a once-daily injection of insulin glargine will reach steady state levels in 2 to 4 days after the first dose, to produce a constant level of insulin.[134] Another type of long-acting insulin analogue (insulin detemir) is in the process of being licensed.

6.1.3.3 Biphasic insulins

Biphasic insulins are pre-mixed insulin preparations containing various combinations of short-acting (soluble insulin or a rapid-acting insulin analogue) and an intermediate-acting insulin. The percentage of short-acting insulin varies from 10% to 50%. These preparations should be administered by subcutaneous injection up to 15 minutes before or soon after a meal.[133,134]

The concentration of insulin is normally 100 units/ml where 1 unit is approximately 36 µg insulin.

6.1.3.4 Is human or animal insulin more appropriate for children and young people with type 1 diabetes?

Human insulin was introduced for the routine treatment of diabetes mellitus in the early 1980s. Structurally, porcine insulin differs from human insulin by 1 amino acid (at the carboxy-terminal position 30 of the B-chain) and bovine insulin differs from human insulin at 3 positions (B30, A8 and A10). Human sequence insulin is available from 2 sources. 'Semisynthetic' human insulin is manufactured by enzymatic substitution of alanine with threonine at position B30 of porcine insulin. 'Biosynthetic' human insulin is manufactured using recombinant DNA technology with baker's yeast or the bacterium Escherichia coli as the host cell. Both are then highly purified to a monocomponent form. In the UK, there is a wide variety of human insulin products available, and it is thought that the majority of children and young people now use human insulins. However, it has been suggested that human insulins were introduced without adequate comparison of efficacy with animal insulin preparations. In addition, there were reports of altered hypoglycaemic awareness after transfer to human insulin.[135]

A Cochrane systematic review looked at 45 studies that included 2156 participants.[135] Many studies were double-blind RCTs, but most were of poor methodological quality. Purified

porcine and semisynthetic insulin were most often investigated. No significant differences in metabolic control or hypoglycaemic episodes between various insulin species were detected. No significant differences in insulin dosage or insulin antibodies were detected between groups in these trials.[135] [evidence level Ia] Outcomes such as health-related quality of life, diabetes complications and mortality were not investigated.[135] [evidence level Ia]

Four studies included in the systematic review were based on children and young people with diabetes.[136–139] These studies, which were based on a total of 270 participants, examined the following outcomes: HbA1,[136,138] fasting plasma glucose,[136,138] insulin dosage,[136,138] insulin antibodies,[137] and adverse effects.[136,138,139] No statistically significant differences between insulin types were found in relation to any of these outcomes. [evidence level Ib]

6.1.3.4.1 Summary

RCTs have not detected differences between human and animal insulins in terms of glycaemic control or development of antibodies. Concerns about increased frequency, severity or reduced awareness of hypoglycaemia with human insulin, and the quantity of insulin antibodies which may be produced in patients on animal insulin have not been confirmed. Choice of insulin is influenced by other factors such as delivery systems and cultural preferences (for example, avoidance of porcine insulin by Muslim and Jewish people).

6.1.3.5 Is soluble insulin or rapid-acting insulin analogue more appropriate for children and young people with type 1 diabetes?

Short- and long-acting insulin analogue technology has developed rapidly over the last 10 years. Analogues are altered molecular versions of a natural substance. The natural hormone is changed slightly by altering the amino acid sequence within the molecule. Analogue insulins are therefore versions of insulin which may have a different profile of action to traditional animal or human insulin.[140]

Two rapid-acting human insulin analogues are available, insulin lispro and insulin aspart.[133] Insulin lispro and insulin aspart have an onset of action of 10–20 minutes and a duration of action of 2 to 5 hours, which is shorter than non-analogue short-acting insulin (soluble insulin or soluble human insulin); as a result, compared with soluble insulin, fasting and preprandial blood-glucose concentrations are higher and postprandial blood-glucose concentrations are lower. Subcutaneous injection of rapid-acting insulin analogue may be given shortly before or shortly after meals,[133] which may help those with unpredictable eating habits (such as infants and pre-school children), those prone to pre-lunch hypoglycaemia, and those who eat late in the evening and are prone to early nocturnal hypoglycaemia.[133]

We identified 4 systematic reviews[141–144] that investigated the effectiveness of rapid-acting insulin analogues in comparison with soluble insulin. [evidence level Ia] None of the systematic reviews considered studies in children and young people exclusively. Two reviews included studies based on patients with type 1 or type 2 diabetes.[141,142] One review used only RCTs from a pharmaceutical company database.[143] In total, 21 RCTs were included in the systematic reviews; the number of studies in each systematic review ranged from 6 to 20. We identified many good-quality RCTs that were published in the 4 years since the previous systematic review was published. These additional studies met our quality criteria for inclusion as part of the evidence. We therefore conducted a meta-analysis of RCTs in children, young people and adults that compared rapid-acting insulin analogues with soluble insulin. The results are reported below and as forest plots in Appendix J:.1.1.

We found a total of 27 good-quality RCTs where rapid-acting insulin analogues were used for at least 1 month in children, young people or adults.[145–170] [evidence level Ib] We found 4 crossover RCTs (n=59, n=23, n=463 and n=22)[151,154,158,167] that examined rapid-acting insulin analogue treatment in children and young people with type 1 diabetes. [evidence level Ib]

Three of these RCTs investigated HbA1clevels and numbers of hypoglycaemic episodes[151,154,158] and one examined patient preference.[167]

6.1.3.5.1 HbA1c

Twenty-three RCTs examined the effect of rapid-acting insulin analogue compared with soluble insulin on HbA1c. Eleven of these studies employed a parallel design (total number of patients in each arm: rapid-acting insulin analogue n=2425; soluble insulin n=1821).[145,149,156,157,160–162,165,166,168,170] [evidence level Ib] HbA1c levels were lower in patients using the rapid-acting insulin analogue compared with soluble insulin in parallel design RCTs (WMD −0.14%, 95% CI −0.19 to −0.08%). Twelve RCTs used a crossover design (total number of patients in each arm: rapid-acting insulin analogue n=2441; soluble insulin n=2439).[146–148,151,153–155,158,159,163,164,169] There was no difference in HbA1c levels when rapid-acting insulin analogue was compared with soluble insulin in crossover RCTs (WMD 0.00%, 95% CI −0.09 to 0.08%). [evidence level Ia]

We conducted 2 separate analyses to compare the effects of rapid-acting insulin analogue and soluble insulin on HbA1clevels. One analysis was based on studies involving children and young people; the second analysis was based on adult studies. Three crossover RCTs looked at children and young people (n=59, n=23 and n=463, total n=545).[151,154,158] [evidence level Ib] The RCTs found no evidence to suggest a difference in HbA1c (WMD −0.03%, 95% CI −0.21 to 0.14%). Nine crossover RCTs included adults (total number of patients in each arm: rapid-acting insulin analogue n=1896; soluble insulin n=1894).[146–148,153,155,159,163,164,169] These RCTs also found no evidence to suggest a difference in HbA1c levels (WMD 0.01%, 95% CI −0.09 to 0.11%).

We found no evidence to suggest a difference in HbA1cbetween types of rapid-acting insulin analogues. There were 8 parallel RCTs examining insulin lispro (WMD −0.13%, 95% CI −0.24 to −0.02%, total number of patients in each arm: rapid-acting insulin analogue n=966; soluble insulin n=999).[145,149,156,157,161,162,168,170] Three parallel RCTs examined insulin aspart (WMD −0.14%, 95% CI −0.20 to −0.07%, total number of patients in each arm: rapid-acting insulin analogue n=1459; soluble insulin n=822).[160,165,166]

6.1.3.5.2 Hypoglycaemic episodes

Seventeen RCTs examined the effect of rapid-acting insulin analogue compared with soluble insulin on the number of hypoglycaemic episodes/30 days. Eight of these studies used a parallel group design (total number in each arm: rapid-acting insulin analogue n=963; soluble insulin n=999) There was no difference in the number of hypoglycaemic episodes when rapid-acting insulin analogue was compared with soluble insulin in the parallel group RCTs (WMD −0.42%, 95% CI −1.53 to 0.68%).[145,149,156,157,161,162,168,170] Nine studies had a crossover design (total number in each arm: rapid-acting insulin analogue n=2129; soluble insulin n=2127).[146,151,152,152,154,155,158,163,169] There was no difference in the number of hypoglycaemic episodes when rapid-acting insulin analogue was compared with soluble insulin in the crossover RCTs (WMD −0.42%, 95% CI −1.11 to 0.27%). However, the overall results for the parallel and crossover studies were heterogeneous and should be interpreted with caution. [evidence level Ia]

Analyses were conducted for children and young people separately from adults in order to examine the effect of rapid-acting insulin analogue compared with soluble insulin on the number of hypoglycaemic episodes/30 days. Three crossover RCTs in children and young people (n=59, n=23 and n=463, total n=545)[151,154,158] [evidence level Ib] showed no difference in the number of hypoglycaemic episodes (WMD −0.35%, 95% CI −0.91 to 0.22%). Six crossover RCTs in adults (total number in each arm: rapid-acting insulin analogue n=1584; soluble insulin n=1582)[146,152,152,155,163,169] showed no difference in the number of hypoglycaemic episodes when rapid-acting insulin analogue was compared with soluble insulin (WMD −0.57%, 95% CI −1.64 to 0.50%). However, the overall result for adults was heterogeneous and so it should interpreted with caution.

No studies investigated the number of hypoglycaemic episodes/30 days of insulin aspart therapy. However, 1 parallel RCT in adults with type 1 diabetes examined the risk of experiencing a hypoglycaemic episode in patients treated with insulin aspart compared with soluble insulin, and found no difference (major hypoglycaemic episodes: RR 0.83, 95% CI 0.59 to 1.18; minor hypoglycaemia: RR 1.01, 95% CI 0.89 to 1.16; n=1070).[160] [evidence level Ib] A crossover design RCT in adults with type 1 diabetes found no significant difference in the number of hypoglycaemic events in patients treated with insulin aspart compared with those treated with soluble insulin (567 versus 615, n=90). However, there was a reduction in major hypoglycaemic events (20 events in 24 patients versus 44 events in 24 patients, p<0.002).[171] [evidence level Ib]

6.1.3.5.3 Patient preference

Four crossover RCTs examined patient preference in relation to rapid-acting insulin analogue and soluble insulin (total n=330).[150,155,159,167] Patients preferred rapid-acting insulin analogue to soluble insulin (RR 2.70, 95% CI 1.65 to 4.42). [evidence level Ia] However, this result should be interpreted with caution as the overall effect was heterogeneous.

We then conducted 2 separate analyses to examine the effects of rapid-acting insulin analogue compared with soluble insulin on patient preference for children, young people and adults. One crossover RCT in children (n=22) showed greater preference for rapid-acting insulin analogue (RR 4.50, 95% CI 1.81 to 11.16).[167] [evidence level Ib] Three crossover RCTs in adults (total n=308)150,155,159 showed greater preference for rapid-acting insulin analogue (RR 2.43, 95% CI 1.40 to 4.22). However, the overall result for adult patients was heterogeneous and so it should interpreted with caution.

6.1.3.5.4 The use of short-acting insulin and rapid-acting insulin analogue for continuous subcutaneous insulin injection (CSII)

A systematic review identified 6 RCTs in the use of rapid-acting insulin analogues compared with soluble insulin in CSII.[172] [evidence level Ia] Five crossover RCTs investigated the use of insulin lispro compared with soluble insulin[173–177] and 1 parallel design RCT with 3 treatment groups investigated the use of insulin lispro, insulin aspart and soluble insulin.[178] [evidence level Ib] The HbA1clevel was found to be significantly improved with insulin lispro (WMD −0.26%, 95% CI −0.47 to −0.06%). Some studies reported fewer hypoglycaemic episodes with analogue insulin but this varied with the definition of hypoglycaemia used. No differences in body weight or insulin dosage were reported.

We identified 2 further RCTs investigating the use of rapid-acting insulin analogues compared with soluble insulin as part of CSII in adults that were excluded from the systematic review because they had study lengths of 1 month and 2 months, respectively.[179,180] [evidence level Ib] One RCT found no significant difference between the 2 treatment groups in terms of HbA1clevels (7.07 ±0.51% versus 6.67 ±0.67%), mean blood glucose levels (9.04 ±0.89 mmol/l versus 9.32 ±1.17 mmol/l) or mean SD of blood glucose (4.44 ±0.49 mmol/l versus 4.82 ±0.83 mmol/l). There was a significant decrease in postprandial blood glucose level (9.43 ±1.39 mmol/l versus 10.49 ±2.05 mmol/l, p<0.05) and hypoglycaemia index (7.1 ±4.6 versus 12.6 ±10.2, p<0.05) in the insulin lispro group compared with the soluble insulin group.[179] [evidence level Ib] The second RCT reported lower HbA1c levels (7.4% versus 7.6%, p=0.047), mean glycaemia (7.4 mmol/l versus 7.6 mmol/l, p<0.001), SD of all blood glucose levels (3.6 mmol/l versus 3.9 mmol/l, p=0.012), mean postprandial glycaemia (8.1 mmol/l versus 9.6 mmol/l, p<0.001) and SD of postprandial blood glucose levels (3.6 mmol/l versus 4.0 mmol/l, p=0.006) in the insulin lispro treatment group than the soluble insulin treatment group. There was no significant difference in mean preprandial glycaemia (8.5 mmol/l versus 8.4 mmol/l, p=0.86), SD of preprandial blood glucose levels (3.4 mmol/l versus 3.6 mmol/l, p=0.86), or the number of hypoglycaemic events (9.7/30 days versus 8.0/30 days, p=0.23) between the insulin lispro treatment group and the soluble insulin treatment group.[180] [evidence level Ib]

Three studies investigated rapid-acting insulin analogues other than insulin lispro and insulin aspart that have not been licensed for use in the UK.[181–183] [evidence level Ib]

6.1.3.5.5 Timing of short-acting insulin and rapid-acting insulin analogue injections

Six RCTs have examined the timing of short-acting insulins and rapid-acting insulin analogues before and after meals.

A 6-week crossover RCT evaluated the administration of short-acting insulin 5 minutes before main meals compared with 30 minutes before main meals (n=15 adults). No significant differences were reported in any of the outcomes that were measured, including glycated haemoglobin, postprandial maximum glucose increase, mean daily glucose profile and total number of hypoglycaemic episodes.[184] [evidence level Ib] A second RCT compared single doses of short-acting insulin given 5 minutes and 30 minutes before breakfast (n=9 children and young people). This RCT found that short-acting insulin injection 5 minutes before breakfast decreased the mean postprandial glucose concentration after 120 minutes, but not at 90 minutes, 150 minutes or 180 minutes.[185] [evidence level Ib]

Another 6-week crossover RCT evaluated the administration of rapid-acting insulin analogues immediately before the start of a meal compared with immediately after a meal or a maximum of 30 minutes after starting a meal (42 children and 34 young people). The study found no differences in glycaemic control (measured by fructosamine and HbA1c), incidence of hypoglycaemia, parent preference or mean blood glucose.[186] [evidence level Ib]

An RCT compared single doses of rapid-acting insulin analogue given 30 minutes before, 15 minutes before, immediately before and 15 minutes after breakfast (n=12 adults). This RCT found no difference in postprandial glycaemia among the treatment groups.[187] [evidence level Ib] A second RCT compared rapid-acting insulin analogue given 10 minutes before and 20 minutes after 4 different types of meal (high-carbohydrate and high-fat meals, both given in liquid and solid form) (n=20 adults). This RCT found differences in blood glucose at some time points.[188] [evidence level Ib]

Another RCT examined short-acting insulin given 40 minutes, 10 minutes and immediately before a meal, and rapid-acting insulin analogue given 20 minutes before, immediately before and 15 minutes after a meal (n=18 adults). This RCT found significant improvements in postprandial blood glucose excursions at 60, 90 and 120 minutes with the injection of rapid-acting insulin analogue 20 minutes before and immediately before the meal compared with injection of short-acting insulin 40 minutes, 10 minutes and immediately before the meal. Postprandial blood glucose excursions at 60 minutes (but not at 90 and 120 minutes) were significantly higher with a postprandial rapid-acting insulin analogue injection compared with injection of rapid-acting insulin analogue given 20 minutes before or immediately before a meal.[189] [evidence level Ib]

We found 1 study that investigated the time patients with type 1 diabetes left between injecting short-acting insulin and eating, after they had been advised to leave 20 minutes or more before a meal (n=179 adults).[190] [evidence level III] Eighty-four per cent of patients administered their insulin less than 20 minutes before eating, and 26% took their insulin within 5 minutes of eating their meals.

In summary, the RCTs showed inconsistencies in postprandial glucose concentrations with different time lags between short-acting insulin and rapid-acting insulin analogue injections and meals. One RCT suggested that postprandial glucose levels were decreased if rapid-acting insulin analogue was given instead of short-acting insulin.

6.1.3.5.6 Biphasic insulins containing rapid-acting insulin analogues compared with soluble insulin

Three RCTs investigated the used of biphasic insulins containing rapid-acting insulin analogues compared with biphasic insulins containing soluble insulin.

One RCT investigated the used of biphasic insulins containing insulin lispro and insulin lispro protamine suspension compared with soluble insulin and isophane (n=166 adults).[191] [evidence level Ib] The trial found a significantly lower HbA1clevel in the group treated with insulin lispro and insulin lispro protamine suspension compared with soluble human insulin and isophane (7.54% versus 7.92%, p=0.019, difference of 0.38%). There was no significant difference in the incidence of hypoglycaemia between the 2 treatment groups (1.11 versus 1.12 events/person).

The second RCT investigated the used of biphasic insulins containing insulin aspart and insulin aspart protamine suspension compared with biphasic isophane insulin (n=50 adults).[192] [evidence level Ib] There was no difference in the number of hypoglycaemic events between the 2 treatment groups (9 versus 9 events).

The third RCT investigated the used of biphasic insulins containing insulin lispro and isophane compared with soluble insulin and isophane (n=37 adults).[193] [evidence level Ib] The study found no differences in HbA1c levels or incidence of hypoglycaemia.

6.1.3.5.7 Summary

Parallel design RCTs have shown a small improvement in long-term glycaemic control in patients using rapid-acting insulin analogues compared with soluble insulin. We found no evidence of a difference in the number of hypoglycaemic episodes when comparing rapid-acting insulin analogues and soluble insulins. Rapid-acting insulin analogues have been shown to be preferred by some patients because of the increased flexibility in injection times relative to meals.

6.1.3.6 What is the most appropriate intermediate or long-acting insulin for children and young people with type 1 diabetes?

6.1.3.6.1 Insulin glargine

Insulin glargine allows a consistent release of insulin during the day, thereby mimicking natural basal insulin release. Insulin glargine can provide the basal component of multiple daily injection regimens. The prolonged absorption profile of insulin glargine, with no pronounced peaks over 24 hours, allows for once-daily dosing. Furthermore, as it does not require re-suspension prior to administration, it has the potential to reduce inter- and intra-user variability.[194]

A recently published NICE TA provided guidance on the use of insulin glargine.[194] The NICE TA discussed 4 fully published RCTs, 7 RCTs published only as abstracts and 1 unpublished RCT, all of which involved adults only.

Three of the 4 fully published RCTs reported no change in HbA1clevels. One RCT showed that HbA1c levels were reduced more with insulin glargine than with isophane. However, this study lasted 4 weeks whereas HbA1c measurements reflect average glycaemic control over the preceding 6 to 8 weeks.

All 4 fully published studies found that the mean change in fasting plasma glucose was significantly greater in those using insulin glargine (range 1.34 to 2.23 mmol/l). Three RCTs found that insulin glargine significantly reduced fasting blood glucose compared with isophane (difference 0.71 to 1.50 mmol/l). The fourth RCT showed no significant difference between insulin glargine and isophane.[194] [evidence level Ia]

Three RCTs reported severe hypoglycaemia. The first RCT reported that a significantly smaller percentage of people experienced severe hypoglycaemia in the post-titration phase with insulin glargine compared with isophane (1.9% versus 5.6% of patients, respectively, p<0.05). The other RCTs reported no significant differences over the entire trial period or the post-titration phase. Nocturnal hypoglycaemia was reduced with insulin glargine compared with isophane in 2 RCTs (36% versus 56%, respectively, p<0.05). One RCT showed no

difference in nocturnal hypoglycaemia. One RCT reported that a smaller percentage of people experienced symptomatic hypoglycaemia in the whole trial or the post-titration period with insulin glargine compared with isophane (40% versus 49%, respectively, for post-titration phase).[194] [evidence level Ia]

One observational study showed a 1.7% reduction in HbA1clevels after 8 weeks of insulin glargine treatment compared with baseline. This study also showed that 70.3% of people reported fewer hypoglycaemic episodes with insulin glargine. A second observational study reported a 0.36% reduction in HbA1c levels compared with baseline following 6 months of insulin glargine treatment.[194] [evidence level Ia]

The NICE TA, which evaluated the cost effectiveness of insulin glargine, included a systematic review of the economic literature.[194] [evidence level Ia] No cost effectiveness analyses of insulin glargine were identified in the published literature. However, a model constructed for the NICE TA suggested that the cost effectiveness of insulin glargine in type 1 diabetes patients was around £32,000 per quality-adjusted life year (QALY). The model was constructed with and without the assumed loss of quality of life from a hypoglycaemic event. Excluding this additional source of quality of life, the cost per QALY rose to £629,703, suggesting a far lower benefit for the additional cost. The wide difference in the estimates of cost effectiveness demonstrates the fragility of the approach used.

A within-group comparison study published after the NICE TA investigated HbA1clevels and episodes of hypoglycaemia in children and young people with type 1 diabetes treated initially with isophane insulin then with insulin glargine (n=114).[195] [evidence level IIb] The study found that HbA1c was lower and the frequency of non-severe hypoglycaemic events decreased when the children and young people were treated with insulin glargine rather than isophane insulin (HbA1c: 9.3 ±0.13% versus 9.6 ±0.12%, p=0.01; non-severe hypoglycaemia: 2.0 ±0.1 per week versus 1.3 ±0.1 per week, p=0.001).

Insulin glargine has recently received a paediatric licence in the UK for people aged 6 years and over.

6.1.3.6.2 Timing of insulin glargine

An RCT examined the optimum timing (breakfast, dinner or bedtime) of insulin glargine in adults with type 1 diabetes.196 The trial found no differences in mean HbA1c, 24-hour blood glucose profile or incidence of total symptomatic and severe hypoglycaemia. Nocturnal hypoglycaemia occurred in significantly fewer patients in the group who received breakfast insulin glargine (59.5%) compared with dinner (71.9%) or bedtime (77.5%) insulin glargine (p=0.005). [evidence level Ib]

6.1.3.6.3 Insulin detemir

Two published RCTs have compared insulin detemir with long-acting isophane insulin in adults. An RCT lasting 6 months (n=419) found no significant differences in HbA1c (7.60 ±0.09% versus 7.64 ±0.10%, p=0.61), fasting plasma glucose (9.19 ±0.44 mmol l versus 9.94 ±0.52 mmol l, p=0.09) or major hypoglycaemic events (RR 0.65, 95% CI 0.28 to 1.50, p=0.312). The study found a significantly lower body weight (70.9 ±0.28 kg versus 71.8 ±0.33 kg, p=0.001) and fewer minor hypoglycaemic events with insulin detemir (RR 0.72, 95% CI 0.56 to 0.93, p=0.011).[197] [evidence level Ib]

Another RCT, lasting 4 to 6 weeks, reported that there were no significant differences in maximum glucose concentration, area under the curve of 24-hour serum glucose profile, point self-monitored blood glucose profile, mean fructosamine level, or adverse events. Mean serum glucose level was not parallel between the 2 treatment groups: during the night, serum glucose was higher with insulin detemir than with isophane. There were significantly smaller numbers of hypoglycaemic events in the last week of insulin detemir treatment

(insulin detemir 60% of patients had at least 1 hypoglycaemic event versus isophane insulin 77% of patients had at least 1 hypoglycaemic event, p<0.05, n=59).[198] [evidence level Ib]

6.1.3.6.4 Isophane insulin compared with insulin zinc suspension

Three RCTs investigated the use of isophane insulin compared with insulin zinc suspension.[199–201] [evidence level Ib] One of these RCTs included children and young people.[199]

An RCT in children and young people (n=52, age range 5 to 18 years) investigated the use of isophane insulin compared with insulin zinc suspension.199 [evidence level Ib] Glycated haemoglobin level was lower in children treated with isophane insulin (11.1 ±2.2% versus 12.0 ±2.2%). Fasting blood glucose, fructosamine concentration and number of episodes of hypoglycaemia were similar in both groups.

An RCT in adults with type 1 diabetes investigated the use of isophane insulin compared with insulin zinc suspension (n=82).200 [evidence level Ib] The trial found no differences in glycated haemoglobin level (9.2 ±0.1% versus 9.3 ±0.1%), fructosamine level (1.55 ±0.02 mmol/l versus 1.57 ±0.02 mmol/l), fasting blood glucose concentration (8.8 ±0.5 mmol/l versus 9.0 ±0.5 mmol/l), mean blood glucose concentration (8.2 ±.03 mmol/l versus 7.6 ±0.3 mmol/l) or hypoglycaemic event rate.

An RCT in adults with type 1 diabetes investigated the use of isophane insulin compared with insulin zinc suspension (n=18).[201] [evidence level Ib] No difference in HbA1 level was seen between the 2 groups (10.1 ±0.4% versus 9.9 ±0.3%).

6.1.3.6.5 Isophane insulin compared with crystalline insulin zinc suspension

Four RCTs investigated the use of isophane insulin compared with crystalline insulin zinc suspension.[202–205] [evidence level Ib] One of these RCTs included children and young people.[202]

An RCT in children and young people with type 1 diabetes investigated the use of a pre-breakfast and pre-evening meal mixture of isophane and soluble insulin compared with a pre-breakfast mixture of isophane and soluble insulin and a pre-evening meal mixture of crystalline insulin zinc suspension and soluble insulin (n=20, age range 7 to 18 years).[202] [evidence level Ib] The trial found no difference between the treatment groups in terms of HbA1 level (9.1 ±1.7% versus 9.5 ±1.4%). However, patients treated with a pre-evening meal mixture of crystalline insulin zinc suspension and soluble insulin had lower mean fasting blood glucose levels pre-breakfast (9.6 ±1.9 mmol/l versus 10.3 ±2.2 mmol/l, p<0.05) and those treated with a pre-breakfast and pre-evening meal mixture of isophane and soluble insulin had lower mean blood glucose before a bedtime snack (8.4 ±1.9 mmol/l versus 10.0 ±2.1 mmol/l). At no other times were the blood glucose levels different.

An RCT in adults with type 1 diabetes investigated the use of isophane insulin compared with crystalline insulin zinc suspension (n=178).[203] [evidence level Ib] The trial found no differences between the treatment groups in terms of HbA1clevel (7.6 ±0.1% versus 7.7 ±0.1%), rate of severe hypoglycaemia (0.05 ±0.03/patient every 30 days versus 0.07 ±0.04/patient every 30 days).

An RCT in adults with type 1 diabetes investigated the use of isophane insulin compared with crystalline insulin zinc suspension (n=10).[204] [evidence level Ib] Fasting blood glucose levels at 6 a.m. (10.82 ±4.27 mmol/l versus 6.26 ±0.88 mmol/l) and 8 a.m. (14.03 ±1.08 mmol/l versus 9.26 ±1.02 mmol/l) were significantly lower in the patients using crystalline insulin zinc suspension. There were no differences in blood glucose levels at any other times of day.

An RCT in adults with type 1 diabetes investigated the use of isophane insulin compared with crystalline insulin zinc suspension (n=16).[205] [evidence level Ib] The trial found lower glycated

haemoglobin levels in the group treated with crystalline insulin zinc suspension (8.2 ±0.3% versus 7.9 ±0.4%).

6.1.3.6.6 Insulin zinc suspension compared with crystalline insulin zinc suspension

Two RCTs investigated the use of insulin zinc suspension compared with crystalline insulin zinc suspension.[206,207] [evidence level Ib] One of these RCTs included children and young people.[206]

An RCT in children and young people (n=77, age range 5 to 18 years) investigated twice-daily use of crystalline insulin zinc suspension with soluble insulin compared with twice-daily use of insulin zinc suspension with soluble insulin.[206] [evidence level Ib] The trial found no differences in HbA1clevels or in pre-lunch, pre-dinner, bedtime and mid-sleep fasting blood glucose between the 2 groups. However, pre-breakfast fasting blood glucose was lower in the crystalline insulin zinc suspension group compared with the group treated with insulin zinc suspension (10.6 ±0.6 mmol/l versus 12.6 ±0.6 mmol/l, p<0.02).

An RCT in adults with type 1 diabetes investigated the use of insulin zinc suspension compared with crystalline insulin zinc suspension (n=66, age range 18 to 62 years).[207] [evidence level Ib] The trial found no difference in glycated haemoglobin levels between the 2 groups. However, fasting blood glucose levels were lower in patients treated with crystalline insulin zinc suspension (6.6 ±0.5 mmol/l versus 8.2 ±0.5 mmol/l, p<0.05) and the incidence of serious hypoglycaemic events was higher in patients treated with crystalline insulin zinc suspension (0.38 ±0.10 versus 0.09 ±0.04 events/patient/month, p<0.02).

6.1.3.6.7 Summary

No published studies have investigated the effectiveness of insulin glargine and insulin detemir specifically in children and young people. Further research is needed to address these issues, particularly in relation to pre-school children. Insulin glargine may be beneficial for reducing nocturnal hypoglycaemia in children and young people using multiple daily injection regimens. There is no substantive evidence to suggest that any particular type of intermediate or long-acting insulin has greater clinical effectiveness than any other.

6.1.3.7 What is ideal, pre-mixed or self-titrating insulin in children and young people with type 1 diabetes?

6.1.3.7.1 Meaning of pre-mixed and self-titrating insulin

Pre-mixed insulin contains particular combinations of short- and long-acting insulins. Pre-mixed insulins may reduce errors in drawing up insulin, but they reduce flexibility by fixing the ratio of short- and long-acting insulins, allowing no scope for adjustment. Flexibility may be increased by combining different pre-mixed insulin preparations. Pre-mixed insulins may be useful when adherence to an insulin regimen is a problem.

Self-titration involves mixing short- and long-acting insulins in a syringe for administration by a single injection. Self-titrating insulin is often referred to as free-mixing insulin. Self-titrating insulins have been replaced to a large extent by multiple daily injection regimens that involve a single daily intermediate- or long-acting insulin dose and a short-acting insulin or rapid-acting insulin analogue dose with every meal.

6.1.3.7.2 Glycaemic control

Seven RCTs have compared pre-mixed and self-titrating insulin therapy in patients with type 1 diabetes, but only 1 of these involved children and young people (age range 7 to 16 years).[208] [evidence level Ib] Different delivery devices were used in the different treatment groups in 5 of the RCTs (the pre-mixed insulins were administered using pen injectors, whereas the self-titrating insulin was administered using a conventional syringe). Five of the

RCTs were crossover trials, and 4 of the RCTs explicitly received support from pharmaceutical companies. The methodological reporting of the trials was poor.

Six of the RCTs recorded HbA1clevel[209–211] or total glycated haemoglobin (HbA1).[208,212,213] None of the RCTs showed a significant difference in glycated haemoglobin between the pre-mixed and self-titrating groups.[208–212] A further RCT was excluded from this review because, although HbA1 was measured, it was not reported separately for the 2 treatment groups.[213]

A survey of adults with type 1 diabetes investigated HbA1c levels in patients who used pre-mixed insulin compared with those who used separate insulin preparations (n=600).[214] [evidence level IIb] In patients under 35 years pre-mixed insulin (n=62) was associated with higher HbA1c levels than patients using 2 or 4 (n=85 and n=83, respectively) separate insulin injections/day (pre-mixed 7.8 ±0.2% versus 2 separate insulin preparations 6.9 ±0.2%, p<0.001; pre-mixed 7.8 ±0.2% versus 4 separate insulin preparations 7.3 ±0.2%, p<0.05). There was no such association when pre-mixed insulin was compared with 3 separate insulin injections/day (n=38) (pre-mixed 7.8 ±0.2% versus 3 separate insulin preparations 7.6 ±0.2%) or in patients aged 35 years or over (7.5 ±0.2% versus 7.5 ±0.1%).

Four RCTs recorded glucose levels.[208,209,212,215] No significant differences in glucose levels between pre-mixed and self-titrating treatment groups were detected in these RCTs. [evidence level 1b]

Five RCTs recorded hypoglycaemic episodes.[208–210,212,215] No significant differences in the number of hypoglycaemic episodes with pre-mixed and self-titrating insulin were detected in these RCTs. [evidence level 1b]

6.1.3.7.3 Patient preference

Four crossover RCTs surveyed patient preferences at the end of the trials.[208,209,212,215] [evidence level Ib] These studies reported that 82 to 100% of patients preferred pre-mixed insulin delivered by pen to self-titrating insulin delivered by syringe. The results might have been influenced by the questionnaire designs. Strong reported preferences for pen delivery systems might also account for the differences observed.

We found no studies that compared long-term complications following the use of pre-mixed and self-titrating insulins.

6.1.3.7.4 Summary

There are no differences between pre-mixed and self-titrating insulins in terms of glycaemic control (as measured by glycated haemoglobin, glucose levels and/or hypoglycaemic episodes). No trials have evaluated the effectiveness of pre-mixed insulins using comparable devices in children and young people with poor adherence to treatment. Although patients have reported a preference for pre-mixed insulin in some studies, the preferences might be attributable to differences in delivery devices.

Healthcare professionals may find it useful to refer to the recommendations in Section 5 (education) when offering information about insulin preparations.

6.1.4 Methods of delivering insulin

6.1.4.1 Should a pen or a syringe and needle be used for insulin therapy delivery in the treatment of children and young people with type 1 diabetes?

Pen injection devices are of 2 types: either pre-filled cartridges containing insulin, which are used in a non-disposable pen, or pre-filled disposable pens. They aim to make injections easier because they eliminate the need for drawing up insulin from a vial. They may be particularly useful for insulin administration away from home (for example, at school).

An RCT investigated the use of disposable pen devices in children and young people with type 1 diabetes who had previously used syringes and vials.[216] [evidence level 1b] The study reported increased treatment satisfaction (in terms of convenience, flexibility and demands) with the disposable pen compared with syringe and vial. This was reflected in increased patient preference for the disposable pen over the syringe and vial. There were no significant differences in numbers of hypoglycaemic events or problems at injection sites.[216] [evidence level 1b]

Six further RCTs (including 5 crossover trials) compared pen and needle injection devices in patients with type 1 diabetes.[217–222] The RCTs involved a total of 327 patients. None of the RCTs involved children, although 1 involved people aged 16 years and over.[218] Two RCTs explicitly reported pharmaceutical company support,[217,221] the others did not state the source of funding, but they named proprietary devices.

HbA1cwas examined in 4 of the RCTs,[217–219,222] and glycated haemoglobin was examined in 1 RCT.[220] None of the RCTs reported a significant difference in HbA1c levels between pens and syringes.

Glucose levels were reported in all 6 RCTs, but none of the RCTs found a statistically significant difference in glucose levels between those using pens and those using syringes.

Hypoglycaemia was reported in 4 RCTs, but none of the RCTs found a statistically significant difference in the number of hypoglycaemic episodes between those using pens and those using syringes.

Adverse effects, including local injection site reactions, were reported in 2 of the RCTs.[219,220] Neither RCT found a significant difference in the number of adverse effects between pens and syringes.

All 6 RCTs examined patient preference, and all of them found that patients preferred pens (range 74% to 95%). However, this effect may have been influenced by the questionnaire designs, and so the findings should be interpreted with caution.

In addition to the RCTs described above, 4 non-randomised controlled trials have examined the use of syringes and pen devices. The first study evaluated the accuracy and reproducibility of low-dose insulin administration using pen injectors and syringes. This study found a small but statistically significant over-dosing of insulin when using syringes and a small but statistically significant under-dosing with insulin pens (1 unit insulin with NovoPen on average was 0.89 units, SD 0.04; BD-Pen 0.92 units, SD 0.03; 30-unit syringe 1.23 units, SD 0.09; $p<0.01$). There were no significant differences between the volumes of insulin delivered from the 4 quadrants of the insulin pen cartridges.[223] [evidence level IIa]

The second study also examined the accuracy of pen injectors compared with syringes. This study found that pens were more accurate in delivering small amounts of insulin (n=9, 27 observations, absolute error 4.9 ±1.6% versus 9.9 ±2.4%, $p<0.01$), but there was no significant difference in the accuracy of measuring larger amounts of insulin.[224] [evidence level IIa]

The third study (n=10) was performed retrospectively and compared syringes with pens. This study showed that HbA1c (and hence glycaemic control) deteriorated with pen use (HbA1c 9.3 ±1.9% pen versus 8.9 ±1.8% syringe injections, $p<0.01$), although all patients preferred the pens. The pens were early models, and the frequent technical difficulties reported in this study have been resolved for the currently available pens.[225] [evidence level IIb]

The fourth study investigated the use of insulin pens combined with another device. The additional device did not alter glycaemic control or hypoglycaemia incidence, but it did reduce the perception of pain (visual analogue scale of pain perception: 14.9 mm for pen with device versus 19.9 mm for pen alone, $p=0.005$; percentage of patients who experienced

pain 3 to 6 times/week: 10.5% for pen with device versus 22.8% for pen alone).[226] [evidence level Ib]

A survey investigated the views of adults with type 1 diabetes who underwent a 6-week trial of pen devices for insulin administration.[227] [evidence level III] The patients had previously used syringes and vials. In this study, 76.5% of patients said they would probably or definitely continue to use the pen (n=194), 74% agreed with the statement that they preferred pen to syringe, and 84% agreed with the statement that the pen was more convenient than the syringe (n=315). The study also investigated the views of physicians, 91% of whom agreed with the statement that it was easier to start patients new to insulin with a pen than with a syringe, and 85% of whom agreed with the statement that they were more confident in their patients' ability to deliver an insulin dose with a pen than with a syringe.[227] [evidence level III]

6.1.4.1.1 Disposable versus reusable pens

A study compared insulin wastage in reusable and disposable pens and the insulin saving practices of patients.[228] [evidence level III] The study showed that there was more wasted insulin with reusable pens with 1.5 ml cartridges than with 3 ml disposable pens (2113 units/patient/year wastage for 1.5 ml reusable pens compared with 831 units/patient/year for 3 ml disposable pens). The study highlighted that 4.5% of patients gave incorrect doses to avoid waste, and 24.5% of patients gave 2 injections to avoid waste.[228] [evidence level III]

A second study interviewed adults with type 1 diabetes after supplying them with a new design of disposable pen.[229] [evidence level III] The patients preferred the new design, but it was not clear whether the preference for the new design was due to general design features or the fact that the pen was disposable.[229] [evidence level III]

6.1.4.1.2 Summary

Only patient preference differs between pens and syringes, with patients preferring pens to syringes. No studies have looked specifically at long-term complications in children and young people. Some people find syringes easier to handle. Syringes may be more comfortable for people with small hands, and it may be easier to administer insulin to small children using syringes.

6.1.4.2 What is the ideal length of needle for the injection of insulin in children and young people with type 1 diabetes?

An RCT has compared needles of 2 different lengths in 50 children and young people with type 1 diabetes.[230] [evidence level Ib] This RCT did not report any substantive outcomes, such as pain or patient preference. The insulin was administered by a nurse and the main outcome was site of needle point. With longer (12.7 mm) needles 86% of insulin injections were performed intramuscularly, and with shorter (8 mm) needles 38% of insulin injections were visualised into muscle (48% in the arm and 28% in the thigh region).

We found no studies that evaluated patient preference or long-term complications in relation to needle length.

Another RCT compared multi-injection (sprinkler) and conventional needles in 10 adults with type 1 diabetes.[231] [evidence level IIa] This RCT found that sprinkler needles significantly increased the absorption rate of the initial insulin dose. The study did not report any substantive outcomes, including pain or patient preference. No studies were found that evaluated the use of sprinkler needles in children and young people.

An observational study of insulin injection technique in mainly adult patients in 7 European countries found that lipohypertrophy and bruising were not associated with needle length (n=1002).[232] [evidence level III]What is the ideal technique for the injection of insulin in children and young people with type 1 diabetes?

6.1.4.2.1 Subcutaneous versus intramuscular insulin injections

We found no studies that examined long-term complications of subcutaneous or intramuscular insulin injections. However, short-term effects were investigated in 2 studies. One study looked at the absorption profile of insulin over 2 days when radio-labelled long-acting insulin was injected intramuscularly and subcutaneously at the same time, in adults with type 1 diabetes (n=11). Intramuscular insulin injections were absorbed faster than subcutaneous injections, and subcutaneous injections resulted in a more constant rate of absorption throughout the 24-hour study period. Intra-patient variation in absorption was significantly lower for subcutaneous injections than for intramuscular injections.[233] [evidence level IIa]

A second RCT compared subcutaneous and intramuscular injections of short-acting insulin in adults with type 1 diabetes (n=10).[234] [evidence level Ib] The RCT lasted 4 days. Mean blood glucose concentrations did not differ significantly between treatment groups, but the coefficient of variation of blood glucose was lower with intramuscular injections (32.9 ±3.6% versus 42.6 ±3.3%, p<0.01). Intramuscular injections were not reported to be more painful than subcutaneous injections.

An observational study in children and young people measured the distances from skin to muscle fascia by ultrasonography at standard injection sites on the outer arm, anterior and lateral thigh, abdomen, buttock and calf. The distances from skin to muscle fascia were greater in females than males. In the majority of males, the distances were less than the length of the needle (12.5 mm) at all sites except the buttock, whereas in the majority of females the distances were greater than 12.5 mm except at the calf. In this study, 78% of the children and young people injected at an angle of 90 degrees, and 75% raised a skin-fold before injecting (n=32).[235] [evidence level III]

An observational study of 64 children and young people showed that 30% of injections were made intramuscularly. The child being male, having a lower body mass index, and having a shorter distance from the skin surface to muscular fascia were all associated with increased use of intramuscular injections.[236] [evidence level III]

6.1.4.2.2 Injection through clothing

A study in adults investigated the safety of injecting insulin through clothing compared with conventional subcutaneous injection. No severe adverse events were reported, and there was no significant increase in problems with injecting through clothing. However, there were reports of bruising and blood stains on clothes. Patients found that injecting through clothing was beneficial in terms of convenience and time saving (n=42).[237] [evidence level Ib]

6.1.4.2.3 Skin pinching and angle of needle

A study compared the effectiveness of 2 insulin injection techniques in adults: 1 group was instructed to grasp a skin-fold, insert the needle at an angle of 45 degrees, release the skin-fold, and then inject insulin; the other group was instructed to grasp a skin-fold, insert the needle perpendicularly, and then inject insulin while still grasping the skin-fold.[238] [evidence level Ib] The study reported no differences in glycaemic control or incidence of hypoglycaemia between treatment groups. Patients preferred the technique where the needle was inserted at an angle of 45 degrees and the grip on the skin-fold was released before injecting insulin (n=1002).[238] [evidence level Ib]

An observational study of insulin injection techniques in mainly adult patients in 7 European countries found that 70% used a pinch-up technique. The patients who used the pinch-up technique had lower HbA1clevels than those who did not (7.9% versus 8.2%, p=0.032), but there was no association between use of the pinch-up technique and occurrence of lipohypertrophic lesions. However, HbA1c was not associated with injecting perpendicularly into the abdomen or not pinching-up in the thigh, and lipohypertrophy was not associated

with the angle of injection (n=1002).[232] [evidence level III] The same study found an association between leaving the pen in for longer and lower HbA1c levels (p=0.001), but no association with lipohypertrophic lesions. Patients who inspected injection sites regularly had lower HbA1c levels (p=0.03). Lipohypertrophy was not associated with the presence of bruising at the site of injection, the sex of the patient, the angle of injection, or disinfection of the skin before injecting.[232] [evidence level III]

6.1.4.3 What is the ideal anatomical place (injection site) for the injection of insulin in children and young people with type 1 diabetes?

Three studies have shown that insulin is absorbed at different rates in different parts of the body. A study involving 7 adults with type 1 diabetes showed that insulin injected into the abdomen was absorbed faster than insulin injected into the leg, and that the postprandial blood glucose rise was affected by differences in absorption rate in that the rise was highest in the leg, followed by the arm, followed by the abdomen.[239] [evidence level Ib] A second study in adults with type 1 diabetes reported that the postprandial rise was higher after abdominal injection than after injection into the thigh (n=22).[240] [evidence level 1b] A third study in adults with type 1 diabetes reported that glucose excursions were larger when insulin was injected into the thigh rather than the abdomen, and an increased frequency of low nocturnal blood glucose levels was observed when insulin was injected into the thigh rather than the abdomen (n=35).[241] [evidence level 1b]

A non-randomised controlled study investigated the site (extremity versus abdominal wall) and timing of morning insulin injections in children and young people with type 1 diabetes. The evaluation took place on a single occasion and involved 23 children and young people.[242] [evidence level IIb] The effects of injection on glycaemic control were poorly reported and unclear.

We found no studies that examined patient acceptance or long-term complications of different injection sites.

6.1.4.3.1 Rotation of insulin injection sites

One study in adults investigated rotating injection sites (thigh, abdomen and arm) compared with use of the abdomen only (n=12). The study found higher mean plasma glucose levels and higher variation in plasma glucose levels in the patients who rotated injection sites compared with the group who injected into the abdomen only (plasma glucose level: 3.7 ±0.3 mmol/l versus 2.7 ±0.2 mmol/l, p<0.001; mean variation of plasma glucose level: 17.4 ±2.2 mmol2/l2 versus 9.2 ±1.4 mmol2/l2, p<0.001).[243] [evidence level Ib]

An observational study of insulin injection techniques in mainly adult patients in 7 European countries found that 38% of patients rotated injection sites each time they injected regular insulin, but this was not associated with different HbA1clevels or lipohypertrophic lesions (p=0.088, n=1002).[232] [evidence level III]

6.1.4.3.2 Visual aids for identifying injection sites

A study investigated a new visual aid for the identification of injection sites for children with type 1 diabetes aged 6 to 11 years. The new aid, a bear with stickers, led the children to have significantly fewer errors on date, body location and exact site. Overall, children preferred the visual aid, but when stratified by age only the younger age group (6 to 8 years) showed a significant preference, and when stratified by sex only females showed a significant preference (n=58).[244] [evidence level IIa]

6.1.4.4 Single versus multiple use of needles

Three studies looked at the re-use of needles. An observational study instructed 14 children and young people to use syringes 7 times unless adverse events (such as the needle

becoming dull, bent skin, or infection) occurred. The children and young people re-used the needles 6.3 times on average. There were no incidents of infection requiring antibiotic therapy.[245] [evidence level IIb–III] A second observational study in adults showed no relationship between bacterial contamination and the number of times a needle was used (n=20).[246] [evidence level IIa] A survey asked patients whether they would continue to re-use syringes if they were available free on prescription; 86% of respondents said 'yes', and 13% said 'no' (n=179).[247] [evidence level III]

An observational study of insulin injection techniques in mainly adult patients in 7 European countries found that 41% of patients re-used needles. There was no association between re-use of needles and lipohypertrophic lesions (p=0.067), although those who re-used needles and injected into smaller zones (5 cm by 4 cm) had a higher risk of lipohypertrophic lesions (p=0.0001, n=1002).[232] [evidence level III]

6.1.4.5 Disposal of sharps

A survey of people with type 1 diabetes (33 children and young people and 69 adults) found that less than half recalled receiving information on the disposal of sharps (14% for disposal of needles and 34% for the disposal of lancets). Needle clippers or sharps boxes were used by 64% of the people for needle disposal and 30% of the people for lancet disposal. If the person had remembered receiving information they were more likely to use needle clippers and/or a sharps bin for needle and lancet disposal (needle disposal: OR 6.4, 95% CI 2.2 to 17.8; lancet disposal: OR 15.4, 95% CI 4.2 to 55.8).[248] [evidence level III]

A second survey (n=179) examined patients' views in relation to disposal of needles and other sharps. In this study, 78% of patients disposed of sharps in household waste, 78% considered their method of disposal to be safe, and 75% thought the provision of sharps bins was a reasonable idea.[247] [evidence level III]

6.1.4.6 Insulin jet injectors

We found 1 RCT that examined the use of jet injectors compared with syringes in adults with type 1 diabetes over two 4-week periods (n=14 adults). Five patients dropped out because of technical problems with the jet injector. Jet injectors were associated with a higher glycated haemoglobin (9.8%, SE 1.2% versus 9.1%, SE 1.1%, p<0.05). No difference was seen in the frequency of hypoglycaemic reactions between the delivery devices. There was no difference in anxiety for the 2 delivery devices among non-needle-phobic patients (n=8) or needle-phobic patients (n=6).[249] [evidence level Ib]

Three evaluation studies examining patient preference for delivery device were found. One found 70% of the adults surveyed preferred jet injectors to conventional syringes (n=42).[250] [evidence level III] A second study in adults (n=8) found fewer patients preferred jet injectors to disposable syringes (1/7 versus 7/8)[251] [evidence level III] A third study (n=10) found 7 adult patients preferred disposable pens, 3 had no preference, and none had a preference for the jet injector.[252] [evidence level III]

One evaluation study examined pain reported by children and young people after a single administration of insulin by jet injector compared with syringe, both administered by a doctor (n=41).[253] [evidence level III] The study found no difference in mean pain score. The jet injector produced lesions in 25/41 patients, bleeding in 21/41, leakage in 11/41, painful infiltrate in 4/41, wheal in 3/41, haematoma and delayed pain in 2/41; however, no comparison was made with insulin delivery by syringe.

One evaluation study, in children and young people, examined pain from 2 different jet injector devices (n=14).[254] [evidence level III] The study found a new jet injector was associated with a smaller number of children and young people sometimes, often or always receiving pain from insulin administration than the old jet injector (64% versus 28%, p=0.01). The study also found the new jet injector was associated with greater pain than the old jet

injector (pain measured as very, quite or reasonably painful: 28% versus 8%, p=0.02). There was no difference in adherence to insulin regimen, difficulties with device or local reaction to insulin administration between the 2 jet injectors.

6.1.4.7 Inhaled insulin

We found no RCTs on the use of inhaled insulin in children and young people with type 1 diabetes. A systematic review found 6 RCTs that compared inhaled insulin to subcutaneous insulin injections.[255] [evidence level Ia] Three trials were in patients with type 1 diabetes 256 to 258 and 3 trials in patients with type 2 diabetes.[259–261] [evidence level Ib]

All trials showed comparable glycaemic control for inhaled insulin compared with an entirely subcutaneous regimen. Three trials, 1 involving patients with type 1 diabetes and 2 involving patients with type 2 diabetes, had sufficient information to allow meta-analysis of HbA1cchange from baseline to be conducted (WMD −0.12%, 95% CI −0.28 to 0.03%). All 5 trials that investigated patient satisfaction reported significantly greater satisfaction with inhaled insulin. All 3 trials that investigated quality of life showed significant improvements with inhaled insulin compared with subcutaneous insulin. There was no difference in the total number of hypoglycaemic episodes in any of the trials. Four trials reported rates for severe hypoglycaemic episodes; 3 of these found no difference, but 1 trial in patients with type 1 diabetes found an increase in severe hypoglycaemic episodes in patients treated with inhaled insulin (RR 1.97, 95% CI 1.28 to 3.12). Three trials reported no difference in weight change, and 1 trial reported a significantly smaller increase in body weight in patients treated with inhaled insulin compared with subcutaneous insulin injections. Three studies reported greater incidence of cough in those using inhaled insulin.[255] [evidence level Ia]

6.1.4.8 Intranasal insulin

We found no RCTs on the use of intranasal insulin in children and young people with type 1 diabetes. A crossover RCT in adults investigated the clinical effectiveness of gelified intranasal insulin over 6 months (n=16).[262] [evidence level Ib] Four of the 16 patients withdrew from the study because of nasal burning and persistent sinusitis. There was no difference between the treatments in terms of HbA1clevel at 6 months (8.3 ±0.1% versus 8.6 ±0.1%), or total number of episodes of hypoglycaemia during the study (87.9 ±2.5 versus 87.7 ±2.5). There was an association between weight gain and intranasal insulin (1.6 ±0.4 kg versus −0.8 ±0.1 kg, p<0.05). A second crossover RCT in adults investigated the clinical effectiveness of intranasal insulin over a 1-month period (n=31).[263] [evidence level Ib] Twelve patients withdrew from the study because of metabolic dysregulation, compliance with nasal mucosa investigation or hypoglycaemia. There was an association between increased HbA1c level and intranasal insulin (8.1% versus 7.8%, p<0.01). However, no difference was seen in the number of hypoglycaemia episodes.

6.1.4.9 Indwelling catheters

An RCT investigated the use of indwelling catheters as injection aids at the onset of diabetes in children and young people (n=41).[264] [evidence level Ib] Pain was lower for the group treated with indwelling catheters than insulin pens (median 0.8 cm versus 1.5 cm, p=0.006). Sixteen out of 20 chose to continue using indwelling catheters after the study ended, and 9 out of the 20 were still using indwelling catheters after 6 months.

6.1.5 Recommendations

The current recommendations can be found at http://www.nice.org.uk/guidance/ng18

6.1.6 Research recommendations

4. **[2004] Research is needed to compare the effectiveness of continuous subcutaneous insulin infusion (or insulin pump therapy) and multiple daily injection regimens in children and young people with type 1 diabetes.**

5. **[2004] Research is needed to evaluate the effectiveness of long-acting insulin analogues in children and young people with type 1 diabetes.**

6. **[2004] Further research is required to evaluate the effectiveness of insulin delivery systems in children and young people with type 1 diabetes.**

7. **[2004] Research is needed to compare the effectiveness of insulin delivery modes (for example, dermal, nasal, oral and pulmonary) in children and young people with type 1 diabetes.**

6.2 Natural history of type 1 diabetes

Although considerably decreased, significant endogenous insulin production is often present at diagnosis of type 1 diabetes. For many patients this endogenous insulin production is a major factor in the occurrence of a 'partial remission phase' or 'honeymoon period'.

The partial remission phase has been defined as a period when an insulin dosage of less than 0.5 units/kg body weight/day results in an HbA1clevel of less than 7%,39 or when an insulin dosage of less than 0.3 units/kg body weight/day results in an HbA1c level of less than 6%.[40] [evidence level III]

There is a wide variation in the prevalence of a partial remission phase in children and young people with type 1 diabetes. An observational study found that 80% of children and young people with newly diagnosed type 1 diabetes experienced a partial remission phase that lasted at least 3 months.[39] [evidence level III] A second study found that 65% of children and young people experienced a partial remission phase.[41] [evidence level III] However, a consensus guideline suggested that 30 to 60% of children and young people experience a partial remission phase.[15] [evidence level IV]

6.2.1 Factors determining the length of the partial remission phase

Two observational studies found no association between the sex of children and young people and the presence or duration of a partial remission phase.[39,40] [evidence level III] However, a third observational study found that males with type 1 diabetes were more likely to experience a partial remission phase than females (occurrence of remission: 73% in males versus 53% in females, RR 1.38, 95% CI 1.08 to 1.76; duration of remission: 279 ±22 days in males versus 210 ±25 days in females, $p<0.01$).[41] [evidence level III]

Four observational studies found that younger children were less likely than older children to experience a remission phase, and that younger children had shorter remission phases than older children. One study compared children diagnosed before the age of 5 years to those diagnosed after the age of 5 years (remission phase of at least 3 months: 50% under 5 years versus 90% over 5 years, $p<0.0005$; average duration of remission phase: 7.3 ±8.4 months versus 13.1 ±8.6 months, $p<0.05$).39 [evidence level III] A second study found that a remission phase occurred in 0%, 16%, 5% and 23% of children aged 5 years or younger, 5.1 to 9 years, 9.1 to 12 years and over 12 years, respectively ($p=0.01$).[40] [evidence level III] The same study found that residual C-peptide secretion was significantly reduced during the first year of disease in children with disease onset before the age of 5 years ($p<0.001$).[40] [evidence level III] Another study found that the age of onset of type 1 diabetes was greater

in children who experienced a partial remission phase than in other children (7.6 ±0.4 years versus 6.3 ±0.5 years, p<0.05).[41] [evidence level III]

6.2.2 Insulin treatment during the partial remission phase

We found no studies relating to the optimisation of insulin treatment during the partial remission phase. However, 1 study evaluated guidance aimed at reducing insulin dosage in response to self-monitoring of blood glucose levels in young people with newly diagnosed type 1 diabetes who presented with ketosis.[42] [evidence level III] This study showed that, on average, the insulin dosage was reduced from 62 units/day to 33 units/day while maintaining preprandial blood glucose levels of 4 to 7 mmol/l.[42] [evidence level III].

6.2.3 Insulin regimens for prolonging the partial remission phase

We found 2 RCTs that compared the effectiveness of continuous subcutaneous insulin infusion (CSII), or 'insulin pump therapy', with once-/twice-daily insulin injection therapy in children and young people with newly diagnosed type 1 diabetes. One study in which the children and young people were followed up for 2 years found CSII was associated with lower HbA1clevels from 2 months after diagnosis, but that it did not prolong endogenous insulin production (n=30).[43,44] [evidence level Ib] An earlier RCT in young people aged 13 to 19 years found no difference in HbA1c levels 1 year after the start of CSII compared with once-/twice-daily insulin injection therapy (n=14).[45] [evidence level Ib]

We found 1 RCT that compared the effectiveness of continuous venous insulin infusion for the first 28 to 62 days of treatment with once-daily subcutaneous insulin injections in young people with newly-diagnosed type 1 diabetes. During the intervention period continuous venous insulin infusion was associated with lower HbA1clevels (10.9 ±0.6% versus 14.6 ±0.7%, p<0.005), and lower fasting plasma glucose levels and urinary glucose excretion, but after the intervention period finished there was no difference in HbA1c (n=14).[46] [evidence level Ib]

We found 1 non-randomised intervention study that compared the effectiveness of a closed loop insulin delivery system (artificial pancreas) for around 5 days with CSII in young people with newly diagnosed type 1 diabetes 3 to 5 days after diagnosis. The closed loop insulin delivery system was associated with a higher proportion of patients who had a remission period (18/23 versus 3/10). There were no differences in duration of remission period or mean basal or postprandial blood glucose levels (n=33).[47] [evidence level IIa]

6.2.4 Immunotherapy for prolonging the partial remission phase

The use of immunotherapy in type 1 diabetes has been investigated over the past 20 years. We found studies that investigated 8 different therapies.

6.2.4.1 Cyclosporin

The effectiveness of cyclosporin compared with placebo was investigated in 2 RCTs. One RCT investigated cyclosporin in combination with insulin therapy compared with a placebo with insulin therapy in patients with type 1 diabetes between the ages of 10 and 35 years.[48] [evidence level Ib] The study found cyclosporin treatment to be associated with insulin-free remission at 6 and 12 months (38.7% versus 19.1%, p<0.001, n=54 at 6 months; 24.2% versus 9.8%, p<0.002, n=31 at 12 months). A follow-up to the study using matched pairs of patients found that at 6 months after discontinuation of the treatment HbA1cwas higher in the cyclosporin-treated group than the placebo group. However, at 15 months after discontinuation of the treatment there was no difference between the cyclosporin-treated group and the placebo group.[49] [evidence level IIa]

A second RCT compared cyclosporin plus insulin therapy with placebo plus insulin therapy in patients aged 15 to 40 years with type 1 diabetes (n=122).[50] [evidence level Ib] Cyclosporin treatment was associated with insulin-free remission at 9 months (24.1% versus 5.8%, p<0.01) but not at 6 months (25.4% versus 18.6%).

A non-randomised intervention study investigated the effectiveness of 2 different doses of cyclosporin in children and young people (n=28).[51] [evidence level IIa] There was no difference between the average HbA1clevels in the groups of children and young people with different doses of cyclosporin. High-dose cyclosporin (target trough plasma levels of 200 ng/ml) was associated with a higher number of children and young people in insulin-free remission at 6 months compared with low-dose cyclosporin (target trough plasma levels of 100 mg/ml) (3/6 versus 5/14). A cohort study investigated the effectiveness of cyclosporin in children and young people, including some of the children and young people from the above non-randomised intervention study (n=83 treated with cyclosporin, n=47 not treated with cyclosporin).[52] [evidence level IIa] Children and young people treated with cyclosporin had lower HbA1c levels than those not treated with cyclosporin (HbA1c approximately 1 to 1.5% lower in cyclosporin-treated children during the first 4 years of follow-up) and a lower frequency of hypoglycaemia/patient (0.03 ±0.03 versus 0.23 ±0.09, p<0.05).

6.2.4.2 Nicotinamide

A meta-analysis[53] of 7 RCTs [54–59] investigated the effectiveness of nicotinamide compared with placebo in children, young people and adults with type 1 diabetes (n<211, exact number not reported). There was no difference in HbA1clevels between patients treated with nicotinamide and placebo (standardised difference 0.08% at 6 months, approximate 95% CI −0.67 to 0.83%). [evidence level Ia]

The effectiveness of nicotinamide compared with placebo was investigated in 1 RCT in young adults (n=21, mean age 23 years in the nicotinamide group versus 26 years in the placebo group).[60] [evidence level Ib] There were no differences in HbA1clevels at 6, 12 or 24 months (5.7 ±0.5% versus 5.4 ±0.9% at 6 months; 6.0 ±0.6% versus 5.8 ±0.9% at 12 months; 6.6 ±0.9% versus 6.0 ±0.4% at 24 months). In both groups, similar numbers of patients experienced an insulin-free remission or partial remission (2/11 versus 3/9 in insulin-free remission and 4/11 versus 4/10 in partial remission at 6 months; 3/11 versus 3/9 in partial remission at 12 months; 1/11 versus 1/9 in partial remission at 2 years).

A controlled study (unknown if randomised) investigated the effectiveness of nicotinamide compared with placebo in children, young people and young adults (n=16, age range 10 to 35 years).[61] [evidence level IIa] Nicotinamide was associated with an increase in patients experiencing an insulin-free remission (5/7 versus 2/9 at 6 months; 3/7 versus 0/9 at 1 year) and a decrease in HbA1clevels (7%, SE 0.46% versus 7.7%, SE 0.7% at 6 months; 6.4%, SE 0.6% versus 8.6%, SE 0.5% at 1 year).

6.2.4.3 Nicotinamide and cyclosporin

The effectiveness of cyclosporin and nicotinamide combined compared with nicotinamide alone and a control group was investigated in children, young people and young adults in an RCT (n=90, age range 7 to 40 years).[62] [evidence level Ib] There was no difference in the total number who experienced a remission period by 1 year (7/30 versus 5/30 versus 2/30). However, at 3 months the cyclosporin and nicotinamide combination was associated with an increased number of clinical remissions (6/30 versus 1/30 versus 0/30, p=0.05) and nicotinamide alone was associated with a longer duration of clinical remission than was the cyclosporin plus nicotinamide and control (7 ±3 months, p<0.02).

6.2.4.4 Methylprednisolone

The effectiveness of methylprednisolone has been investigated in 2 studies. One controlled study without randomisation investigated children and young people treated with intravenous methylprednisolone pulse therapy in combination with multiple subcutaneous insulin injections compared with a control group receiving only multiple subcutaneous insulin injections (n=31).[63] [evidence level IIa] At 12 months, methylprednisolone treatment was associated with an increase in the number of children and young people having had a remission period (4/16 versus 1/11 with complete remission where no insulin required; 9/16 versus 1/11 with partial remission involving 50% reduction in insulin dosage, p<0.01), an increase in the duration of remission (6.6 ±4.6 months versus 3.1 ±2.3 months, p<0.01), and a decrease in HbA1clevels (9.2 ±3.6% versus 10.5 ±1.9%, p<0.01). A controlled study without randomisation in children, young people and adults investigated oral methylprednisolone with insulin therapy compared with insulin therapy alone (n=25).[64] [evidence level IIa] All patients in the study underwent a remission period. Oral methylprednisolone was associated with an increased duration of remission (p<0.001), although there were no differences in HbA1c levels. The study discussed several adverse effects that may be associated with oral methylprednisolone.

6.2.4.5 Prednisone

One RCT has investigated the effectiveness of prednisone in adults (n=25).[65] [evidence level Ib] Prednisone was associated with an increase in partial remission compared with placebo (6/9 versus 2/10). Adverse events (facies lunaris and epigastralgia) were reported.

6.2.4.6 Indometacin

One RCT has investigated the effectiveness of indometacin in adults (the same RCT as above, n=25).[66] [evidence level Ib] No association was seen between indometacin and partial remission compared with placebo (1/4 versus 2/10). An adverse event (headache) was reported.

6.2.4.7 Theophylline

One RCT has investigated the effectiveness of theophylline in adults (the same RCT as above, n=10).[66] [evidence level Ib] Theophylline was associated with an increase in partial remission compared with placebo (4/5 versus 2/4).

6.2.4.8 Thymopentin

One RCT has investigated the effectiveness of thymopentin in young people and young adults (n=48, age range 12 to 31 years).[67] [evidence level Ib] Thymopentin was associated with an increase in partial remission compared with control (7/16 versus 3/30 at 6 months; 9/16 versus 2/30 at 1 year; p range ≤0.05 to 0.01). There were no differences in HbA1clevels (8.8 ±0.4% versus 8.7 ±0.3% at 1 month; 6.2 ±0.2% versus 6.5 ±0.1% at 6 months; 6.4 ±0.4% versus 7.5 ±0.5% at 1 year).

6.2.4.9 Interferon

One RCT has investigated the effectiveness of interferon in young people and young adults with type 1 diabetes (n=16, age range 15–25 years).[68] [evidence level Ib] No difference was seen in the number of patients experiencing a remission phase at 1 year (6/20 versus 12/23), nor in HbA1clevels (8.9 ±0.3% versus 9.1 ±0.4% at 1 month; 8.1 ±0.5% versus 7.9 ±0.5% at 6 months; 8.6 ±0.6% versus 9.7 ±0.7% at 12 months; 9.8 ±0.6%, n=9 versus 9.5 ±0.7%, n=9 at 30 to 36 months).

6.2.4.10 Methotrexate

One RCT has investigated the effectiveness of methotrexate in children and young people (n=10).[69] [evidence level Ib] No difference was seen in the number of patients experiencing a remission phase at 18 months (1/5 versus 3/5). Adverse effects were investigated and found to be minimal.

6.2.4.11 Azathioprine

One RCT has investigated the effectiveness of azathioprine in children and young people (n=49).[70] [evidence level Ib] No difference was seen in the number of patients experiencing a remission phase (7/24 versus 10/25 at 6 months; 4/24 versus 4/25 at 1 year), nor in HbA1clevels (7.2 ±0.4% versus 6.6 ±0.2% at 6 months; 7.7 ±0.3% versus 7.1 ±0.3% at 12 months). Adverse effects were investigated and no difference was found in the number of infections between the 2 groups. However, there was a greater number of skin lesions reported in the azathioprine-treated children and young people.

Healthcare professionals may find it useful to refer to the recommendations in Section 5 (education) when offering information about the natural history of type 1 diabetes.

6.2.5 Recommendations

The current recommendations can be found at https://www.nice.org.uk/guidance/ng18

6.3 Oral drug treatment for type 1 diabetes

Many patients with type 1 diabetes are unable to achieve stable blood glucose levels despite receiving intensive insulin therapy. In these patients, increasing the insulin dose to achieve a target postprandial blood glucose concentration carries a risk of hypoglycaemia several hours after a meal.[265]

Oral antidiabetic drugs are used for patients with type 2 diabetes. Several studies have evaluated the use of oral antidiabetic drugs combined with insulin for the treatment of patients with type 1 diabetes.

There are several types of oral antidiabetic drugs: acarbose (an inhibitor of intestinal alpha glucosidases), sulphonylureas, biguanides, prandial insulin-releasing agents, and thiazolidinediones.

6.3.1 Acarbose

Acarbose acts by inhibiting the enzymes responsible for the breakdown of complex carbohydrates in the gut, thereby prolonging digestion, reducing the rate at which glucose is absorbed into the blood stream and attenuating the postprandial rise in blood glucose concentration.266 Acarbose can reduce postprandial hyperglycaemia in patients with type 1 diabetes, although it has been little used for this purpose. Increased flatulence deters some from using acarbose, although this adverse effect tends to decrease with time. Acarbose is not recommended for use in children under 12 years.[133,134]

Nine RCTs[265–273] [evidence level Ib] (including 7 crossover trials) have investigated the use of acarbose in patients with type 1 diabetes. None of the RCTs involved children or young people.

HbA1cwas recorded in 3 of the RCTs.267,[268,270] [evidence level Ib] Two RCTs reported statistically significant reductions in HbA1c of 0.48% (n=264)[267] and 1.1% (n=14)[270] [evidence level Ib] with acarbose compared with placebo. The third RCT found no significant change in HbA1c (n=123).[268] [evidence level Ib]

Glucose levels were recorded in 8 of the RCTs. Glucose levels were significantly lower with acarbose compared with placebo in 7 of the RCTs,[267–273] but there was no significant difference in the remaining study (n=15).[266] [evidence level Ib]

Hypoglycaemic episodes were recorded in 8 RCTs. Four RCTs reported that hypoglycaemic episodes occurred almost twice as frequently with acarbose as with placebo.[266,269–271] [evidence level Ib] One study reported more frequent episodes of hypoglycaemia with placebo, but this was a very small crossover trial (n=7) with high rates of hypoglycaemia.[273] [evidence level Ib] The remaining studies reported no significant differences between acarbose and placebo in the number of hypoglycaemic episodes.[267,268,272] [evidence level Ib]

Lipid control was measured in 5 of the RCTs. Three of the RCTs reported that there was no significant difference in lipid control between acarbose and placebo.[265,267,271] [evidence level Ib] Another RCT reported a reduction in high-density lipoprotein cholesterol with acarbose, although other lipids were unchanged (n=121).[268] [evidence level Ib] The fourth study reported a reduction in triglycerides in the acarbose group (n=14).[270] [evidence level Ib]

Blood pressure was measured in 2 of the RCTs, although neither RCT found a significant difference in blood pressure between acarbose and placebo treatment groups.[266,272] [evidence level Ib]

Adverse effects were reported in 7 of the RCTs. Six of these RCTs reported that there were almost twice as many adverse effects in the acarbose treatment group compared with the placebo treatment group. Most of the adverse effects involved gastrointestinal symptoms, such as flatulence, diarrhoea and abdominal pain.[266–268,270–272] [evidence level Ib]

Another RCT examined whether low- or high-fibre diets reduced adverse effects (n=123).[268] [evidence level Ib] There were no significant differences between the low- and high-fibre groups in this study.

Discontinuation of treatment was higher with acarbose than with placebo in 2 of the RCTs.[267,268] [evidence level Ib] There was no significant difference in drop-out rates between the acarbose and placebo treatment groups in another study (n=30).[271] [evidence level Ib] None of the studies examined patient acceptance or long-term complications.

6.3.2 Sulphonylureas

Sulphonylureas are used for type 2 diabetes. They act by increasing insulin secretion and are only effective when some residual pancreatic beta-cell activity is present.[133]

Ten RCTs have examined the effectiveness of the sulphonylureas (glibenclamide, gliclazide, glipizide, glyburide and tolazamide) in the treatment of patients with type 1 diabetes.

6.3.2.1 Glibenclamide

Three small crossover RCTs and 1 parallel RCT (total 57 adults) have investigated the use of glibenclamide in patients with type 1 diabetes. Four of these RCTs measured glycated haemoglobin, 3 of which found no significant difference between glibenclamide and placebo treatment groups.[274–276] [evidence level Ib] The fourth RCT found that glibenclamide reduced glycated haemoglobin levels compared with placebo in people who were C-peptide secretors (7.5 ±0.9% versus 8.1 ±0.5%, p=0.05, n=20), although no such effect was observed in non-C-peptide secretors.[277] [evidence level Ib] The sub-group of C-peptide secretors may have had maturity-onset diabetes, rather than type 1 diabetes.

Two RCTs found no significant difference in mean blood glucose level between glibenclamide and placebo treatment groups.[274,276] [evidence level Ib] Another RCT reported a significantly decreased mean daily blood glucose in C-peptide secretors using glibenclamide compared with placebo (7.4 ±1.5 mmol/l versus 8.4 ±1.7 mmol/l, p=0.02,

n=20), but not in non-C-peptide secretors.[277] [evidence level Ib] A small RCT showed that glibenclamide decreased pre- and postprandial blood glucose compared with placebo (n=10).[275] [evidence level Ib]

One RCT examined adverse effects.[277] [evidence level Ib] This study found that 1 patient suffered several serious hypoglycaemic reactions while receiving glibenclamide, but no other patient was similarly affected. No studies have investigated patient acceptance or long-term complications of glibenclamide.

6.3.2.2 Gliclazide

A small RCT (n=22) involving patients aged 12–25 years with newly diagnosed type 1 diabetes found that glycated haemoglobin and plasma glucose did not differ significantly between gliclazide and placebo treatment groups.[278] [evidence level Ib]

6.3.2.3 Glipizide

A small RCT (n=9) involving adults with type 1 diabetes found that blood glucose curves and areas under the curves did not differ between glipizide and placebo treatment groups.[279] [evidence level Ib]

6.3.2.4 Glyburide

Two RCTs with a total of 74 patients have investigated the use of glyburide in adults with type 1 diabetes. One RCT showed no sustained improvements in total glycated haemoglobin and HbA1cbetween glyburide and placebo treatment groups, although a difference was observed at 6 weeks.[280] [evidence level Ib] The second RCT showed no significant differences between glyburide and placebo in HbA1c and plasma lipids.[281] [evidence level Ib] Glucose concentrations differed significantly between the 2 treatment groups at the start of this RCT, and so glucose measurements recorded during the RCT cannot be easily interpreted.[281] [evidence level Ib]

6.3.2.5 Tolazamide

Two RCTs have investigated the use of tolazamide. In the first RCT children and young people aged 3 to 17 years with newly diagnosed type 1 diabetes were followed for 15 months. There were no significant differences in HbA1 or blood glucose between tolazamide and placebo.[282] [evidence level Ib] The second RCT followed male adults for 12 weeks, and showed that tolazamide treatment significantly reduced fasting plasma glucose and HbA1clevels compared with placebo.283 [evidence level Ib]

6.3.3 Biguanide

Metformin, the only biguanide currently available, acts by decreasing glucogenesis and by increasing the peripheral utilisation of glucose. Metformin only acts in the presence of insulin.[133]

6.3.3.1 Metformin

Three RCTs, 1 non-randomised controlled study and 3 non-controlled intervention studies have examined the effectiveness of metformin. One small RCT (n=27) involving young people showed that metformin lowered HbA1c and fasting glucose levels but increased mild hypoglycaemia compared with placebo (change in HbA1c: −0.3 ±0.7% versus 0.3 ±0.7%, p=0.03; change in fasting glucose levels: −0.9 ±3.8 mmol/l versus −0.5 ±3.2 mmol/l, p=0.04; hypoglycaemia: 1.75 ±0.8 events/patient/week versus 0.9 ±0.4 events/patient/week, p=0.03).[284] [evidence level Ib]

Another small RCT (n=26) involving young people showed that metformin lowered HbA1cand fasting glucose levels but increased mild hypoglycaemia compared with placebo (change in HbA1c, −0.9%, 95% CI −1.6 to −0.1%, p<0.05 versus 0.3%, p>0.05).[285] [evidence level Ib]

Another small RCT (n=10) involving adults attached to an artificial pancreas for a euglycaemic hyperinsulinaemic clamp showed that metformin increased the amount of glucose infused compared with placebo, but there were no significant differences in lactate, total cholesterol or triglycerides.[286] [evidence level Ib]

A non-randomised controlled study in adults showed that metformin significantly lowered plasma glucose values, but there were no significant differences in total cholesterol, high-density lipoprotein cholesterol or triglyceride levels. Transient abdominal pain and nausea were reported in the first week of metformin treatment (n=14).[287] [evidence level IIa]

One non-controlled intervention study showed that metformin decreased the diurnal glycaemic profile at 2 out of 7 time points, decreased the range of glucose levels, and improved the glycaemic control index. However, there were no differences in fasting blood glucose levels in a separate group of 5 patients (n=15, age not reported).[288] [evidence level III] Two other non-controlled intervention studies showed no significant difference in HbA1clevels with metformin treatment.[289,290] [evidence level IIb] One of these studies also showed that metformin did not change fasting glycaemia, total cholesterol, high-density lipoprotein cholesterol or triglyceride levels (n=12, age not reported).[290] [evidence level IIb]

6.3.4 Thiazolidinediones

The effectiveness of prandial insulin-releasing agents and thiazolidinediones (the glitazones pioglitazone and rosiglitazone) in children and young people with type 1 diabetes has not been evaluated.

6.3.5 Summary

The RCTs in which the effectiveness of acarbose has been investigated in adults suggest that acarbose reduces glycated haemoglobin and blood glucose concentrations. However, acarbose is associated with an increased risk of hypoglycaemia and gastrointestinal adverse effects.

The effectiveness of acarbose in children and young people has not been investigated, and acarbose is not licensed in children and young people under 12 years.

Oral antidiabetic drugs are not widely used in the UK, although there has been some interest in using metformin to treat overweight patients with type 1 diabetes. We found 1 RCT that suggested that metformin has a beneficial effect in overweight young people with type 1 diabetes. Other oral antidiabetic drugs are not beneficial in patients with type 1 diabetes.

6.3.6 Recommendations

The current recommendations can be found at https://www.nice.org.uk/guidance/ng18

6.3.7 Research recommendations

8. What is the clinical and cost effectiveness of non-insulin agents (for example, metformin) combined with insulin treatment in children and young people with type 1 diabetes?

6.4 Dietary management in type 1 diabetes

6.4.1 Introduction

This section was updated in 2015.

Dietary advice was considered in the 2004 guideline, but dietary advice based on carbohydrate counting or on glycaemic index were not addressed as specific topics. The 2015 guideline update includes specific review questions related to both of these topics (see Section 6.4.3 and Section 6.4.4, respectively). Although the 2015 guideline development group phrased their review questions in terms of 'dietetic' advice, the terminology 'dietary advice' was used in the final recommendations to mirror other NICE guidelines related to diabetes.

The 2004 guideline evidence reviews that related to dietary advice have been modified to reflect the scope of the 2015 update (that is, so that topics are not duplicated in 2004 and 2015 text) while retaining general discussion of topics related to dietary advice (see Section 6.4.2). The 2004 recommendations related to diet and the recommendations arising from the 2015 update are presented together in Section 6.4.5.

6.4.2 Dietary advice in general

Nutritional management in children and young people with type 1 diabetes aims to establish eating habits that optimise glycaemic control. The choice of food should provide sufficient energy and nutrients for optimal growth and development, as well as reducing risk factors for future cardiovascular disease. Consideration of cultural, ethnic and family traditions should be taken into account. Dietary modification in specific circumstances such as illness and exercise may also be required.

There is limited evidence concerning the optimal type of dietary therapy and the nutritional requirements of children and young people with diabetes.[9,420] [evidence level IV] However, there is a consensus that children and young people with diabetes have the same basic nutritional requirements as other children and young people for the promotion of good health.[15,421] [evidence level IV] Where there is an absence of evidence relating to children or young people, studies involving young adults are presented below.

There are no published dietary guidelines for children and young people with type 1 diabetes in the UK. Guidelines previously produced for adults with type 1 diabetes by the British Diabetic Association (now Diabetes UK),[422,423] [evidence level IV] the International Society for Pediatric and Adolescent Diabetes,[15] [evidence level IV] and the American Diabetes Association[424] [evidence level IV] recommend that the total daily energy intake should be distributed as follows:

- carbohydrates >50% (encourage high fibre carbohydrate)
- protein 10 to 15% (decreasing with age from 2 g/kg body weight/day in early infancy to 1 g/kg body weight/day in older children and young people)
- fat 30 to 35% (less than 10% saturated fat, less than 10% polyunsaturated fat, and more than 10% mono-unsaturated fat).

In addition, the Department of Health (now through the Food Standards Agency) recommends the consumption of 5 portions of fruit and vegetables per day.[425] [evidence level IV]

Neonates, infants and pre-school children will require individualised dietary assessment to determine their energy needs.

A 1998 survey of consultant paediatricians who provide care for children and young people with diabetes aged under 16 years in the UK found that 86% of clinics regularly had dietitians in attendance, 76% of these being paediatric dietitians.[18] [evidence level III]

Two studies surveyed the energy intake of children with type 1 diabetes. One study found that total energy intake was different for children with type 1 diabetes compared with children without diabetes (boys: mean 6536 kJ, SD 846 kJ versus mean 6933 kJ, SD 1243 kJ, $p<0.05$; girls: mean 5815 kJ, SD 720 kJ versus mean 6414 kJ, SD 925 kJ, $p<0.01$). The composition of energy intake was different for children with type 1 diabetes compared with children without diabetes (protein: 19% versus 15%, $p<0.01$; carbohydrates: 53% versus 50%, $p<0.05$; fat: 28% versus 35%, $p<0.001$; sucrose: 3% versus 16%, $p<0.001$).[426] [evidence level III] A second study found the mean intake of protein and cholesterol in children under the age of 10 years to be approximately the same as current recommendations, although the saturated fat intake exceeded current recommendations, and the fibre intake was lower than the recommended level; 10 to 40% of the sample had inadequate intakes of vitamin D, vitamin E and zinc.[427] [evidence level III]

We found 1 RCT (n=23, age range 14 to 21 years) that investigated the effect of increasing the mono-unsaturated fat intake of young people with type 1 diabetes. The study showed a significant increase of 6.8% in mono-unsaturated fatty acid intake in young people taking a high mono-unsaturated fat diet for 12 weeks as compared with baseline. There was no difference in mono-unsaturated fatty acid intake in the control group and there were no significant differences between the 2 treatment groups in terms of changes from baseline to end of study for total plasma cholesterol, low-density lipoprotein cholesterol, triglycerides, HbA1c, blood pressure, body weight, or insulin dosage. No statistical comparison was made between the treatment groups, and adherence to diet was poor.[428] [evidence level Ib–IIb]

We found 1 relevant RCT on the effect of protein intake on renal function in people with type 1 diabetes. This crossover RCT (n=16, age range 15 to 23 years) found a significant decrease in glomerular filtration rate with a low protein diet (10% of total energy intake) versus the usual protein diet (20% of total energy intake). The effect was more pronounced in hyperfiltrating patients.[429] [evidence level Ib]

We found no studies that looked at changes in the amount of fibre in the diet of children and young people.

We found 4 studies that investigated the effect of sucrose on glycaemia response in the diet of children and young people with type 1 diabetes. The first study, a crossover RCT (n=10, age range 7 to 12 years), found no significant differences between a sucrose-free diet and a sucrose-containing diet in terms of blood glucose levels (total area under the glucose response curve 204 ±13 mmol/l/hour) or urinary glucose levels (35.6 ±7.5 g/day versus 34.5 ±7.5 g/day).[430] [evidence level Ib]

The second study investigating sucrose was a parallel group RCT (n=10, age range 7 to 16 years). The study found no significant differences in terms of the rise in blood glucose levels among children and young people with type 1 diabetes who ate breakfast consisting of oatmeal alone, oatmeal with sucrose, oatmeal with protein, or oatmeal with sucrose and protein.[431] [evidence level Ib]

The third study investigating sucrose intake was a parallel group RCT (n=9, age range 11 to 16 years). The study found significantly lower glycaemic responses between a 17% sucrose diet and a 2% sucrose diet over a 4-hour study period (area under the curve 37 ±3.5 mmol/l versus 42 ±4.7 mmol/l).[432] [evidence level Ib]

The fourth study investigating sucrose intake was a quasi-randomised controlled trial (n=28, age range 8 to 26 years). The study found no significant difference between a 5% sucrose diet and a sucrose-free diet for up to 127 days in HbA1clevels (9.1% versus 9.0%) in children and young people with type 1 diabetes.[433] [evidence level IIa]

An observational study investigated children's and young people's adherence to dietary advice (n=69). The study found that, on average, 24% of the children's and young people's food choices deviated from their prescribed meal plans. Children and young people consumed greater total energy than the prescribed level (inpatient: actual 9718 ±2583 kJ versus prescribed 8897 ±2282 kJ, p=0.0001; outpatient: actual 9835 ±2617 kJ versus prescribed 8277 ±1712 kJ, p=0.005), less protein energy content than prescribed (inpatient: actual 19 ±2% versus prescribed 21 ±2%, p=0.0001; outpatient: actual 15 ±5% versus prescribed 20 ±3%, p=0.0001) and more fat energy than prescribed (inpatient: actual 39 ±6% versus prescribed 34 ±3%, p=0.0001; outpatient: actual 39 ±4% versus prescribed 33 ±4%, p=0.0001).[436] [evidence level III]

Several short-term studies have evaluated the effects of nutritional composition and timing of snacks on glycaemic control. Evidence suggests that a bedtime snack reduces the risk of nocturnal hypoglycaemia. One study showed that omitting morning and afternoon snacks had no significant effect on blood glucose.

The first RCT (n=16, age range 16 to 39 years) found that ingestion of sucrose (7%) added to snacks versus control (sucrose-free 1%) for 5 days did not affect short-term blood glucose control (8.8 mmol/l versus 7.4 mmol/l).[437] [evidence level Ib]

A second RCT (n=51, age range 14 to 22 years) found that the ingestion of an evening snack containing cornstarch versus a standard snack significantly reduced the incidence of hypoglycaemic events at midnight (6/218 versus 30/222, p<0.001) and at 7 a.m. (9/218 versus 212/222, p<0.05).[438] [evidence level Ib]

A third RCT (n=14, age range 2 to 6 years) showed cornstarch supplementation versus placebo at bedtime for 5 nights significantly reduced the percentage of nights with hypoglycaemia (7.1% versus 22.9%).[439] [evidence level Ib]

A fourth RCT (n=18, age range 6 to 17 years) found that morning or afternoon snacks (approx 554–606 kJ) versus no snacks for 4 days did not significantly affect mean glucose levels.[440] [evidence level Ib]

A fifth RCT (n=8, age range 11 to 14 years) showed no significant difference in mean increase in blood glucose level after ingestion of fruit such as apple or banana when compared with pure glucose.[441] [evidence level Ib]

A crossover RCT in children and young people with type 1 diabetes (n=29, age range 3 to 16 years) showed that a 10 g carbohydrate supplement at bedtime significantly reduced the incidence of nocturnal hypoglycaemia (<3.0 mmol/l: 2/10 versus 10/11) when compared with an early evening snack but no carbohydrate at bedtime.[442] [evidence level Ib]

Historically, diets for people with type 1 diabetes were often monotonous and restrictive, especially for children and young people.[443] [evidence level IV] The advent of foods labelled suitable for people with diabetes in the 1970s resulted in high levels of consumption.[444] [evidence level IV] However, these foods were not suitable because they were generally high in fat and carbohydrate. In 1992 this led the British Diabetic Association (now Diabetes UK) to recommend that confectionery and biscuits labelled as suitable for people with diabetes were unnecessary and should be discouraged.[15,421] [evidence level IV]

Artificial sweeteners are used in a range of products by people with diabetes, for example, no-added-sugar drinks. The Food Standards Agency regulates the quantity of sweeteners added to these foods in line with government food safety regulations.[445]

Training in flexible, intensive insulin management to improve dietary freedom has not been evaluated in children and young people with type 1 diabetes.

Religious or cultural fasting and/or feasting can affect glycaemic control. Although children and young people, and people with illness, are normally exempt from religious fasting, it is recognised that some children and young people will fast.[446] [evidence level III]

Healthcare professionals may find it useful to refer to the recommendations in Section 5 (education) when offering information about diet.

6.4.3 Dietary advice based on carbohydrate counting

This section was updated in 2015.

6.4.3.1 Review question

What is the effectiveness of dietetic advice based on carbohydrate counting in maintaining glycaemic control in children and young people with type 1 diabetes?

6.4.3.2 Introduction

The objective of this review question is to determine whether dietary advice using carbohydrate counting is effective in children and young people with type 1 diabetes. The term carbohydrate counting is taken here to mean the calculation of ratios of insulin to carbohydrate as used with multiple daily injection regimens or continuous subcutaneous insulin infusion (CSII; insulin pump therapy); that is, level 3 carbohydrate counting in the American Dietetic Association classification.

The American Dietetic Association classifies approaches to carbohydrate counting using the following 3 levels (see Gillespie 1998 and Rabasa-Lhoret 1999).

- Level 1 – consistent carbohydrate intake. At this level the principle that carbohydrate is the food component that raises blood glucose is introduced and a consistent intake of carbohydrate is encouraged based on prespecified amounts of food.
- Level 2 – pattern management principles. At this level regular consumption of carbohydrate continues, the principle of using a consistent baseline insulin dosage is introduced and the person with diabetes is encouraged to monitor blood glucose levels frequently. Blood glucose patterns in response to intake of carbohydrate (and other food) and changes that occur with administration of insulin and exercise are explained. People learn to adjust insulin dosages or to alter their carbohydrate intake or patterns of exercise to achieve specific blood glucose targets.
- Level 3 – insulin:carbohydrate ratios. This level is appropriate for people using multiple daily injection regimens or insulin pump therapy. It involves calculating insulin:carbohydrate ratios that are individualised according to age, sex, pubertal status, duration of diabetes, time of day and activity. Pre-meal insulin is adjusted according to estimated carbohydrate content of meals and snacks using the specified insulin:carbohydrate ratios.

The comparator of interest for this review question was generic dietary advice that did not take account of level 3 carbohydrate counting.

The outcomes prioritised for inclusion in the review were:

- HbA1c (minimum follow-up 6 months)
- severe hypoglycaemic episodes
- postprandial hyperglycaemia (for example glucose excursions or larger area under the glucose concentration curve)
- adherence to diabetes management (including self-management)
- changes in body mass index (BMI) standard deviation score (SDS)
- health-related quality of life

- satisfaction of children, young people and families with the intervention.

6.4.3.3 Description of included studies

Two RCTs were identified for inclusion for this review question (Enander 2012; Goksen 2014).

The first study (Enander 2012) involved 45 children and young people with type 1 diabetes (age range 5.0 to 19.5 years) using continuous subcutaneous insulin infusion (insulin pump therapy) who had not previously practiced carbohydrate counting. The study compared a single session of dietary advice based on carbohydrate counting with usual dietary education. All participants also received supporting literature to reinforce the advice.

At baseline, the mean haemoglobin A1c (HbA1c) and standard deviation (SD) was 7.6±0.9%, the mean duration of illness was 8.0±3.8 years and the mean body mass index-standard deviation score (BMI-SDS) was 0.93±1.1 kg/m^2. Five children and young people dropped out of the study and their data were not used.

Of the priority outcomes defined by the guideline development group, only mean HbA1c, BMI-SDS and the number of severe hypoglycaemic episodes were reported in this study. The other priority outcomes – postprandial hyperglycaemia (for example glucose excursions or larger area under the glucose concentration curve), adherence to treatment, health-related quality of life and satisfaction of children, young people and families with treatment – were not reported.

The second study (Goksen 2014) involved 110 children and young people with type 1 diabetes (age range 7.0 to 18.0 years) using the traditional exchange-based meal plan and using glargine/detemir basal–bolus insulin regimens (fixed doses of insulin for food and changing the doses based on blood glucose levels). The study compared a 2-week carbohydrate counting programme by a diabetologist, dietitian and nurse with nutritional and diabetes education as usual. All participants were followed up at 3-monthly intervals and training or education was repeated as required.

At baseline, the mean haemoglobin A1c (HbA1c) was 8.10±1.00% in the carbohydrate counting group and 8.43±1.52% in the control group. The mean duration of illness was 8.08±3.91 years in the carbohydrate counting group and 8.97±4.42 years in the control group. The mean BMI-SDS was −0.23±1.11 kg/m^2 in the carbohydrate counting group and 0.15±1.24 in the control group. Three participants from the carbohydrate counting group did not attend follow-up visits regularly or could not acquire adequate carbohydrate counting skills after training and were excluded. In the control group, 5 participants withdrew consent and 18 participants did not attend the 3-month follow-up visits regularly and were excluded.

Of the priority outcomes defined by the guideline development group, only mean HbA1c and BMI-SDS were reported in this study. The other priority outcomes – postprandial hyperglycaemia, adherence to treatment, health-related quality of life and satisfactions of children, young people and families with treatment – were not reported.

6.4.3.4 Evidence profile

The evidence profile for this review question (dietary advice based on carbohydrate counting) is presented in Table 29.

Table 29: Evidence profile for effectiveness of dietary advice based on carbohydrate counting in maintaining glycaemic control in children and young people with type 1 diabetes

Number of studies	Number of children and young people		Effect		Quality
	Carbohydrate counting	Treatment as usual	Relative (95% confidence interval)	Absolute (95% confidence interval)	
HbA1c value (%) at 12 months					
2 (Enander 2012; Goksen 2014)	78	46	NA	WMD 0.38 lower (0.77 lower to 0.01 higher)	Moderate
HbA1c value (%) at 24 months					
1 (Goksen 2014)	52	32	NA	MD 0.89 lower (1.61 to 0.17 lower)	Moderate
BMI-SDS at 12 months					
2 (Enander 2012; Goksen 2014)	78	46	NA	WMD 0.28 lower (0.68 lower to 012 higher)	Moderate
BMI-SDS at 24 months					
1 (Goksen 2014)	52	32	NA	MD 0.14 lower (0.66 lower to 0.38 higher)	Moderate
Severe hypoglycaemic episodes (over the 12-month study)					
1 (Enander 2012)	0/30 (0%)	0/15 (0%)	NA[a]	MD 0.00 (NC)	Moderate

BMI-SDS body mass index standard deviation score, HbA1c glycated haemoglobin, MD mean difference, NA not applicable, NC not calculable, WMD weighted mean difference
a. Unknown as no events reported in either treatment group

6.4.3.5 Evidence statements

Two studies (total 124 participants) showed little change in HbA1c with the use of dietary advice using carbohydrate counting for 12 months. The quality of the evidence was moderate.

One study (total 84 participants) showed little change in HbA1c with the use of dietary advice using carbohydrate counting for 24 months. The quality of the evidence was moderate.

Two studies (total 124 participants) showed little change in BMI-SDS with the use of dietary advice using carbohydrate counting. The quality of the evidence was moderate.

One study (total 84 participants) showed little change in BMI-SDS with the use of dietary advice using carbohydrate counting. The quality of the evidence was moderate.

One study (total 45 participants) examined the incidence of severe hypoglycaemic episodes over 12 months but no episodes were reported. The quality of the evidence was moderate.

No evidence was identified for outcomes related to changes in postprandial hyperglycaemia (for example glucose excursions or larger area under the glucose concentration curve), adherence to treatment, health-related quality of life or satisfaction of children, young people and families with treatment.

6.4.3.6 Health economics profile

A systematic literature search did not identify any relevant economic evaluations addressing dietary advice based on carbohydrate counting in maintaining glycaemic control in children and young people with type 1 diabetes.

Although this review question was prioritised initially for health economic analysis, it was not expected that recommendations would lead to change in current practice. Carbohydrate counting can be seen as an adjunct to a regimen of multiple daily injections but the studies included in the guideline review did not provide evidence related to carbohydrate counting and multiple daily injections as a combined package of care.

6.4.3.7 Evidence to recommendations

6.4.3.7.1 Relative value placed on the outcomes considered

The guideline development group prioritised the same outcomes for this review as for the review on dietary advice based on glycaemic index for children and young people with type 1 diabetes.

The group agreed that HbA1c value was the highest priority outcome for both review questions because, in their view, if the use of a particular dietary regimen resulted in a reduction in HbA1c by near to or greater than 0.5 percentage points (or 5.5 mmol/mol) then this would represent an important clinical benefit to a child or young person with type 1 diabetes. This decision was underpinned by the group's knowledge of research in adults with type 1 diabetes (The Diabetes Control and Complications Trial Research Group 1993), which showed that a 1 percentage point decease in HbA1c halved the risk of diabetes-related complications, including retinopathy and nephropathy. The guideline development group considered that this result could be meaningfully extrapolated to cover the population of children and young people with type 1 diabetes of relevance in this question.

The group considered that severe hypoglycaemic episodes and postprandial hyperglycaemia were important outcomes for consideration in determining the effectiveness of dietary advice based on either carbohydrate counting or glycaemic index. It was assumed that with good glycaemic control, adherence to dietary advice would be more likely, and vice versa.

The group also prioritised BMI-SDS, adherence to treatment, health-related quality of life and satisfaction of children, young people and families with treatment as important outcomes.

6.4.3.7.2 Consideration of clinical benefits and harms

While the studies identified for inclusion did not show improvements in HbA1c at 12 or 24 months that met the predefined threshold for a minimally important difference (MID) of 0.5 percentage points, or even a statistically significant improvement in HbA1c with dietary advice based on carbohydrate counting, there was a trend towards improvement with a mean difference of 0.3 percentage points. Although this did not achieve the MID identified by the guideline development group before conducting the evidence review, the trend towards an improvement in HbA1c was consistent with the group's expectations. There were strong physiological and clinical reasons to support offering level 3 carbohydrate counting for children and young people using multiple daily injections or CSII (insulin pump therapy).

Based on the clinical experience of guideline development group members and the fact that dietary advice based on carbohydrate counting combined with multiple daily injections more closely resembles normal physiological processes than diet and insulin regimens based on prescribed eating patterns, it seemed possible that its use would have benefits. This decision was underpinned by the group's clinical consensus that a variation in carbohydrate intake of as little as 10 g could result in a measurable difference in blood glucose when using a fixed dose of insulin.

No evidence was identified for consideration by the guideline development group in relation to changes in postprandial hyperglycaemia (for example glucose excursions or larger area under the glucose concentration curve).

One of the studies identified for inclusion considered the incidence of severe hypoglycaemia, but in this study no such episodes were reported in either treatment group and this provided

some reassurance that the use of carbohydrate counting is not associated with hypoglycaemia as an adverse event.

The group decided a priori that no change in BMI-SDS would represent a clinical benefit. Neither study showed a statistically significant alteration in BMI-SDS with the use of dietary advice based on carbohydrate counting.

Although no evidence was found for the adherence to treatment outcome, it was considered that with good glycaemic control adherence to dietary advice might be more likely. It was also agreed that benefits in terms of adherence to treatment, health-related quality of life and the satisfaction of children, young people and families with treatment could reasonably be expected even in the absence of evidence to this effect because this type of dietary management allows children and young people more flexibility and control over what they eat, and this, in the group's experience, is very important.

The guideline development group recognised that for some children and young people carbohydrate counting could prove difficult but they concluded that the risks from failure to perform carbohydrate counting correctly were not significant and that not providing the advice also presented a risk.

In light of all these considerations the group concluded that advice based on carbohydrate counting was likely to be a useful element of dietary advice.

6.4.3.7.3 Consideration of health benefits and resource use

The guideline development group considered that resources needed to deliver dietary advice based on carbohydrate counting were justified given its unproven but likely potential to improve glycaemic control. It was agreed that dietary advice based on carbohydrate counting as an adjunct to multiple daily injection therapy contributed to better self-care and independent diabetes management in the long run (especially if the advice was delivered from diagnosis) and this also contributed to the group's assessment that this intervention represents a cost-effective use of resources. The group also noted that dietary advice based on carbohydrate counting was already established in UK clinical practice and therefore that recommending it would not result in an uplift in resources.

6.4.3.7.4 Quality of evidence

The group noted that the evidence was limited to 2 studies, which together provided evidence on only 3 of the 7 outcomes prioritised by the guideline development group. The group attributed the lack of evidence to the fact that carbohydrate counting is already well established in clinical practice and therefore it is difficult to obtain funding for trials in this area.

The quality of the evidence was rated as moderate for all outcomes on the grounds of imprecision but the group considered that the studies had generally been well controlled and that the only significant variation between the treatment groups had been the intervention of interest. They therefore felt confident about attributing the benefits identified to the use of dietary advice based on carbohydrate counting. The group noted that the 'usual care' delivered to the participants in the control group in one of the included studies was quite comprehensive (comparable to level 2 dietary advice described above) and all participants were using continuous subcutaneous insulin infusion (insulin pump therapy) which is, in itself, associated with good glycaemic control (see Section 6.1.2.5 on insulin pump therapy). The group felt that both factors might mean that the effects shown in the study probably underestimated the usefulness of dietary advice based on carbohydrate counting in the context of insulin regimens based on multiple daily injections.

6.4.3.7.5 Other considerations

The guideline development group noted that the clinical outcomes used to measure the effectiveness of dietary advice based on carbohydrate counting would always be influenced by all other aspects of diabetes care, such as the type of insulin therapy and the frequency and type of blood glucose monitoring.

It was noted that children and young people and their parents or carers may feel more reassured about the safety of multiple daily injection regimens if they understand the relationship between carbohydrate and insulin intake.

6.4.3.7.6 Key conclusions

The guideline development group recommended that level 3 carbohydrate-counting education should be offered from diagnosis to children and young people with type 1 diabetes who are using multiple daily injections or insulin pump therapy, and to their family members or carers (as appropriate). The group also recommended that the education be repeated at intervals following diagnosis. The group clarified in the recommendations that level 3 carbohydrate counting means carbohydrate counting with adjustment of insulin dosage according to an insulin:carbohydrate ratio.

The group recommended that children and young people with type 1 diabetes who are changing their insulin regimen and their family members or carers (as appropriate) should be offered dietary advice tailored to the new treatment.

6.4.4 Dietary advice based on glycaemic index for type 1 diabetes

6.4.4.1 Review question:

What is the effectiveness of dietetic advice based on glycaemic index in maintaining glycaemic control in children and young people with type 1 diabetes?

6.4.4.2 Introduction

The objective of this review question is to determine whether dietary advice based on glycaemic index is effective in children and young people with type 1 diabetes in terms of maintaining glycaemic control. The guideline development group noted that knowledge about foods with a low glycaemic index and those with a high glycaemic index could be relevant for the update. The review was limited to RCTs and systematic reviews of RCTs, but no systematic reviews were identified. The comparator of interest was dietary advice (including carbohydrate counting) that did not take account of glycaemic index.

The outcomes prioritised for inclusion in the review were:

- HbA1c (minimum follow-up 6 months)
- severe hypoglycaemic episodes
- postprandial hyperglycaemia (for example glucose excursions or larger area under the glucose concentration curve)
- adherence to diabetes management (including self-management)
- changes in body mass index (BMI) standard deviation score (SDS)
- health-related quality of life
- satisfaction of children, young people and families satisfaction with the intervention.

6.4.4.3 Description of included studies

Two RCTs were identified for inclusion for this review question (Collier 1988; Gilberston 2001).

The first study (Collier 1988) included 7 children and young people with type 1 diabetes (mean age 12±2 years): this used a cross-over design to assess the effect of a low glycaemic index diet compared with the participant's standard diet. Detailed dietary histories were taken and a test diet was constructed on an individual basis to resemble the participant's standard diet, but with low glycaemic index foods substituted for high glycaemic index foods. Participants were instructed on an individual basis and cooking instructions and recipes for dishes using low glycaemic index foods were supplied, along with sample menus if needed.

The only guideline development group priority outcome reported in this study was postprandial hyperglycaemia following a standard carbohydrate meal.

The second study (Gilbertson 2001) involved 104 children and young people with type 1 diabetes (mean age 10.5±1.6 years): this compared a single session of dietary advice based on glycaemic index with advice based on carbohydrate exchange. All participants also received supporting literature to reinforce the advice. At baseline, the mean haemoglobin A1c (HbA1c) was 8.4±1.3%. The study did not report either the mean body mass index (BMI) or mean fasting plasma glucose at baseline.

Of the guideline development group-defined priority outcomes, evidence was identified for postprandial hyperglycaemia (Collier 1988), mean HbA1c (Gilbertson 2001) and adherence to treatment (Gilbertson 2001). In addition, the mean number of hypoglycaemic and hyperglycaemic episodes per month (Gilbertson 2001) was considered by the group to be a proxy for the number of participants with severe hypoglycaemic episodes and postprandial hyperglycaemic episodes. Hypoglycaemia was defined as less than 3.5 mmol/litre and hyperglycaemia as more than 15 mmol/litre. The other priority outcomes – the number of participants with severe hypoglycaemic episodes, BMI-standard deviation score (BMI-SDS), health-related quality of life and satisfaction with treatment – were not reported.

6.4.4.4 Evidence profile

The evidence profiles for this review question (dietary advice based on glycaemic index) are presented in Table 30 and Table 31.

Table 30: Evidence profile for effectiveness of dietary advice based on glycaemic index in maintaining glycaemic control in children and young people with type 1 diabetes, glycaemic index diet versus standard diet

Number of studies	Number of children and young people		Effect		Quality
	Glycaemic index	Standard diet	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Postprandial hyperglycaemia change from baseline to 6 weeks					
1 (Collier 1988)	7	7	Blood glucose after standard meal reduced from baseline in low glycaemic index phase ($p<0.05$) No significant change in blood glucose after standard meal when compared with baseline in normal diet phase.		Moderate

Table 31: Evidence profile for effectiveness of dietary advice based on glycaemic index in maintaining glycaemic control in children and young people with type 1 diabetes, glycaemic index diet versus carbohydrate exchange diet

Number of studies	Number of children and young people		Effect		Quality
	Glycaemic Index	Carbohydrate exchange	Relative (95% confidence interval)	Absolute (95% confidence interval)	
HbA1c value (%) change from baseline to 12 months					
1 (Gilbert 2001)	51 (changed from 8.3 ±1.4 at baseline to 8.0 ±1.0 at 12 months)	38 (no change, was 8.6 ±1.4 at baseline and at 12 months)	NA	MD in change in values between groups 0.3 lower (0.89 lower to 0.29 higher)	Moderate
Mean number of hypoglycaemic episodes (preprandial blood glucose <3.5 mmol/litre) per month					
1 (Gilbertson 2001)	51 (6.9 ±6.8 episodes at 12 months)	38 (5.8 ±5.5 episodes at 12 months)	NA	MD 1.1 more (1.46 more to 3.66 fewer)	High
Mean number of hyperglycaemic episodes (preprandial blood glucose >15 mmol/litre) per month					
1 (Gilbertson 2001)	51 (11.2±9.8 episodes at 12 months)	38 (16.8±11.8 episodes at 12 months)	NA	MD 5.6 fewer (10.22 to 0.98 fewer)	High
Number adhering to treatment (up to 12 months)					
1 (Gilbertson 2001)	46/55 -83.60%	32/49 -65.30%	RR 1.28 (1.01 to 1.62)	183 more per 1000 (from 7 more to 405 more)	Moderate

MD mean difference, NA not applicable, RR relative risk

6.4.4.5 Evidence statements

Although no benefit in terms of HbA1c reducing by 0.5 percentage points or more was demonstrated, 1 study (total 89 participants) showed a change in HbA1c was associated with the use of dietary advice using glycaemic index. The quality of the evidence was high.

One study (total 89 participants) showed a change in the mean number of hyperglycaemic episodes (preprandial blood glucose more than 15 mmol/litre) with the use of dietary advice based on glycaemic index. The quality of the evidence was high.

One study (total 89 participants) showed no change in the number of hypoglycaemic episodes (preprandial blood glucose less than 3.5 mmol/litre) per month. The quality of the evidence was high.

One study (total 14 participants) showed a significant reduction in postprandial blood glucose level compared with baseline after a 6 week low glycaemic index diet. No reduction in postprandial blood glucose level was seen after 6 weeks of a standard diet. The quality of the evidence was moderate.

One study (total 104 participants) showed a greater proportion of participants adhering to treatment with the use of dietary advice based on glycaemic index. The quality of the evidence was moderate.

No evidence was identified for outcomes relating to changes in BMI-SDS, health-related quality of life or satisfaction with treatment.

6.4.4.6 Health economics profile

A systematic literature search did not identify any relevant economic evaluations addressing dietary advice on glycaemic index in order to maintain glycaemic control in children and young people with type 1 diabetes.

This question was not prioritised for health economic analysis as it was not expected that recommendations would lead to change in current practice.

6.4.4.7 Evidence to recommendations

6.4.4.7.1 Relative value placed on the outcomes considered

The guideline development group prioritised the same outcomes for this review as for the review on dietary advice based on carbohydrate counting for children and young people with type 1 diabetes.

The group agreed that HbA1c value was the highest priority outcome for this question because, in their view, if the use of dietary advice based on glycaemic index resulted in a reduction in HbA1c by near to or greater than 0.5 percentage points (or 5.5 mmol/mol) then this would represent an important clinical benefit to a child or young person with type 1 diabetes. This decision was underpinned by the group's knowledge of research in adults with type 1 diabetes (The Diabetes Control and Complications Trial Research Group 1993) which showed that a 1 percentage point decease in HbA1c halved the risk of diabetes-related complications. The guideline development group considered that this result could be meaningfully extrapolated to cover the population of children and young people with type 1 diabetes of relevance in this question.

The group considered that severe hypoglycaemic episodes and postprandial hyperglycaemia were important outcomes for consideration in determining the effectiveness of dietary advice based on glycaemic index. With good glycaemic control adherence to dietary advice would be more likely.

The group prioritised BMI-SDS, adherence to treatment, health-related quality of life and satisfaction of children, young people and families with treatment as important outcomes.

6.4.4.7.2 Consideration of clinical benefits and harms

One identified study compared dietary advice based on glycaemic index with an alternative dietary strategy using carbohydrate exchange. While this was a comparison of 2 alternative dietary strategies, it did suggest benefit from dietary advice based on glycaemic index in terms of a significant reduction in hyperglycaemic episodes. It did not show a significant alteration in HbA1c, nor did it show a difference between the groups in severe hypoglycaemic episodes. The guideline development group noted that in this trial the intensity of dietary education and support provided was less than that which is generally provided in current clinical practice in the UK.

While there was limited clinical trial evidence in children and young people, the group was aware of a Cochrane review of RCTs that provided strong evidence of improved glycaemic control in a mixed population that predominantly included adults with a diagnosis of type 2 diabetes (HbA1c decreased by 0.5 percentage points together with a reduction in hypoglycaemic episodes with a low glycaemic index diet). Based on physiological principles, the guideline development group believed that similar benefits would be expected in children and young people.

Low glycaemic food items produce a slower post-prandial rise in blood glucose and more gradual subsequent reduction. Such foods are therefore less likely to cause a sudden or marked rise in blood glucose and this can facilitate glycaemic control using effective insulin dose adjustments. The guideline development group therefore believed that dietary advice

ased on glycaemic index would be expected to improve overall glycaemic control. This would be an important benefit, given the known association between such control and avoidance of cardiovascular complications (The Diabetes Control and Complications Trial Research Group 1993). Many foods with low glycaemic index are derived from fruit and vegetables and the guideline development group believed therefore that a diet emphasising such foods could have advantageous properties in terms of 'healthy eating' and potentially a reduction in cardiovascular risk.

On the other hand, the group recognised the possibility that a diet based on low glycaemic index foods could also potentially be an unhealthy one. Some low glycaemic index foods are high in fat. Pizza, for example, has a low glycaemic index because its high fat content delays gastric emptying. A diet containing large amounts of foods high in fat, particularly saturated fats, may be associated with increased cardiovascular risks. Such foods are also high in energy concentration and increase the risk of excessive weight gain. The study included in this review did not report BMI-SDS as an outcome. Nevertheless, the guideline development group considered that excessive weight gain would be an important potential adverse effect with low glycaemic diets. The group considered that these risks could be avoided if dietary advice based on low glycaemic index was provided within the context of information on the need to maintain a balanced diet and avoiding excessive fat intake.

6.4.4.7.3 Consideration of health benefits and resource use

The guideline development group considered that resources needed to deliver dietary advice based on glycaemic index were justified by the evidence of its beneficial effect in reducing hyperglycaemic episodes and their consensus view was that such a reduction would lead to long-term health benefits too. They also noted that dietary advice based on glycaemic index was already established in UK clinical practice and, therefore, that recommending it would not result in an associated uplift in resources.

6.4.4.7.4 Quality of evidence

The guideline development group noted that the evidence was limited to 2 studies, one of which evaluated effectiveness of a less intensive form of dietary education and support than is generally provided in current clinical practice in the UK, although this study reported 4 of the 7 outcomes prioritised by the group. The quality of the evidence for 2 of the 4 outcomes (HbA1c and adherence to treatment) was downgraded to moderate on the grounds of imprecision. Participants in the control arm of the trial received education on a dietary programme based on carbohydrate exchanges while the experimental arm received education based on a flexible, low glycaemic index regimen. The study did not, therefore, compare the effectiveness of a low glycaemic index regimen in groups who otherwise received similar dietary advice. The standard use of carbohydrate counting with most insulin regimens means that glycaemic index advice is usually used in addition to carbohydrate counting in clinical practice. That said, the guideline development group considered that the trial had generally been well controlled and that it was clear that the only significant variation between the groups had been the intervention of interest and so they felt confident about attributing the benefits identified to the use of dietary advice based on glycaemic index. The group noted that the participants in the study were receiving twice-daily insulin injections and that this did not reflect best practice in the UK but they concluded that because some children and young people do still use twice-daily insulin injection regimens, this was not of significant concern overall.

6.4.4.7.5 Other considerations

The guideline development group noted that any change in diet would require insulin use to be reconsidered carefully and adjusted accordingly.

6.4.4.7.6 Key conclusions

In light of the considerations summarised above the guideline development group concluded that dietary advice based on glycaemic index should be recommended as an important element in the management of type 1 diabetes in children and young people.

The group recommended that children and young people with type 1 diabetes and their family members or carers (as appropriate) should be supported to develop a good working knowledge of nutrition and how it affects their diabetes. The group also recommended explaining regularly how healthy eating (including eating foods with a low glycaemic index, fruit and vegetables, and appropriate types and amounts of fats) can reduce the risk of cardiovascular disease, and supporting children and young people with type 1 diabetes to adjust their food choices accordingly.

The guideline development group recommended discussing with children and young people with type 1 diabetes and their family members or carers (as appropriate) the nutritional composition and timing of snacks, and encouraging children and young people with type 1 diabetes to eat at least 5 portions of fruit and vegetables each day. Other recommendations reflecting the guideline development group's considerations summarised above were to explain to children and young people with type 1 diabetes and their family members or carers (as appropriate) that a low glycaemic index diet may help to improve blood glucose control and reduce the risk of hyperglycaemic episodes, and to offer advice and education to promote a low glycaemic index diet.

6.4.5 Recommendations

The current recommendations can be found at http://www.nice.org.uk/guidance/ng18

6.4.6 Research recommendations

9. What is the impact of educating children and young people with type 1 diabetes and their family members or carers (as appropriate) about their glycaemic index from diagnosis?

6.5 Exercise

Exercise should be encouraged in all young people with type 1 diabetes. In general, the advantages of exercise relate more to protective cardiovascular effects and psychological wellbeing than to improvements in glycaemia control.

There are limited numbers of studies investigating exercise in children and young people with type 1 diabetes. Most observations are extrapolated from studies involving adults.

Clinical experience demonstrates that exercise in children and young people with type 1 diabetes can lead to metabolic disturbances occasionally leading to hyperglycaemia and ketosis or, more frequently, to hypoglycaemia. Exercise-induced hypoglycaemia is caused by the fall in blood glucose concentration which accompanies exercise. This is due to imbalances between plasma insulin levels and available plasma glucose. Additionally carbohydrate intake may be inadequate. In most people exercise-induced hypoglycaemia is readily recognised and treated with carbohydrate remedies (see Section 6.5). Of concern is nocturnal hypoglycaemia following increased exercise, which may develop more insidiously.

Understanding the glycaemic response to different types of exercise, and changes in insulin and dietary management, is essential for optimal blood glucose control and prevention of exercise-induced hypoglycaemia.

6.5.1 Short-term effects of exercise

We found no RCTs or systematic reviews that addressed diet during exercise in children and young people with type 1 diabetes. A small case–control study involving 7 young people with type 1 diabetes found that reducing insulin dose by 50 to 66% in anticipation of postprandial exercise of moderate intensity resulted in near-normal glycaemic values and prevented hypoglycaemia.[447] [evidence level III] This study also suggested that intake of 25 to 30 g of glucose in the case of unplanned postprandial exercise of 45 minutes' duration may prevent hypoglycaemia.[447] [evidence level III]

We found no studies that specifically addressed the relationship between choice of injection site and exercise performance in children and young people with type 1 diabetes. However, a case–control study based on adults examined absorption of insulin injected subcutaneously into the leg, arm or abdomen 1 hour before an intermittent leg exercise test (n=11).[448] [evidence level III] This study reported that leg exercise accelerated insulin absorption from the leg, but not from the arm or abdomen, implying that injection of insulin into the arm or abdomen may reduce the risk of exercise-induced hypoglycaemia. This study also reported that fasting blood glucose levels were unchanged on control and exercise days, regardless of the site of injection.

We found no studies that addressed the effect of exercising with raised ketone levels in children and young people. A study in adults showed that exercising at the time of high blood glucose in the presence of positive ketonuria may precipitate further hyperglycaemia and ketosis.[449] [evidence level IIa]

Clinical experience from children's diabetes camps recognises that there is increased risk of hypoglycaemia during water sports and at times of cold and exhaustion.

6.5.2 Long-term training

Several studies show that training alters insulin action with increased glucose sensitivity and individuals who alter their exercise regimens will require adjustment of insulin and dietary regimens.

A small RCT in children with type 1 diabetes (n=19) showed an improvement in overall glycaemic control (HbA1) with regular sustained exercise compared with 30 minutes' vigorous exercise 3 times/week for 12 weeks (11.3 ±0.5% versus 13.3 ±0.5%, $p<0.05$). In addition, fasting blood glucose levels were reduced in the exercising group compared with the control group (mean difference −5.7 mmol/l, 95% CI −10.3 to 1.1 mmol/l). There was no significant change in the volume of oxygen consumption, as measured by peak VO2max.[450] [evidence level Ib]

A second RCT with 32 children and young people looked at the effect of a once-a-week training programme for 3 months. There was no change in glycated haemoglobin level, urine glucose, or the volume of oxygen consumption as measured by peak VO2max.[451] [evidence level Ib]

Neither of the above RCTs reported hypoglycaemic events in relation to exercise.[450,451] [evidence level Ib]

We performed a meta-analysis to combine the results of the 2 RCTs and found no difference in the volume of oxygen consumption as measured by peak VO2max for children and young people who received an exercise intervention (WMD 1.90%, 95% CI −1.14 to 5.20%). The results of the meta-analysis are also presented as a forest plot in Appendix J:.1.2.

We found no RCTs or systematic reviews that specifically addressed the issue of frequency, duration or type of exercise in children and young people with type 1 diabetes, or the ideal time for children and young people with type 1 diabetes to exercise.

The absorption of insulin from different sites during exercise has been studied, but no effect on blood glucose has been reported.[448] [evidence level III]

There is a substantial literature on the benefits of exercise in terms of the prevention of macrovascular disease in the general population.[452] [evidence level II] We found no studies that showed that having type 1 diabetes alters this benefit.

Healthcare professionals may find it useful to refer to the recommendations in Section 5 (education) when offering information about exercise.

6.5.3 Recommendations

The current recommendations can be found at https://www.nice.org.uk/guidance/ng18

Management of type 1 diabetes – targets for and monitoring of glycaemic control

6.6 Introduction

This section was updated in 2015.

The evidence reviews in the 2004 guideline related to monitoring glycaemic control in children and young people with type 1 diabetes covered:

- clinical monitoring of blood glucose (including monitoring of glycated haemoglobin via HbA1c)
- self-monitoring of blood glucose (including urine or blood monitoring)
- glycaemic targets relevant to age
- frequency and timing of measuring glycaemic parameters
- methods for self-monitoring of blood glucose (including continuous glucose monitoring systems [CGMS]).

The 2015 update scope covered HbA1c targets and the following aspects of glucose monitoring strategies:

- blood glucose targets
- frequency of capillary blood glucose testing (sometimes referred to as finger-prick testing)
- comparative effectiveness of capillary blood glucose testing and continuous glucose monitoring
- comparative effectiveness of continuous glucose monitoring performed intermittently and continuous glucose monitoring performed in real time.

The evidence identified in relation to the 2015 update review question about HbA1c targets and the guideline development group's interpretation of the evidence are presented in Section 6.7.9. The 2004 guideline evidence reviews that related to clinical monitoring of blood glucose other than in terms of specifying the target for HbA1c (including the comparative effectiveness of clinical monitoring and self-monitoring of blood glucose) have been retained in Section 6.7.1 to Section 6.7.8.

The evidence identified in relation to the 2015 update review question about blood glucose targets and the guideline development group's interpretation of the evidence are presented in Section 6.8.3. The evidence identified in relation to the 2015 update review question about the frequency of capillary blood glucose testing and the guideline development group's interpretation of the evidence are presented in Section 6.9.4. The 2004 guideline evidence reviews that related to self-monitoring of blood glucose and the frequency and timing of measuring glycaemic control other than in terms of targets for blood glucose and the frequency of capillary blood glucose testing have been retained in Section 6.8.1, Section 6.8.2 and Section 6.9.1 to Section 6.9.3.

The evidence identified in relation to the 2015 update review questions about continuous blood glucose monitoring and the guideline development group's interpretation of the evidence are presented in Section 6.10.10 and Section 6.10.11. The 2004 guideline evidence reviews that related to methods of self-monitoring blood glucose other than in terms of comparative effectiveness of capillary blood glucose testing and continuous glucose monitoring, and comparative effectiveness of continuous glucose monitoring performed intermittently and continuous glucose monitoring performed in real time, have been retained in Section 6.10.1 to Section 6.10.9.

The 2004 recommendations related to monitoring glycaemic control and the recommendations arising from the 2015 update are presented together in Section 6.11.

6.7 Clinical monitoring of blood glucose

6.7.1 Parameters for measuring glycaemic control

Good blood glycaemic control is 1 of the main treatment objectives in diabetes. Several different parameters can be used as indicators of glycaemic control: glycated haemoglobin (for example, HbA1c), glycated serum proteins (for example, fructosamine), fasting blood glucose and random plasma glucose.

6.7.2 Glycated haemoglobin

Glycated haemoglobin is formed when haemoglobin molecules bind to glucose, a process that occurs in people with or without diabetes. Higher ambient blood glucose concentrations are associated with more glycation of haemoglobin. The average lifespan of red blood cells is 90 to 120 days. Measuring the amount of glycated haemoglobin in the blood provides an indicator of the patient's average glucose level for the previous 6 to 12 weeks. Patients with diabetes have higher concentrations of glucose in their blood and thus elevated glycated haemoglobin levels. Total glycated haemoglobin is measured by affinity chromatography.[291]

A 1998 survey of consultant paediatricians who provide care for children and young people with diabetes aged under 16 years in the UK found that 88% of respondents indicated that glycated protein was measured routinely at each clinic visit, 84% using HbA1c, 4% using HbA1 and 1% using fructosamine.[18] [evidence level III]

6.7.3 HbA1c

Glycated haemoglobin occurs in several variants and can be measured using several different methods. Haemoglobin A contributes 90% of the total. Use of cation-exchange chromatography has shown that haemoglobin A can be separated into at least 3 components, HbA1a, HbA1b and HbA1c. These components have been found to be elevated in people with diabetes. Studies have found a strong relationship between HbA1c and fasting blood sugar levels over the preceding weeks in children, young people and adults with diabetes,[292,293] and in people without diabetes. HbA1c is the most frequently used measure of glycated haemoglobin in clinical practice, but some laboratories continue to use total glycated haemoglobin or HbA1 assays. HbA1c is detected by cation-exchange chromatographic and electrophoretic methods.[291]

The wide range of methods available for measuring glycated haemoglobin means that techniques that measure different species (HbA1 and HbA1c) produce results that are not comparable. Laboratories using the same methods to measure the same species can have widely different reference ranges and give varying results with patient samples. Given these problems, laboratories should, at a minimum, provide clinicians with information about the assay method used, the non-diabetic range and assay performance.[291,294]

Standardised methods for estimating glycated haemoglobin are currently being developed and should be adopted when available.[291] It has been recommended that DCCT-aligned HbA1c measurements should be used to monitor long-term glycaemic control. 'DCCT-aligned HbA1c' means traceability of the assay standardisation to United States National Glycohemoglobin Standardization Program reference standards (or to the International Federation of Clinical Chemistry standard, with adjustment to the DCCT norm) and participation in a national quality assurance scheme. The new chemical standard for HbA1c developed by the International Federation of Clinical Chemistry, which reads lower by about 2 percentage points, will be the basis of primary calibration of instruments from 2004

onwards. However, this does not preclude reporting to DCCT-aligned levels. At a meeting organised by the Department of Health in July 2003, patients' organisations and professional bodies expressed the view that reporting to DCCT-aligned levels should continue until a change of policy is agreed internationally.

It has been suggested that HbA1c is preferable to HbA1 as a parameter for assessing glycaemic control because when plotting mean blood glucose concentration against glycated haemoglobin fractions the slope is greater for HbA1c than for HbA1 and lowest for HbA1a and HbA1b. Also, HbA1a and HbA1b are positively correlated with age and negatively correlated with length of storage of blood samples; however, age and length of storage do not have such a great effect on HbA1c.[293] [evidence level III]

One study showed that HbA1c values varied markedly between different individuals, but were fairly consistent in the same individual over time, so that patients with the same blood glucose control may give glycated haemoglobin values that vary by at least 1 to 2%.[295] [evidence level III] Another study showed a marked variability among individuals, showing fluctuations of more than ±1% in 50% of patients from year to year.[296] [evidence level III] This may have implications for setting targets for individual patients to attain satisfactory glycaemic control.[291] [evidence level III]

A systematic review of blood glucose monitoring in diabetes concluded that glycated haemoglobin should be regarded as the most appropriate test of long-term glycaemia.[291] [evidence level Ia] The systematic review found that glycated haemoglobin testing was cost effective.[291] [evidence level Ia]

Indirect evidence from the DCCT85 [evidence level Ib] and the United Kingdom Prospective Diabetes Study[297] [evidence level Ib] suggested that glycated haemoglobin monitoring in patients with type 1 diabetes would be clinically and cost effective. There is no evidence of the clinical effectiveness of different testing frequencies, but 3-monthly tests in patients with type 1 diabetes may be reasonable.[291] [evidence level III]

A 1998 survey of consultant paediatricians who provide care for children and young people with diabetes aged under 16 years in the UK found that of the 84% of respondents who indicated that HbA1c was measured routinely at each clinic visit, 86% used capillary methods as opposed to venous sampling for collection of blood samples.[18] [evidence level III]

Studies have shown that haemoglobin variants and derivatives, shortened erythrocyte survival and other factors can interfere with glycated haemoglobin test results.[4] [evidence level IV]

6.7.4 Glycated serum proteins

Serum proteins also undergo a process of glycation. The turnover of human serum albumin is much shorter (half-life 25 days) than that of haemoglobin (half-life 120 days) and thus the degree of glycation of serum proteins provides a similar index of glycaemia as does haemoglobin, but over a shorter period of time.[298,299] [evidence level III] Measurements of total glycated serum protein and glycated serum albumin correlate well with one another and both have been suggested as methods for monitoring glycaemic control.[291]

6.7.5 Fructosamine

Fructosamine assay is the most widely used technique for measuring glycated serum protein.[300] Fructosamine correlates with the average blood glucose levels of the previous 2 to 3 weeks and can therefore be used to detect shorter or more recent fluctuations in blood glucose than can glycated haemoglobin. A standardised fructosamine test is available, making results from different laboratories comparable. In addition, fructosamine can be measured using instruments found in most clinical biochemistry laboratories and so results

may be obtained more rapidly and at lower cost than glycated haemoglobin.[301] [evidence level IV]

The validity of serum fructosamine is largely based on the ability of fructosamine to predict glycated haemoglobin levels. Nine cross-sectional studies compared fructosamine with HbA1cor HbA1. Early studies found a correlation between fructosamine and glycated haemoglobin (n=239).[302–304] [evidence level III] However, later studies suggested that fructosamine was not a good predictor of glycated haemoglobin (n=324).[305–307] [evidence level III] Two further studies showed poor agreement between different categories of glycaemic control (good, moderate and poor) calculated from tertiles of fructosamine and HbA1 levels (n=550).[308,309] [evidence level III] Another study showed that fructosamine levels had significantly higher intra-subject variance than HbA1c (n=172).[310] [evidence level III] Glycated serum albumin, HbA1c and fructosamine respond differently to changes in glycaemic control (n=100).[306] [evidence level III] The clinical utility of routine fructosamine and protein has not been clearly established and further studies are needed to resolve this issue.[291] [evidence level III]

6.7.6 Fasting plasma glucose and random blood glucose testing

Studies have shown that there is a significant correlation between HbA1c and fasting blood glucose in people with type 1 diabetes. Other studies have shown that fasting plasma glucose and random blood glucose measurements alone are not sufficiently accurate to provide clinical information, despite the obvious cost advantages.[291,311] [evidence level III] Fasting blood glucose and serum fructosamine measurements cannot replace HbA1c measurements, but may have a use for assessing control over short and intermediate periods of time.[291] [evidence level III]

6.7.7 Laboratory and near-patient glycated haemoglobin testing

Obtaining glycated haemoglobin results during a consultation has potential benefits for patients and clinicians. Clinicians who have immediate access to indicators of a patient's long-term control can make immediate, responsive changes to insulin therapy or diet, avoiding the need for a follow-up appointment.

Limited data are available for the effectiveness of near-patient testing. In a controlled study of patients attending a diabetes clinic, HbA1cwas measured in 2 groups, 1 through near-patient testing and 1 through routine laboratory testing. The study found that patients with poor diabetes control were more likely to have a change in their management if managed with access to near-patient testing compared with normal laboratory testing (n=599 patients of all ages with type 1 and type 2 diabetes).[312] [evidence level IIa] The study also found that the use of near-patient glycated haemoglobin testing resulted in higher costs/clinic visit. However, the annual costs were similar for conventional and near-patient testing, because patients receiving near-patient testing made fewer clinic visits. A second RCT compared immediate feedback of HbA1c with reporting HbA1c after the clinic (n=113 adults). The study showed no difference in the change in HbA1c levels between the 2 groups after 1 year.[313] [evidence level Ib] An early non-controlled study that asked patients to send blood samples before their clinic visits so that the results could be available at the clinic showed a decrease in HbA1 after 15 months in adults with type 1 and type 2 diabetes (from 10.8 ±2.3% to 10.1 ±2.2%, $p<0.05$, n=206).[314] [evidence level IIa] The use of near-patient glycated haemoglobin testing in primary care has not been adequately evaluated.[315] [evidence level III]

6.7.8 Clinical monitoring of blood glucose versus self-monitoring

A systematic review of blood glucose monitoring studies[291] did not provide evidence to support the clinical effectiveness of self-monitoring in type 1 diabetes. The results were considered to be inconclusive because the studies were generally neither well conducted nor well reported and they had low statistical power.[291] [evidence level III] The DCCT provided

evidence for the effectiveness of a package of care that included self-monitoring. Previous reviews suggested that major efforts should be undertaken to increase the use of self-monitoring of blood glucose by individuals with all types of diabetes.[83] [evidence level IV]

The systematic review identified 8 RCTs involving children, young people and adults[316–323] and 16 non-controlled studies. None of the studies was set up to test the effect of monitoring versus no monitoring. One of 8 RCTs demonstrated an effect of self-monitoring of blood glucose on blood glucose control in terms of blood glucose levels before and after self-monitoring began.[291] [evidence level Ia]

6.7.8.1 Summary

Glycated haemoglobin is the only measure of glycaemic control that has been shown to be associated with long-term complications of diabetes. The simplest and best predictor of glycaemic control is HBA1c.[15] [evidence level IV]

6.7.9 Optimal HbA1c target

This section was updated in 2015.

6.7.9.1 Review question

What is the optimal HbA1c target for children and young people with type 1 diabetes?

6.7.9.2 Introduction

The purpose of this review is to determine the optimal HbA1c target that children and young people with type 1 diabetes should aim to achieve. Targets should aim to minimise the risk of long-term complications without incurring an increased risk of hypoglycaemic episodes. The search for this question included randomised controlled trials (RCTs) and systematic reviews of RCTs as well as comparative observational studies such as cohort studies and case-control studies.

The guideline development group defined 4 priority outcomes for this review. These included both physical and psychosocial outcomes. Physical outcomes comprised glycaemic control determined by hypoglycaemic episodes (however defined) and contact with the diabetes care team as a measure of healthcare utilisation. Psychosocial outcomes comprised health-related quality of life and the satisfaction of children, young people and their families with the intervention. Comparisons were to be made between outcomes according to target values for HbA1c and/or HbA1c values achieved.

Studies included in the 2004 evidence review related to glycaemic targets relevant to age were considered for inclusion in the 2015 update review, but none of them met the inclusion criteria as they were not studies that evaluated outcomes associated with setting specific HbA1c targets (see below).

6.7.9.3 Description of included studies

No studies met the inclusion criteria for this review and no evidence table was generated. Although there was a recommendation specifying an HbA1c target for children and young people with type 1 diabetes in the 2004 guideline, it was based on guideline development group consensus in the absence of direct evidence about the optimal target to use and so no studies cited in the 2004 review were carried forward for inclusion in this review.

6.7.9.4 Evidence profile

No studies were identified for this review question and so there is no evidence profile.

6.7.9.5 Evidence statements

No evidence was identified for this review.

6.7.9.6 Health economics profile

A systematic literature search did not identify any relevant economic evaluations addressing optimal HbA1c targets for children and young people with type 1 diabetes.

This question was not prioritised for health economic analysis as a target of itself does not incur an opportunity cost, although the target may affect the choice of interventions used.

6.7.9.7 Evidence to recommendations

6.7.9.7.1 Relative value placed on the outcomes considered

The same outcomes were used as for blood glucose targets in type 1 diabetes (see Section 6.11). The guideline development group carefully balanced the psychological impact with the health benefits of reduced risk of long-term complications.

6.7.9.7.2 Consideration of clinical benefits and harms

There is no threshold of HbA1c below which long-term complications do not occur, however there is evidence that lower HbA1c leads to better long-term outcomes (this was shown through evidence included for the 2004 guideline in questions related to insulin regimens and long-term complications [The Diabetes Control and Complications Trial Research Group 1993; The DCCT/EDIC Research Group 2003]).

An HbA1c threshold of 6.5% (DCCT units) was developed jointly with the developers of the guidance for type 1 diabetes in adults because although older studies indicated an association between lower HbA1c values and an increased risk of severe hypoglycaemia, this relationship is less clear with modern management strategies. As described in Section 0, DCCT units (percentages) were used by the guideline development group in their consideration of evidence related to HbA1c for this guideline (to allow inclusion of historical evidence) but the group was aware that current practice is to use International Federation of Clinical Chemistry (IFCC) units (mmol/mol) and the group preferred to specify HbA1c levels in recommendations using these units. The equivalent DCCT units were presented alongside IFCC units in the recommendations to guide people who remain more familiar with DCCT units. Using this approach, the HbA1c target value recommended by the guideline development group is 48 mmol/mol, which equates to the target of 6.5% in DCCT units).

The guideline development group for this update was aware of the considerations of the guideline development group for the guideline on type 1 diabetes in adults and noted some differences in the approach to be taken for children and young people with type 1 diabetes (compared with adults). Specifically:

- Considerations about making exceptions regarding the HbA1c target because of the person's 'occupation' were felt not to be relevant for the majority of children and young people with type 1 diabetes (the majority of them will not have a job).
- The guideline development group preferred the term 'life goals' to 'aspirations' whereas the latter was used in the recommendations for adults with type 1 diabetes.
- Considerations about 'vascular' complications were felt not to be relevant for children and young people with type 1 diabetes.
- The guideline development group felt it was important to emphasise the possibility of distress arising from strict HbA1c targets and they added a new consideration regarding potential for conflict between the child or young person with type 1 diabetes and their family with regard to HbA1c targets, noting that an important distinction between diabetes care for a child or young person and that for an adult is the need in the former case to

work with the individual with diabetes and their parents and other family members or carers (as appropriate). The guideline development group further recognised the importance of agreement between the parties involved in decision-making and that a compromise between the preferences of the child or young person and their parents, families or carers (as appropriate) may be necessary.

The guideline development group noted that aligning recommended targets for HbA1c for children, young people and adults with type 1 diabetes would assist with transition from paediatric to adult services.

Finally, the group noted that very young children have a reduced awareness of hypoglycaemia and a reduced capability to manage hypoglycaemia and that this provides an example of why individualised targets may be required.

6.7.9.7.3 Consideration of health benefits and resource use

The guideline development group noted that a study was excluded from the guideline review (Swift 2010) because no relevant outcomes were reported. This study addressed whether setting tighter targets for HbA1c levels was associated with achievement of lower HbA1c levels, rather than the impact of a tighter HbA1c target on adverse outcomes. The study demonstrated that those healthcare professionals who aim for tighter glycaemic control achieve tighter glycaemic control in the children and young people they care for. The study also highlighted the importance of the entire diabetes team sharing the same targets consistently; lower team targets are associated with better glycaemic control.

Achieving a target may have opportunity costs both in terms of the interventions and actions required to improve glycaemic control and in terms of health outcomes associated with a particular level of HbA1c. However, although tight targets could potentially lead to increased hypoglycaemia, there are also likely to be reductions in long-term diabetes complications arising from tighter glycaemic control.

6.7.9.7.4 Quality of evidence

No evidence was identified for inclusion for this review question, but the guideline development group did not prioritise this area for future research because the members agreed that consensus among the group and joint decision-making with the developers of the guideline on type 1 diabetes in adults would lead to practicable recommendations.

6.7.9.7.5 Other considerations

The guideline development group noted that the principle of agreeing individualised targets for HbA1c would allow the child or young person and their parents, families or carers (as appropriate) to reflect individualised needs.

The guideline development group was aware of the considerations that had resulted in the 2004 recommendation related to the HbA1c target for children and young people with type 1 diabetes. In particular, the 2004 guideline had noted that the optimal level of glycaemic control for children and young people with type 1 diabetes was an area of considerable discussion, with a need to balance the long-term benefits of low blood glucose reducing risks of long-term complications with the short-term risk of hypoglycaemia. The 2004 guideline emphasised the long-term effects of hypoglycaemia on cognitive function (see Section 7.3). The overall conclusion of the 2004 guideline with regard to HbA1c was that lower HbA1c levels had been shown to be associated with fewer and delayed microvascular complications in young people aged over 13 years.[91]

The views expressed by stakeholders commenting on the draft guideline for consultation were divergent, with healthcare professionals being more likely to favour tighter targets for HbA1c and stakeholders representing children and young people with type 1 diabetes and their family members or carers tending to consider tighter targets as setting them up to fail. The guideline development group considered all of the comments very carefully and sought

to achieve a balance by specifying an overall target of 48 mmol/mol (6.5%) for those in whom it is achievable (as this is based on evidence), while at the same time providing reassurance for children and young people and their families or carers that targets should be individualised to take account of personal circumstances. This is reflected in the order in which the recommendations are presented, with the explanation of the benefits of safely achieving and maintaining the lowest attainable HbA1c preceding the recommendation about the ideal HbA1c target level being 48 mmol/mol (6.5%) or lower to minimise the risk of long-term complications. The phrasing of the guideline recommendations in general was also chosen so as to avoid using judgemental terms such as 'good' and 'poor' blood glucose control (in these specific cases the terms 'optimal' and 'suboptimal' are used instead).

Although the guideline development group agreed that the HbA1c target for children and young people with type 1 diabetes should be set at 48 mmol/mol (6.5%) they recognised that this might not be achieved in every case. In accordance with recommendations in the guideline on type 1 diabetes in adults, the group made an additional recommendation that diabetes services should document the proportion of children and young people with type 1 diabetes who achieve an HbA1c level of 53 mmol/mol (7%) or lower.

6.7.9.7.6 Key conclusions

The recommended target HbA1c level of 48 mmol/mol (6.5%) represents a tightening of glycaemic control compared with the 2004 guideline (which recommended that children and young people with type 1 diabetes and their families should be informed that the target for long-term glycaemic control was an HbA1c level of less than 7.5% without frequent disabling hypoglycaemia and that their care package should be designed to attempt to achieve this). The guideline development group emphasised that the result of the change would be to reduce the risk of long-term complications of type 1 diabetes in a population that will have a long duration of diabetes because the condition starts before adulthood.

6.8 Self-monitoring of blood glucose

6.8.1 Urine or blood home glucose testing

A meta-analysis of 4 RCTs (3 in children and young people and 1 in adults) showed a significant difference in glycated haemoglobin between blood glucose monitoring and urine glucose monitoring (WMD −0.567%, 95% CI −1.073 to −0.061%, n=162), suggesting that blood glucose testing lowers glycated haemoglobin compared with urine testing; however, with different assumptions the difference between blood and urine testing became non-significant.[291,316,318,321,323] [evidence level Ia]

Three studies in the systematic review [318,319,322] involving children, young people and adults found no difference in the number of hypoglycaemic episodes between blood and urine monitoring[291] [evidence level Ia] However, a further pseudo-randomised controlled trial that was not included in the systematic review reported a significant decrease in HbA1c following training in blood glucose testing compared with urine glucose testing (n=43).[321] [evidence level IIa]

The systematic review concluded from 2 studies that children, young people and adults prefer blood monitoring or a combination of blood and urine testing to urine testing alone; however, these conclusions are limited.[291] [evidence level III]

6.8.2 Reliability and validity of self-monitoring

Portable monitors may show significant differences from reference methods and the magnitude of these differences may vary between different models of monitor, between different devices of the same model and according to blood glucose levels. These differences may often be of little clinical relevance, but may sometimes be important,

particularly at low blood glucose values. However, analytical errors may often be small in comparison with observer errors.[291] [evidence level III]

The development of memory monitors has shown that patients with diabetes often make incomplete or incorrect recordings of blood glucose values in their diary records. A continuous monitor with a memory, or further training in blood glucose testing, may aid patients who make recording errors. General visual impairment and impairment of colour vision can also cause a problem with visually read strips.[291] [evidence level III]

Severe haemolysis in blood samples may affect readings from some monitors and the use of small sample volumes can lead to erroneously low readings with most models of monitor. Other technological influences and clinical conditions (for example, low temperature) may sometimes affect results.[291] [evidence level IV]

The findings suggest that there is a need for formal training and updating of skills in the use of monitors so that accurate results may be obtained.[291] [evidence level IV]

6.8.3 Optimal blood glucose targets

This section was updated in 2015.

6.8.3.1 Review question

What are the optimal blood glucose targets for children and young people with type 1 diabetes?

6.8.3.2 Introduction

The objective of this review question is to determine the optimal blood glucose target range in terms of minimising the HbA1c level without incurring hypoglycaemia as an adverse effect. The 2004 recommendation stated that children and young people with type 1 diabetes and their families should be informed that the optimal targets for short-term glycaemic control are a pre-prandial blood glucose level of 4 to 8 mmol/litre and a post-prandial blood glucose level of less than 10 mmol/litre.

The outcomes prioritised for inclusion in the review were:

- glycaemic control
- severe hypoglycaemic episodes (frequency)
- nocturnal hypoglycaemic episodes (frequency)
- any hypoglycaemic episode (however defined; frequency)
- contact with the diabetes care team as a measure of healthcare utilisation
- health-related quality of life
- satisfaction of children, young people and families with the intervention.

Studies included in the 2004 evidence review related to glycaemic targets relevant to age were considered for inclusion in the 2015 update review, but none of them met the inclusion criteria as they were not studies that evaluated outcomes associated with setting specific blood glucose targets (see below).

6.8.3.3 Description of included studies

No studies met the inclusion criteria for this review and no evidence table was generated. Although there was a recommendation specifying preprandial and postprandial blood glucose targets for children and young people with type 1 diabetes in the 2004 guideline, it was based on guideline development group consensus in the absence of direct evidence

about the optimal targets to use and so no studies cited in the 2004 review were carried forward for inclusion in this review.

6.8.3.4 Evidence profile

No studies were identified for this review question and so there is no evidence profile.

6.8.3.5 Evidence statements

No evidence was identified for inclusion in this review.

6.8.3.6 Health economics profile

A systematic literature search did not identify any relevant economic evaluations addressing optimal blood glucose targets for children and young people with type 1 diabetes.

This question was not prioritised for health economic analysis as a target of itself does not incur an opportunity cost, although the target may affect the choice of interventions used.

6.8.3.7 Evidence to recommendations

6.8.3.7.1 Relative value placed on the outcomes considered

The guideline development group agreed that HbA1c value was the highest priority outcome for this question because, in their view, if specific blood glucose targets resulted in a reduction in HbA1c by near to or greater than 0.5 percentage points (or 5.5 mmol/mol) then this would represent an important clinical benefit to a child or young person with type 1 diabetes. This decision was underpinned by the group's knowledge of research in adults with type 1 diabetes (The Diabetes Control and Complications Trial Research Group 1993) which showed that a 1 percentage point decease in HbA1c halved the risk of diabetes-related complications.

The group also prioritised outcomes related to the incidence of glycaemic control-related adverse events as they were aware that these were potential harms associated with different targets as well as proxy indicators for poor HbA1c.

The group prioritised contact with the diabetes team as a measure of healthcare utilisation and 2 psychosocial outcomes (health-related quality of life and satisfaction of children, young people and families with treatment) because they noted that trying to meet specific targets can be a source of anxiety or stress for some children and young people, as well as testing itself being potentially uncomfortable or difficult.

6.8.3.7.2 Consideration of clinical benefits and harms

In the absence of evidence, the guideline development group consensus was that tighter blood glucose control than recommended in the 2004 guideline would be beneficial. There was a shared feeling within the group that it was beneficial to established tight control as early as possible (preferably from diagnosis) and so the group felt that lower targets were particularly beneficial for children and young people with type 1 diabetes.

6.8.3.7.3 Consideration of health benefits and resource use

It was noted that a target of itself does not incur an opportunity cost although the target may affect the choice of intervention. The guideline development group felt that if a lower target contributed to tighter glycaemic control then the cost of any interventions used to achieve the target would be outweighed by savings gained from long-term health benefits.

6.8.3.7.4 Quality of evidence

No evidence was identified for inclusion in the 2015 update review. The guideline development group noted that the evidence included in the 2004 guideline was of poor quality.

6.8.3.7.5 Other considerations

The guideline development group noted the importance of setting targets that the child or young person could live with and that if the targets set were too narrow then they would become difficult to comply with.

In general, the group wished to encourage consistency between targets for children and young people with type 1 diabetes and those for adults with type 1 diabetes to encourage adherence in people of all ages. Although no new evidence based on studies involving children and young people was identified for inclusion in the 2015 update, the group agreed that it was generally important to update the guidance for children and young people to be consistent with the guidance for adults. In certain circumstances, however, the targets should be slightly different, specifically with regard to the target range for fasting blood glucose. The adult guidance took account of the likelihood that people with type 1 diabetes who are older than 18 years will usually wish to drive motor vehicles, whereas the over-riding concern for children and young people with type 1 diabetes is to achieve tight control since they are likely to have many years' duration of diabetes after diagnosis, increasing their risk of developing long-term complications. Thus a lower limit of 5 mmol/litre for the target range is appropriate for adults, while a lower limit of 4 mmol/litre is appropriate for most children and young people. The group recognised, however, that young people aged 16 years or older might wish to drive motor vehicles and therefore the minimum target level for young people should be 5 mmol/litre when driving.

The group also noted that during periods of fasting and in the presence of co-existing conditions, certain psychosocial factors and lifestyle choices targets might become more difficult to achieve and that the diabetes team would need to consider this as part of individualised care.

6.8.3.7.6 Key conclusions

The guideline development group recommended the following target ranges to optimise short-term blood glucose (or, more correctly, plasma glucose) control:

- a fasting level of 4 to 7 mmol/litre on waking and
- a level of 4 to 7 mmol/litre before meals at other times of the day
- a level of 5 to 9 mmol/litre after meals
- a level of at least 5 mmol/litre when driving.

The recommendations emphasised the importance of explaining the rationale for the targets, including the link between blood glucose and HbA1c targets.

6.9 Frequency and timing of measuring glycaemic parameters

6.9.1 Frequency of glycated haemoglobin testing

A systematic review looked at the optimal frequency of glycated haemoglobin testing, but concluded that the optimal frequency had not been established.[291] [evidence level Ia] Given the relatively slow change in glycated haemoglobin accompanying changes in plasma glucose, 1 study recommended that no more than 4 to 6 glycated haemoglobin assays should be performed each year for patients with type 1 diabetes.[328] The American Diabetes Association recommended that glycated haemoglobin measurements should be performed in

accordance with clinical judgements. American Diabetes Association consensus opinion recommended glycated haemoglobin testing at least twice/year in patients with stable glycaemic control who are meeting treatment goals. Testing should be more frequent (quarterly) in patients whose therapy has changed or who are not meeting glycaemic control targets.[329] [evidence level III]

We found no further evidence on the recommended frequency of monitoring HbA1c.

6.9.2 Frequency of glycated serum protein testing

A systematic review discussed the issue of optimal frequency of glycated serum protein through fructosamine testing, but no optimum frequency was established.[291] [evidence level Ia] The American Diabetes Association stated that glycated serum protein should not be considered equivalent to measurement of HbA1c because it only indicates glycaemic control over a short period of time. Therefore, glycated serum protein assays would have to be performed on a monthly basis to gather the same information as 3 or 4 measurements of HbA1c/year.[329] [evidence level III] The systematic review noted that patients could improve their fructosamine values by increasing adherence to insulin therapy 1 or 2 weeks before the test and that caution should be taken in the interpretation of glycated serum protein measurements unless performed frequently.[291]

We found no further evidence on the recommended frequency of monitoring fructosamine.

6.9.3 Timing of testing glycaemic control parameters

We found no evidence relating to the timing of glycated haemoglobin testing or self-monitoring of blood glucose. Blood glucose varies at different times of the day because blood glucose levels are affected by a variety of factors including the time since the last meal, the content of meals and exercise. Preprandial blood glucose monitoring is recommended in patients who alter their insulin dose according to their blood glucose level because this is when the bolus insulin dose is given.

Summary

There is no evidence on the clinical effectiveness of different frequencies or times for glycated haemoglobin testing. Optimal glycaemic control can only be assessed and maintained by frequent and accurate monitoring.

6.9.4 Frequency of capillary blood glucose testing

This section was updated in 2015.

6.9.4.1 Review question

How frequently should finger-prick blood glucose testing be performed in children and young people with type 1 diabetes?

6.9.4.2 Introduction

Capillary blood glucose monitoring (finger-prick testing) is usual practice for people with type 1 diabetes. The objective of this review question is to identify the optimal frequency of capillary blood glucose monitoring (at any site on the body) in children and young people with type 1 diabetes. The question is designed to reveal which frequency (or range of frequencies) of capillary blood glucose monitoring is associated with optimal glycaemic control and thus a reduced risk of long-term complications.

The review protocol for this question incorporated 2 distinct components to the evidence review. The first of these was restricted to RCTs that compared capillary blood glucose monitoring up to 4 times per day with capillary blood glucose monitoring at least 5 times per day. The second component focused on the association between frequency of capillary blood glucose monitoring per day and glycaemic control.

The outcomes prioritised for inclusion in the review were:

- glycaemic control
  - HbA1c (minimum follow-up 6 months)
  - severe hypoglycaemic episodes
  - nocturnal hypoglycaemic episodes
  - diabetic ketoacidosis (DKA; number of episodes)
- adherence to diabetes management (including self-management)
- health-related quality of life
- satisfaction of children, young people and families with the intervention (including the impact of pain associated with capillary blood glucose testing).

6.9.4.3 Description of included studies

No RCTs met the inclusion criteria for the first component of the evidence review (comparison of capillary blood glucose monitoring up to 4 times per day with capillary blood glucose monitoring at least 5 times per day).

Thirteen observational studies met the inclusion criteria for the second component of the evidence review (association between frequency of capillary blood glucose monitoring and glycaemic control) (de Beaufort 2013; Campbell 2014; Dorchy 1997; Haller 2004; Helgeson 2011; Ingerski 2011; Levine 2001; McGrady 2009; Miller 2013; Moreland 2004; Nordly 2005; Svensson 2009; Ziegler 2011).

The sample size in the included studies ranged from 132 to 26,723 children and young people. Where mean age was reported it ranged from 8±2.0 years to 15.7±1.4 years and where the age range was reported it varied from 0–15 years to 0–18 years. Between 46.7% and 56% of the study populations were female and the gender of the children or young people was not reported in 2 studies.

The mean and standard deviation (SD) of the frequency of capillary blood glucose monitoring ranged from 4.0±1.8 times per day to 4.83±1.45 times per day in 5 studies. The frequency of capillary blood glucose monitoring ranged from:

- 0 to 10 or more times per day in 2 included articles based on the same study (Campbell 2014; Miller 2013)
- 0 to 8 times in 1 study
- 2.5 to 8.3 times per day across 18 paediatric centres in 1 study
- 2 to 5 or more times per day in 2 studies.

One study reported the frequency per week as a median of 23 with 10th and 90th percentiles of 8 and 37, respectively. Another study did not report the frequency of capillary blood glucose monitoring in the study population.

The mean HbA1c ranged from 6.6±1.2% to 9.0±1.8% and was not reported in 3 studies. The mean duration of diabetes was 4.0±3.0 years in 1 study and ranged from 0.8 years to 16.8 years in 6 studies. The mean duration of diabetes was not reported in the remaining studies.

Body mass index (BMI) was reported in 3 studies and ranged from 20.0±3.6 kg/m^2 to 21.5±3.8 kg/m^2. BMI standard deviation score (BMI-SDS) was reported in 2 studies and ranged from 0.51±0.92 to 0.75±1.15. Neither BMI nor BMI-SDS was reported in 8 studies.

Of the priority outcomes defined by the guideline development group (HbA1c, severe hypoglycaemic episodes, nocturnal hypoglycaemic episodes, diabetic ketoacidosis [DKA], adherence to treatment, health-related quality of life and satisfaction with treatment), only HbA1c-related outcomes were reported in all 13 studies. Five of the studies (de Beaufort 2013; Haller 2004; Ingerski 2011; Levine 2001; Moreland 2004) reported data on the a priori outcome of the association between the frequency of capillary blood glucose monitoring and HbA1c either by presenting the correlation coefficient (r) value or an R^2 value to explain how much variation in HbA1c was caused by the frequency of capillary blood glucose monitoring. Where possible the reported R^2 was converted into a correlation coefficient. This was possible only where the frequency of capillary blood glucose monitoring tests alone was used in regression analysis. Where the R^2 value was calculated for multiple variables including frequency of capillary blood glucose monitoring then the reported data were not used in this review.

Eight studies (Dorchy 1997; Haller 2004; Helgeson 2011; Levine 2001; McGrady 2009; Nordly 2005; Svensson 2009; Ziegler 2011) reported the post-hoc outcome of adjustment in HbA1c level associated with each additional capillary blood glucose test, either by reporting an association (regression coefficient beta) or a another numerical value.

Using data collected from the T1D Exchange clinical registry study, Miller (2013) assessed the association between different frequencies of capillary blood glucose testing and HbA1c using general linear regression models controlling for confounders such as insulin delivery method, gender, race or ethnicity and household income. Unadjusted mean HbA1c levels across 3 separate age groups (1 to under 6 years, 6 to under 13 years and 13 to 18 years) stratified by frequency of capillary blood glucose monitoring were reported in this article.

A further article based on the T1D Exchange clinical registry study (Campbell 2014) compared frequencies of capillary blood glucose testing in a group of participants with excellent HbA1c control (defined as HbA1c lower than 7% in the previous 12 months) and a group with poor control group (defined as HbA1c of 9.0% or higher in the previous 12 months). This article reported data for children and young people aged 6 to 17 years.

The association between frequency of capillary blood glucose monitoring and severe hypoglycaemic episodes was reported in 1 study (Ziegler 2011).

6.9.4.4 Evidence profile

The evidence profile for this review question (frequency of self-monitoring of blood glucose) is presented in Table 32.

Table 32: Evidence profile for frequency of self-monitoring of blood glucose in children and young people with type 1 diabetes

Number of studies	Number of children and young people	Relative effect	Absolute effect	Quality
Association between frequency of SMBG and HbA1c, reported as coefficients of associations				
5 (de Beaufort 2013; Haller 2004; Ingerski 2011; Levine 2001; Moreland 2004)	4794	NA	Increased frequency of SMBG was inversely correlated with HbA1c independent of other variables r= −0.17 (p<0.0001) to r = −0.45 (p<0.001)	Low
Association between frequency of SMBG and HbA1c, reported as the probability of frequency of SMBG being associated with excellent control of HbA1c in the previous 12 months compared with the poor control group, SMBG performed 3 to 4 times per day versus 0 to 2 times per day				
1 (Campbell 2014)	3272	Adjusted OR 1.7 (0.7 to 3.9)	NA	Very low

Number of studies	Number of children and young people	Relative effect	Absolute effect	Quality
Association between frequency of SMBG and HbA1c, reported as the probability of frequency of SMBG being associated with excellent control of HbA1c in the previous 12 months compared with the poor control group, SMBG performed 5 to 9 times per day versus 0 to 2 times per day				
1 (Campbell 2014)	3272	Adjusted OR 2.3 (1.0 to 5.1)	NA	Low
Association between frequency of SMBG and HbA1c, reported as the probability of frequency of SMBG being associated with excellent control of HbA1c in the previous 12 months compared with the poor control group, SMBG performed ≥ 10 times per day versus 0 to 2 times per day				
1 (Campbell 2014)	3272	Adjusted OR 7.0 (2.9 to 17.0)	NA	Low
Association between frequency of SMBG and HbA1c, reported as unadjusted mean HbA1c level among children aged 1 to 6 years, SMBG performed 3 to 4 times per day				
1 (Miller 2013)	NA	NA	Unadjusted mean HbA1c level 8.5%	Low
Association between frequency of SMBG and HbA1c, reported as unadjusted mean HbA1c level among children aged 1 to 6 years, SMBG performed 5 to 6 times per day				
1 (Miller 2013)	NA	NA	Unadjusted mean HbA1c level 8.4%	Low
Association between frequency of SMBG and HbA1c, reported as unadjusted mean HbA1c level among children aged 1 to 6 years, SMBG performed 7 to 9 times per day				
1 (Miller 2013)	NA	NA	Unadjusted mean HbA1c level 8.1%	Low
Association between frequency of SMBG and HbA1c, reported as unadjusted mean HbA1c level among children aged 1 to 6 years, SMBG performed ≥ 10 times per day				
1 (Miller 2013)	NA	NA	Unadjusted mean HbA1c level 7.8%	Low
Association between frequency of SMBG and HbA1c, reported as unadjusted mean HbA1c level among children aged 6 to 13 years, SMBG performed 3 to 4 times per day				
1 (Miller 2013)	NA	NA	Unadjusted mean HbA1c level 8.7%	Low
Association between frequency of SMBG and HbA1c, reported as unadjusted mean HbA1c levels among children aged 6 to 13 years, SMBG performed 5 to 6 times per day				
1 (Miller 2013)	NA	NA	Unadjusted mean HbA1c level 8.4%	Low
Association between frequency of SMBG and HbA1c, reported as unadjusted mean HbA1c level among children aged 6 to 13 years, SMBG performed 7 to 9 times per day				
1 (Miller 2013)	NA	NA	Unadjusted mean HbA1c level 8.1%	Low
Association between frequency of SMBG and HbA1c, reported as unadjusted mean HbA1c level among children aged 6 to 13 years, SMBG performed ≥ 10 times per day				
1 (Miller 2013)	NA	NA	Unadjusted mean HbA1c level 7.8%	Low
Association between frequency of SMBG and HbA1c, reported as unadjusted mean HbA1c level among children aged 13 to 18 years, SMBG performed 0 to 3 times per day				
1 (Miller 2013)	NA	NA	Unadjusted mean HbA1c level 10.3%	Low
Association between frequency of SMBG and HbA1c, reported as unadjusted mean HbA1c level among children aged 13 to 18 years, SMBG performed 3 to 4 times per day				
1 (Miller 2013)	NA	NA	Unadjusted mean HbA1c level 9.0%	Low
Association between frequency of SMBG and HbA1c, reported as unadjusted mean HbA1c level among children aged 13 to 18 years, SMBG performed 5 to 6 times per day				
1 (Miller 2013)	NA	NA	Unadjusted mean HbA1c level 8.5%	Low
Association between frequency of SMBG and HbA1c, reported as unadjusted mean HbA1c level among children aged 13 to 18 years, SMBG performed 7 to 9 times per day				
1 (Miller 2013)	NA	NA	Unadjusted mean HbA1c level 8.2%	Low

Number of studies	Number of children and young people	Relative effect	Absolute effect	Quality
Association between frequency of SMBG and HbA1c, reported as unadjusted mean HbA1c levels among children aged 13 to 18 years, SMBG performed ≥ 10 times per day				
1 (Miller 2013)	NA	NA	Unadjusted mean HbA1c level 8.0%	Low
Change in HbA1c for 1 additional test per day				
8 (Dorchy 1997; Haller 2004; Helgeson 2011; Levine 2001; McGrady 2009; Nordly 2005; Svensson 2009; Ziegler 2011)	31,083	NA	HbA1c decreased by between 0.056 percentage points and 0.4 percentage points for each additional test	Low
Association between frequency of SMBG and severe hypoglycaemic episodes				
1 (Ziegler 2011)	26,723	NA	2.38 (±0.54) additional events per 100 patient years for every 1 additional test	Low

HbA1c glycated haemoglobin, NA not applicable, OR odds ratio, p probability, r correlation coefficient, SMBG self-monitoring of blood glucose

6.9.4.5 Evidence statements

Five studies (total 4794 participants) showed an inverse correlation between the frequency of capillary blood glucose monitoring and HbA1c such that as frequency of capillary blood glucose monitoring increased then HbA1c improved. The quality of the evidence for this finding was low.

One study (total number of participants not calculable) showed a higher frequency of capillary blood glucose measurements per day was strongly associated with a lower HbA1c level, and the association held across age groups ranging from 1 to under 6 years, 6 to under 13 years and 13 to under 18 years. The quality of the evidence for this finding was low.

Eight studies (total 31,083 participants) showed that HbA1c decreased by up to 0.4 percentage points with each additional test performed each day. One study showed no additional improvement associated with additional capillary blood glucose monitoring above 5 tests per day. The quality of the evidence for these findings was low.

One study (total 26,723 participants) showed that a higher incidence of severe hypoglycaemic episodes was associated with more frequent capillary blood glucose monitoring. The quality of the evidence for this finding was low.

6.9.4.6 Health economics profile

A systematic literature search did not find any published economic evaluations addressing the optimal frequency of self-monitoring of blood glucose in children and young people with type 1 diabetes.

An original health economic model was developed using the IMS CORE Diabetes Model. This took the form of a ‘what-if’ analysis as observational data from the clinical review showed an association between increased frequency of monitoring and lower HbA1c, but could not be used to evaluate causation. This was because unidentified confounding variables could explain the observed association.

The model assessed the cost effectiveness of the frequency of monitoring blood glucose levels up to a maximum of 5 times per day. This was used as the upper limit as evidence from the largest study in the clinical evidence review showed no additional reduction in HbA1c was associated with testing beyond 5 times per day (Ziegler 2011).

Data from a US study were used to estimate the change in blood glucose levels from increased monitoring (Miller 2013), assuming that changes in blood glucose were causally related to increased self-monitoring. However, to address the uncertainty with this assumption a sensitivity analysis was undertaken to determine the reduction in HbA1c that would be necessary for self-monitoring 5 times per day to be considered cost effective relative to self-monitoring 4 times per day.

The base-case analysis found that increasing self-monitoring up to 5 times daily was cost effective. This was because there was a reduction in diabetes-related complications leading to improvements in health-related quality of life and savings from averted complications which more than offset the increased costs of self-monitoring.

Sensitivity analysis suggested that providing self-monitoring 5 times per day led to a reduction in HbA1c of 0.06 percentage points or more compared with self-monitoring 4 times per day, then it would be considered cost effective. This threshold HbA1c reduction for cost effectiveness was substantially smaller than that used in the base-case analysis. The model is described in detail in Section 19.4.

6.9.4.7 Health economics evidence statement

Original health economic analysis conducted for the guideline indicates that self-monitoring blood glucose 5 times per day could be considered cost effective relative to self-monitoring 4 times per day if it causes a reduction in HbA1c of 0.06 percentage points. The analysis was assessed as partially applicable with serious limitations.

6.9.4.8 Evidence to recommendations

6.9.4.8.1 Relative value placed on the outcomes considered

The guideline development group agreed that HbA1c value was the highest priority outcome for this question because, in their view, if capillary blood glucose monitoring resulted in a reduction in HbA1c by near to or greater than 0.5 percentage points (or 5.5 mmol/mol) then this would represent an important clinical benefit to a child or young person with type 1 diabetes. This decision was underpinned by the guideline development group's knowledge of research in adults with type 1 diabetes (The Diabetes Control and Complications Trial Research Group 1993) which showed that a 1 percentage point decrease in HbA1c halved the risk of diabetes-related complications. The guideline development group considered that this result could be meaningfully extrapolated to cover the population of children and young people with type 1 diabetes of relevance in this question.

The group also selected severe hypoglycaemic, nocturnal hypoglycaemic and DKA episodes as outcomes as they felt that any increase or decrease in the numbers of such events would be important measures of the effectiveness of any blood glucose monitoring strategy.

The group was of the view that adherence to treatment, health-related quality of life and satisfaction of children and young people with treatment were also important outcomes given that capillary blood glucose monitoring is painful and some children and young people find it distressing.

The guideline development group considered that, in this question, a minimum follow-up period of 6 months in both treatment arms would be needed for measurement of HbA1c and a minimum follow-up period of 4 months in both treatment arms would be needed for the other outcomes.

The group was of the view that the ideal study to answer this question would be an RCT comparing 5 or more tests per day with 4 or fewer tests. However, they acknowledged in the review protocol that there are practical difficulties associated with undertaking research of this type and it was expected that such studies were unlikely to be available. As such it was

decided that it would be pragmatic to allow the inclusion of observational study designs from the outset. The group noted that observational studies would be likely to report results in terms of correlation statistics showing associations between test frequency and outcomes of interest.

6.9.4.8.2 Consideration of clinical benefits and harms

All the studies identified for inclusion showed that testing capillary blood glucose more frequently correlated with an improvement in HbA1c. The guideline development group acknowledged that the evidence base reviewed meant that they could not say whether these results were necessarily due to a causal relationship, but they did feel that such an explanation was highly plausible and in keeping with their experience.

A single study found a higher incidence of severe hypoglycaemic episodes with more frequent testing. Again the group noted that this was not necessarily evidence of a causal relationship and it was perhaps just as likely that experiencing more hypoglycaemic episodes might lead to children and young people testing more frequently (rather than increased testing leading to such episodes).

In the absence of specific study data for the remaining prioritised outcomes, the group relied on their experience to assess the potential benefits and harms of more frequent testing in relation to the prioritised outcomes of adherence to treatment, health-related quality of life and satisfaction of children and young people with treatment. They noted that testing is painful and that scarring and loss of sensation can occur if the same body site is used repeatedly. They felt that the child or young person's emotional response to testing would probably vary from individual to individual, with some children and young people finding more frequent testing reassuring, whereas others might find it to be quite an emotional and distressing process. Overall, the group considered that, in the majority of children and young people with type 1 diabetes, the potential harms were not so great as to outweigh the benefits of improved glycaemic control that might be achieved with more frequent testing and that the risk of such harms occurring might be mitigated if appropriate reassurance, encouragement and training was provided by healthcare professionals.

The guideline development group was mindful that capillary blood glucose testing is sometimes used as a safety net as if it were continuous glucose monitoring. Given that there was some risk of harm associated with very frequent capillary blood glucose testing, the group acknowledged that the largest study included in the guideline review showed that the positive association between HbA1c levels and testing plateaued after 5 tests. Based on this, the group agreed that it was important to provide some specific guidance about the number of tests that should be performed routinely so as not to imply that ever greater frequency was always beneficial.

The group also agreed that there were specific circumstances where glycaemic control may be more difficult and/or crucial to the safety of the child or young person and others (for example when driving, drinking alcohol, exercising or during puberty or periods of stress such as school examinations). The group felt that at such times more frequent testing might be appropriate.

6.9.4.8.3 Consideration of health benefits and resource use

The guideline development group noted that costs associated with capillary blood glucose monitoring were the cost of the testing strips and the cost of delivering the education needed to ensure that testing is undertaken safely and the results are interpreted correctly to inform effective diabetes management. The group noted that the monitors used to read strips were provided free of charge by manufacturers of the strips and the education would be necessary with any frequency of capillary blood glucose monitoring. Thus the only uplift in resources associated with more frequent monitoring would be the cost of the additional strips required. The guideline development group felt that these resources would be justified by the evidence

of a positive association between more frequent testing and improved HbA1c and their consensus view that such improved glycaemic control would lead to long-term health benefits. The group felt that recommending a routine monitoring strategy based on 5 capillary blood glucose tests per day was likely to reduce the possibility of excessive monitoring being undertaken beyond the point at which benefits in terms of glycaemic control might be expected. The group also considered that recommending 5 tests per day would improve access to strips.

The guideline development group deliberated on the timing of testing and felt that this would differ depending on the insulin regimen used and as such agreed not to recommend when capillary blood glucose testing should be performed.

6.9.4.8.4 Quality of evidence

The quality of the evidence was low, but as described above, the guideline development group felt that there was sufficient consistency between the outcomes reported and their clinical experience to justify making a strong recommendation. The group also noted that it was the non-randomised study design that led to the low quality rating and that in other respects the studies had been well conducted and steps had been taken to ensure accuracy (for example the biggest study in the guideline review had used data downloaded directly from meters, which would have reduced the risk of reporting bias significantly).

6.9.4.8.5 Other considerations

There were no other considerations.

6.9.4.8.6 Key conclusions

The guideline development group recommended that children and young people with type 1 diabetes and their family members or carers (as appropriate) should be advised to routinely perform at least 5 capillary blood glucose tests per day. Another recommendation related to the frequency of capillary blood glucose testing was to advise children and young people with type 1 diabetes and their family members or carers (as appropriate) that more frequent testing is often needed (for example with physical activity and during intercurrent illness) and that they should have enough test strips for this.

6.10 Methods of self-monitoring blood glucose

6.10.1 Home blood glucose monitoring compared with no home blood glucose monitoring

We found 5 studies that compared home blood glucose monitoring with no home blood glucose monitoring. An observational study found a correlation between the frequency of home blood glucose monitoring and HbA1c levels ($r = -0.20$, $p<0.001$, n=288 children and young people). There was also a correlation between the actual frequency compared with the doctor's suggested frequency ($r = -0.20$, $p<0.001$). There was a smaller correlation between the frequency of urine testing and HbA1c levels ($r = -0.07$, $p>0.05$).[330] [evidence level III] A second study looked at patient views of home blood glucose monitoring and found a positive response (75% thought blood glucose monitoring was a 'great help', 25% thought it was a nuisance but of some help, 33% thought they had more hypoglycaemic reactions, 50% thought they had fewer hypoglycaemic reactions and 92% thought that their metabolic control had improved, n=13 adults).[331] [evidence level III] A third study in adults found home blood glucose monitoring was associated with decreased HbA1c levels (mean HbA1c before 10.5% versus after 13.9%, n=7).[332] [evidence level III] However, a non-randomised crossover study in children and young people found no difference in glycated haemoglobin at baseline compared with that after 12 weeks of urine testing with self-monitoring of blood glucose or 12 weeks of urine testing only (n=16).[320] [evidence level IIa] One non-randomised study found

that HbA1 improved from baseline in the intervention group (10.3 ±0.4% to 9.3 ±0.3%, p<0.01 from baseline), but not in the control group (10.6 ±0.7% to 10.4 ±0.6%, not significant, n=40 adults).[333] [evidence level IIa] The same study showed that the rate of nephropathy (albuminuria ≥0.3 g/l) increased in the control group, but not in the intervention group (intervention 15.8% to 15.8% versus control 25% to 16.7%), as did retinopathy (30% to 30% versus 16.7% to 25%), whereas neuropathy increased to a lesser extent in the intervention group than in the control group (intervention 32.4% to 35.0% versus 16.7% to 41.7%).[333] [evidence level IIa]

6.10.2 Monitoring blood glucose with a monitor compared with the laboratory standard

We found 9 studies in adults that looked at the use of home blood glucose monitors compared with the laboratory standard. Studies show that different monitors have different correlation coefficients when compared with the laboratory standard test and different coefficients of variation.[334–342] [evidence level IIb] A consensus statement from the American Diabetes Association recommended that the performance goal of all home blood glucose monitors should be to achieve a total error (analytical plus user) of <10% at glucose concentrations ranging from 1.6 to 22.2 mmol/l (30 to 400 mg/dl).[343] One study found no difference in the accuracy of a monitor when used by medical staff and patients (n=50 adults).[341] [evidence level IIa]

6.10.3 Visually read reagent sticks compared with laboratory standard methods

Three studies looked at the use of visually read reagent strips compared with laboratory standard methods. The studies found that the correlation ranged from r=0.86 to r=0.98.[344,345] [evidence level IIb] The detection of hypoglycaemia had a sensitivity of 44% and a specificity of 95%, and the detection of hyperglycaemia had a sensitivity of 54% and a specificity of 86%.[346] [evidence level IIb]

6.10.4 Self-monitoring of blood glucose with a monitor or a visually read stick

Eight studies investigated the use of self-monitoring of blood glucose with a monitor compared with self-monitoring of blood glucose with a visually read stick.[347–354] A crossover RCT in patients with type 1 diabetes randomised patients to self-monitoring of blood glucose through strips or a monitor for 3 months then crossed-over for a second 3-month period. The study found no difference in HbA1 levels between the treatment groups (n=24 adults).[354] [evidence level Ib] Three observational studies looked at the correlation of self-monitoring of blood glucose using monitors and visually read sticks in comparison with blood glucose measurement from the standard laboratory test. All 3 studies found little difference between the correlation coefficients.[350,351,353] [evidence level III] A non-randomised intervention crossover study found that patients preferred self-monitoring of blood glucose with a monitor compared with visually read strips (19/32 patients preferred monitors versus 9/37 patients preferred visually read strips, n=115 blood samples from outpatients).[352] [evidence level IIa] An observational study found that laboratory standard methods and reagent strips with monitors were more closely correlated (r^2 0.85 to 0.96, n>100 patients with and without diabetes) than laboratory standard methods and visually read reagent strips (r^2 0.69 to 0.90).[348] [evidence level IIb] An RCT looked at the correlation between laboratory standard test, 2 visual strip methods and 2 monitor methods (n=10 children and young people). The study found a range of correlations with the laboratory standard test, the method with the best correlation being a monitor method.[349] [evidence level Ib] A comparative study looked at the correlation coefficients between a monitor and laboratory standard (r=0.97, p<0.0001, n=50) and a visually read stick and the monitor (r=0.921, p<0.001).[347] [evidence level IIb]

6.10.5 Comparison of blood glucose monitors with and without memories

Three studies have investigated the use of self-monitoring of blood glucose using monitors with and without memories. One RCT compared 2 monitors with memories with a diary for recording self-monitored blood glucose measurements (n=179 adults). This RCT found that patients preferred monitors with memories to diaries (81 ±18% versus 77 ±23% versus 68 ±24%, p=0.02). The number of hypoglycaemic events was significantly increased with 1 of the monitors compared with the control (7.9 ±14.0 versus 3.2 ±5.5 events/patient/week, p=0.02). There was no difference in the accuracy of capillary blood glucose determination or HbA1c levels.[355] [evidence level Ib] A second RCT in adults with type 1 diabetes compared monitors with memories with monitors with no memory. This study found a lower HbA1c level in the group of patients using monitors with memories (6.4 ±0.10% versus 6.9 ±0.12%, p=0.004).[356] [evidence level Ib] One observational study looked at the introduction of monitors with memories (n=24 adults). The uptake of the new system was low (24/98) and few patients continued to use the equipment after 3 years (5/28), although the patients who did continue to use the monitors had better glycaemic control (however, this may be because they were a self-selected group).[357] [evidence level IIb]

Three studies have examined patient reliability in relation to recording of self-monitored blood glucose levels.

One study looking at patients with poor glycaemic control investigated the memory recordings of self-monitored blood glucose measurements when patients did not know that the monitors had memories (n=6 adults). The study found 100% of the patients under-reported the number of self-monitored blood glucose measurements taken, and 83% over-reported the number of self-monitored blood glucose measurements taken. However, when the same patients were told that a memory was fitted, under-reporting decreased (from 6/6 to 4/5), over-reporting decreased (from 5/6 to 1/5), and the average number of measurements increased (in 4/5 patients).[358] [evidence level IIb] A similar study that did not look specifically at patients with poor glycaemic control found 10% under-reporting and 34% over-reporting (n=20 young people and adults). However, when the patients were informed that the blood glucose monitors had memories, there was a reduction in over-reporting and an increase in the precision of recordings (over-reporting: 34% versus 1%, p=0.0027; precision: 72% versus 99%, p=0.0037).[359] [evidence level IIa] A third study found that over-reporting correlated with under-reporting (rank correlation r=0.56, p<0.01, n=21 adults), but neither over-reporting nor under-reporting correlated with precision. The clinicians' prediction of the patients' accuracy was associated with overall reliability scores (rank correlation r=0.68, p<0.01) and the HbA1 correlated weakly with readings of self-monitored blood glucose (rank correlation r=0.62, p<0.01) and overall reliability scores (rank correlation r= −0.44, p<0.05).[360] [evidence level IIb]

6.10.6 Computer systems for assisting monitoring glycaemic control

A systematic review of RCTs investigated the use of patient-focused computer-generated information systems for improving care outcomes in patients with diabetes.[361] [evidence level Ia] The systematic review identified 15 RCTs: 10 of these investigated the use of computerised interventions in adults, whereas 5 investigated the use of such systems in children. Thirteen RCTs focused on patients with type 1 diabetes, 1 focused on patients with type 2 diabetes, and 1 focused on patients with type 1 or type 2 diabetes. Significant benefits were associated with use of computerised interventions in 12 of the 15 RCTs. HbA1c was investigated in all 15 RCTs, 6 of which reported a significantly lower HbA1c level in the group that received the computerised interventions. Three RCTs reported significantly lower blood glucose levels in the group that received the computerised interventions, and 1 RCT reported significantly fewer hypoglycaemic events in the group that received the computerised interventions.

Nine studies have looked at computer technology for assisting in the recording of self-monitored blood glucose measurements and in the adjustment of insulin dose. 7 RCTs found no difference in glycaemic control with computer assistance compared with conventional assessment.[362–368] [evidence level Ib] Two of these studies also measured fructosamine,[362,365] and 1 looked at the incidence of hypoglycaemia,[365] but no significant differences in either outcome were reported.

An RCT in adults found a decrease in HbA1c levels in a group in a crossover study that received a computer-assisted blood glucose monitor first and a control monitor second (6.0 ±1.0% versus 6.8 ±0.6%, p=0.03, n=11), but this result was not repeated in the group that received the control monitor first and the computer-assisted monitor second (6.7 ±1.0% versus 6.8 ±0.9%, not significant, n=11).[369] [evidence level Ib] A non-randomised controlled trial in adults assigned the study group to blood glucose monitors without a memory for 1 year and then transferred all the patients to blood glucose monitor with a memory. In this study, the average HbA1c was lower when blood glucose monitors with memories were used (6.4 ±0.10% versus 6.9 ±0.12%, p=0.004, n=22).[370] [evidence level IIa]

An RCT in children and young people (age range 7.6 to 11.9 years) with type 1 diabetes compared computer algorithms and manual algorithms (n=20).[371] [evidence level Ib] There was no difference in pre-meal glycaemia or HbA1c levels. However, the frequency of hypoglycaemia was lower in the group using the computer algorithms than in the group using manual algorithms (1.2 events/week versus 2.3 events/week).

An RCT in young people and young adults (age range 15 to 20 years, n=63) investigated the use of electronic transmission of blood glucose information to the clinic via a modem.[372] [evidence level Ib] The patients receiving the intervention were invited to use the modem to send blood glucose information to the clinic approximately every 2 weeks. The healthcare provider at the clinic reviewed the information transmitted by the patients and contacted patients when changes to treatment were needed, and invited patients to attend the clinic at 0 and 6 months into the study. Patients in the control group visited the clinic at 0, 3 and 6 months and had the option to telephone or fax blood glucose results to the clinic if they wished to or if requested by the physician. The study found no difference between the groups in terms of HbA1c levels (8.6 ±1.7% versus 8.6 ±1.2%, p=0.89), occurrence of mild to moderate hypoglycaemic events (2.9 times/day versus 3.0 times/day, p=0.91) or patient satisfaction.

Cost-analysis was performed on the use of modem-transmitted blood glucose information. The cost estimates included patients'/families' out of pocket expenses and time as well as health service costs and the cost of the new technology. The intervention group incurred fewer expenses and less lost productivity (parental time off work) than the control group (p<0.001). Since there were no reported differences in adverse outcomes, the lower cost of the intervention group made it a viable alternative at almost half the cost ($163 versus $305). However, sensitivity analysis on the resources that are most difficult to value (lost time/productivity, costs of new technology) was not performed. Also, the relatively high reported fee for a clinic visit ($246, range $235 to 310) accounted for most of the cost of the standard care group. The cost of specialist clinic visits for patients of all ages was reported in a survey of UK providers to be £67 at 1997 prices,[373] which is a much lower cost and so the relative cost effectiveness would not be the same in the UK.

6.10.7 Plastic insulin dose guide compared with paper algorithm

An RCT compared a plastic insulin dose guide with a paper algorithm as a guide for patient-adjusted insulin dose in 40 children with type 1 diabetes. The study found no significant difference in HbA1clevels. However, mean blood glucose levels decreased with the dose guide compared with the algorithm (9.2 ±1.2 mmol/l versus 11.8 ±1.6 mmol/l), whereas patient acceptance increased with the dose guide (5.0 versus 3.4 Likert 0 to 5 scale), and the

time needed to teach the patient to use the guide increased (from 18 to 43 minutes).[374] [evidence level Ib]

6.10.8 Alternative body sites for blood glucose monitoring

Seven observational studies examined the impact of blood glucose monitoring at alternative sites. None of the studies looked specifically at children or young people, and none of the studies investigated long-term outcomes related to complications or glycaemic control. Seven studies compared blood glucose measurements from the traditional site (the finger) to those from an alternative site (for example, the arm). Six studies found strong correlations between forearm blood glucose monitoring and finger blood glucose monitoring.[375–380] [evidence level IIa] One study found changes in blood glucose after a meal may be identified at finger sites before detection at forearm or thigh sites.[381] [evidence level IIa] Two studies looked at patient acceptability of alternative sites for blood glucose monitoring. One study found that 76% of patients preferred a monitor that could be used for sites other than the finger (n=121 patients with type 1 or type 2 diabetes).[382] [evidence level IIa] The second study reported that 97% of patients found arm blood glucose testing less painful than finger testing (n=378 patients with type 1 or type 2 diabetes).[378] [evidence level IIa]

6.10.9 Invasive and non-invasive continuous glucose monitoring systems

6.10.9.1 Introduction

Self-monitoring of blood glucose provides a snapshot of glucose levels during the day, but marked glycaemic excursions can be missed in periods when no glucose level is taken. Continuous glucose monitoring systems (CGMS) measure interstitial fluid glucose and provide information about continuous glucose fluctuations that is not captured by intermittent blood glucose testing.[383] [evidence level IV]

CGMS requires calibration with finger-stick tests and supplement, but do not replace, conventional blood glucose testing.[383] [evidence level IV] CGMS measurements correspond to blood glucose values taken approximately 13 to 18 minutes earlier and may differ from blood glucose monitor readings.[383] [evidence level IV] We identified 2 groups of CGMS: invasive designs and non-invasive designs.

6.10.9.2 Invasive continuous glucose monitoring systems

Invasive continuous glucose monitoring systems can be used for up to 72 hours.[384] [evidence level IV]

We found 2 RCTs evaluating the invasive CGMS MiniMed®. In one RCT (n=11 children and young people), the intervention group used the invasive CGMS for 18 days out of a 30-day period as well as performing at least 4 blood glucose tests/day. The intervention group was compared with a control group that performed at least 4 blood glucose tests/day. For both groups, glucose monitoring results were reported to a member of the diabetes clinic staff, and insulin dose adjustments were made over the telephone. More asymptomatic biochemical hypoglycaemic events were identified in the intervention group (12.8 ±1.6 versus 6.7 ±1.1), and these resulted in more changes of insulin dose (11.5 ±1.5 versus 5.2 ±0.9). There was no significant difference between HbA1c levels in the 2 groups after 3 months. The groups showed no significant difference in fear of hypoglycaemia, or DCCT quality of life.[385] [evidence level Ib] The second RCT investigated the use of a CGMS for 3 days every 2 weeks, creating a profile that was used to adjust insulin therapy at follow-up visits every 6 weeks, compared with patients who used a CGMS for 3 days every 2 weeks without making the results available to patients or diabetes team with insulin therapy adjustments being made solely on the basis of 7-point blood glucose profiles recorded by the patients (n=27, age range 7 to 19 years). The study found that HbA1c levels were reduced when there was

access to the results of the CGMS compared with when there was no access (7.31% versus 7.65%, p=0.011).[386] [evidence level Ib]

We also found 24 studies that evaluated the use of invasive CGMS compared with blood glucose monitoring.[387–410] [evidence level IIb] Of these, 18 investigated the same invasive CGMS as the above RCTs, and 5 investigated other invasive CGMS. Ten studies showed strong correlations between glucose levels measured by invasive CGMS and conventional blood glucose monitoring.[387–389,393,396,399,403,404,407,410] [evidence level IIa] Invasive CGMS detected more asymptomatic biochemical hypoglycaemia.[392,393,406,408] [evidence level IIa] Short-term use of invasive CGMS combined with information advising patients when and how to change insulin regimen and/or dose was found to reduce HbA1c compared with baseline in 1 study in children and 2 studies in adults (child study: reduction at 3 months 0.40 ±0.94%, reduction at 6 months 0.43 ±0.87%;408 first adult study: 8.5 ±0.9% versus 10.3 ±0.6%, p<0.01, n=10 adults;397 second adult study: 8.5 ±0.9% versus 10.3 ±0.6%, p<0.01, n=10 adults).[397] [evidence level IIa] However, a further study found no change in HbA1c levels.[393] [evidence level IIa] 4 studies that evaluated pain and irritation with invasive CGMS reported that the devices were tolerated with only occasional adverse events.[388,400,403,405] [evidence level IIa] One study reported strong reaction to adhesive (2/66 children).[409] [evidence level IIa]

6.10.9.3 Non-invasive blood glucose monitoring

Several systems for measuring glucose non-invasively through the skin are currently being investigated. These include electrochemical enzyme sensors, transcutaneous near-infrared spectroscopy,[411,412] optical glucose sensors and infrared spectroscopy.[413]

Electrochemical enzyme sensors have shown strong correlations between glucose measured continuously and that measured conventionally. However, the device was reported to be uncomfortable, causing redness, itching and tingling.[414–416] [evidence level IIa]

One RCT investigated the use of electrochemical enzyme sensors in children and young people with type 1 diabetes (n=40). The study found a reduction in HbA1c (8.4% versus 9.0%, no SD given, p<0.05), an increase in the frequency of detection of hypoglycaemia (blood glucose ≤ 70 mg/dl, no values given, p<0.0003), There was no change in fear of hypoglycaemia (59 ±14.3 versus 56.4 ±9.6) or quality of life (81.3 ±11.7 versus 79.8 ±15.5).[417] [evidence level Ib] A pilot study conducted as part of this RCT evaluated the cost effectiveness and cost/QALY of standard care versus standard care plus the electrochemical enzyme sensor. The study reported resource use and costs in the USA and used a simulation model to predict future lifetime costs and outcomes of children in both groups. Cost effectiveness ratios were reported as costs/life year and costs/QALY but without description of how the QALY weights were derived.[418] The cost of standard care was $6252/year and the cost of enhanced care with the electrochemical enzyme sensor was $9127 for the first year and $9017/year thereafter. The simulation model showed that enhanced care yielded an additional 0.66 QALYs and the cost/additional QALY was $61,326 (approximately £33,000/QALY). These preliminary results, which were not based on long-term follow up, suggested that enhanced care with the electrochemical enzyme sensor was an effective but expensive option for monitoring glucose.[418]

6.10.9.4 Summary

Regular monitoring of glycated haemoglobin is part of the intensive package of care. The most appropriate measure for long-term glycaemic control is DCCT-aligned HbA1c, which is the only means of glycaemic control that has been shown to be correlated with long-term complications of diabetes.

Continuous blood glucose monitoring may be a useful tool in giving detailed information on blood glucose trends during regimen optimisation. A Canadian health technology

assessment reported that continuous glucose monitors may benefit patients having difficulty controlling their blood sugar or during initiation or monitoring of CSII therapy.[383] [evidence level IV] Continuous blood glucose monitoring may also be useful where unidentified hypoglycaemia occurs, especially at night-time, but further research is needed before such systems can be recommended for routine use for optimisation of glycaemic control.

There is evidence that monitors compare satisfactorily with laboratory methods, but there is no evidence that using a monitor provides better control than using visually read sticks. However, patients prefer using monitors. There is no evidence that monitors with memories that are connected to computer systems improve glycaemic control.

Healthcare professionals may find it useful to refer to the recommendations in Section 5 (education) when offering information about monitoring glycaemic control.

Frequent episodes of hypoglycaemia can affect cognitive function, especially if they occur at a young age. Studies relating to cognitive disorders in children and young people with type 1 diabetes are discussed in Section 9.4.

6.10.10 Capillary blood glucose testing compared with continuous glucose monitoring

This section was updated and replaced in 2022. See www.nice.org.uk/guidance/ng18/evidence for the 2022 evidence review.

6.10.10.1 Review question

This section was updated and replaced in 2022. See www.nice.org.uk/guidance/ng18/evidence for the 2022 evidence review.

6.10.10.2 Introduction

This section was updated and replaced in 2022. See https://www.nice.org.uk/guidance/ng18/evidence for the 2022 evidence review.

6.10.10.3 Description of included studies

This section was updated and replaced in 2022. See https://www.nice.org.uk/guidance/ng18/evidence for the 2022 evidence review

6.10.10.4 Evidence profile

This section was updated and replaced in 2022. See https://www.nice.org.uk/guidance/ng18/evidence for the 2022 evidence review

6.10.10.5 Evidence statements

This section was updated and replaced in 2022. See https://www.nice.org.uk/guidance/ng18/evidence for the 2022 evidence review

6.10.10.6 Health economics profile

This section was updated and replaced in 2022. See https://www.nice.org.uk/guidance/ng18/evidence for the 2022 evidence review

6.10.10.7 Evidence to recommendations

This section was updated and replaced in 2022. See www.nice.org.uk/guidance/ng18/evidence for the 2022 evidence review

6.10.11 Intermittent versus real-time continuous glucose monitoring

This section was updated and replaced in 2022. See www.nice.org.uk/guidance/ng18/evidence for the 2022 evidence review

6.10.11.1 Review question

This section was updated and replaced in 2022. See www.nice.org.uk/guidance/ng18/evidence for the 2022 evidence review

6.10.11.2 Introduction

This section was updated and replaced in 2022. See www.nice.org.uk/guidance/ng18/evidence for the 2022 evidence review

6.10.11.3 Description of included studies

This section was updated and replaced in 2022. See www.nice.org.uk/guidance/ng18/evidence for the 2022 evidence review

6.10.11.4 Evidence profile

This section was updated and replaced in 2022. See www.nice.org.uk/guidance/ng18/evidence for the 2022 evidence review

6.10.11.5 Evidence statements

This section was updated and replaced in 2022. See www.nice.org.uk/guidance/ng18/evidence for the 2022 evidence review

6.10.11.6 Health economics profile

This section was updated and replaced in 2022. See www.nice.org.uk/guidance/ng18/evidence for the 2022 evidence review

6.10.11.7 Evidence to recommendations

This section was updated and replaced in 2022. See www.nice.org.uk/guidance/ng18/evidence for the 2022 evidence review

6.10.11.7.1 Relative value placed on the outcomes considered

This section was updated and replaced in 2022. See www.nice.org.uk/guidance/ng18/evidence for the 2022 evidence review

6.10.11.7.2 Consideration of clinical benefits and harms

This section was updated and replaced in 2022. See www.nice.org.uk/guidance/ng18/evidence for the 2022 evidence review

6.10.11.7.3 Quality of evidence

This section was updated and replaced in 2022. See www.nice.org.uk/guidance/ng18/evidence for the 2022 evidence review

6.10.11.7.4 Key conclusions

This section was updated and replaced in 2022. See www.nice.org.uk/guidance/ng18/evidence for the 2022 evidence review

6.11 Recommendations

The current recommendations can be found at https://www.nice.org.uk/guidance/ng18

6.12 Research recommendations

10. This research recommendation has been removed from the 2022 update

11. This research recommendation has been removed from the 2022 update

12. This research recommendation has been removed from the 2022 update

6.13 Management of type 1 diabetes – ketone monitoring

6.13.1 Review question

What is the effectiveness of blood ketone monitoring compared with urine ketone monitoring for the prevention of diabetic ketoacidosis?

6.13.2 Introduction

Insulin deficiency leads to an increase in blood glucose levels and increased production of ketones. If untreated, these increased levels lead to progressive dehydration and acidosis. Symptoms of diabetic ketoacidosis (DKA) can range from nausea, vomiting and abdominal pain to tachycardia, hyperventilation, hypotension and unconsciousness. Without intervention, serious complications, such as cerebral oedema and acute kidney failure, can develop.

The most common triggers for DKA are unrecognised onset of diabetes, inadequate insulin in the presence of other illness and missed insulin treatment in children and young people with known diabetes. The 2004 guideline recommended that children and young people with type 1 diabetes have blood and/or urine ketone testing strips available as well as short-acting or rapid-acting insulin analogues during intercurrent illness. The 2015 update scope covered the effectiveness of blood ketone monitoring compared with urine ketone monitoring for the prevention of DKA in children and young people with type 1 diabetes, a topic that was not addressed specifically in the 2004 guideline, although further research to evaluate the role of blood ketone monitoring in preventing DKA was recommended in the 2004 guideline.

The objective of the review question for the 2015 update is to compare the clinical and cost effectiveness of blood ketone monitoring and urine ketone monitoring in the prevention or early detection of DKA in children and young people with type 1 diabetes.

The outcomes prioritised for inclusion in the review were:

- development of DKA (number of episodes)
- severity of DKA (measured by pH at admission)
- hospital admission rates
- mortality
- contact with the diabetes care team (for example to interpret ketone measurements and determine appropriate action) as a measure of healthcare utilisation
- adherence to diabetes management (including self-management)
- health-related quality of life
- satisfaction of children, young people and families with the intervention.

6.13.3 Description of included studies

One RCT was identified for inclusion (Laffel 2005). The study compared efficacy of blood 3-hydroxybutyrate (3-OHB) monitoring with that of traditional urine ketone testing in sick day management at home. The study was carried out in the USA and included 123 children, young people and young adults aged 3 to 22 years who had been diagnosed with type 1 diabetes for at least 1 year. Participants with recurrent DKA or known emotional problems were excluded from the study. All participants were asked to check ketones during acute illness or stress, when glucose levels were elevated (at least 13.9 mmol/litre on 2 consecutive readings) or when they had symptoms of ketosis (for example nausea, vomiting or abdominal pain). The participants were given logbooks to record the date and time of insulin dosages, glucose results, blood or urine ketone measurements and episodes of illness.

Although this study enrolled participants aged 18 years and over it was included in the guideline review on the basis that a large proportion of the participants were within the age range relevant to the guideline (51.2% were prepubertal or pubertal and the remaining 48.8% were postpubertal). Furthermore, the guideline development group was of the view that in the UK DKA in young adults is often treated with the paediatric protocol as it is considered safer.

Only 1 guideline development group priority outcome – hospital admission rates – was reported. The other priority outcomes – development of DKA, severity of DKA, mortality, contact with the diabetes care team, health-related quality of life and satisfaction with treatment – were not reported. A second outcome (adherence to sick-day rules) was, however, reported by the included study and so the relevant data were extracted for the guideline review.

6.13.4 Evidence profile

The evidence profile for this review question (effectiveness of blood ketone monitoring compared with urine ketone monitoring for the prevention of DKA) is presented in Table 33.

Table 33: Evidence profile for effectiveness of blood ketone monitoring compared with urine ketone monitoring for the prevention of diabetic ketoacidosis

Number of studies	Number of children and young people		Effect		Quality
	Blood ketone monitoring	Urine ketone monitoring	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Hospital admission rates: incidence of acute complications as a proxy for admission rates					
1 (Laffel 2005)	62	61	NA	MD 0.37 lower (0.74 lower to 0.00)	Low
Adherence to ketone monitoring: percentage of time ketones checked on sick days					
1 (Laffel 2005)	62	61	NA	90.8% of time for blood ketone monitoring and 61.3% of time for urine ketone monitoring[a]	Low

NA not applicable, MD mean difference
a. The study authors reported statistical significance of p<0.001

6.13.5 Evidence statements

Hospital admission rates

The evidence from 1 study (total 123 participants) comparing blood ketone monitoring with urine ketone monitoring demonstrated that blood ketone monitoring was associated with

fewer episodes of emergency assessment or hospitalisation than was urine ketone monitoring. The quality of evidence was low.

Adherence to ketone monitoring

The evidence from 1 study (total 123 participants) comparing blood ketone monitoring with urine ketone monitoring demonstrated that children and young people were more likely to perform blood ketone monitoring compared with urine ketone monitoring. The quality of evidence was low.

6.13.6 Health economics profile

A systematic literature search did not find any published evidence comparing the cost effectiveness of blood ketone monitoring with urine ketone monitoring for the prevention of DKA in children and young people with type 1 diabetes.

This question was prioritised for health economic analysis and an original health economic model was developed for this guideline. Cost utility analysis was not undertaken as the only guideline development group priority outcome identified in the clinical evidence review related to hospital admission. Instead the model took the form of a cost minimisation analysis, noting that a monitoring strategy with lower rates of hospitalisation would be likely, everything else being equal, to have better health-related quality of life.

The results of the model suggested that blood ketone monitoring was £787 cheaper than urine ketone monitoring, as higher monitoring costs with blood ketone monitoring were more than offset by reduced hospitalisation costs. A probabilistic sensitivity analysis suggested that there was a very high probability that blood ketone monitoring was cost effective even after allowing for uncertainty in the difference in hospitalisation between the 2 monitoring strategies. The model is described in detail in Section 19.5.

6.13.7 Health economics evidence statement

Original health economic analysis conducted for the guideline indicates that blood ketone monitoring dominates urine ketone monitoring in children and young people with type 1 diabetes. The analysis was assessed as partially applicable with potentially serious limitations.

6.13.8 Evidence to recommendations

6.13.8.1 Relative value placed on the outcomes considered

The purpose of ketone monitoring is to detect elevated ketone levels before the point at which they become harmful and DKA occurs. For this reason the guideline development group considered that if either blood or urine ketone monitoring was associated with higher rates of DKA, more severe DKA, hospital admission or mortality then this would be an important clinical harm and the group therefore prioritised these outcome measures.

Commonly, ‘sick-day rules’ relating to the management of ketones state that if testing indicates high ketone levels then contact should be made with the diabetes team. As such the guideline development group was also interested to know whether a particular ketone monitoring strategy was associated with more frequent contacts than was the other.

The group also selected health-related quality of life and satisfaction of children, young people and families with treatment to try to assess whether either monitoring strategy was associated with psychosocial issues.

Very little evidence related to any of these outcomes was identified for inclusion in the guideline review. Moreover, the group noted that death is a rare outcome and so considered it unsurprising that no evidence was found for this outcome.

The group felt that adherence to 'sick-day rules' was an adequate proxy for the a priori selection of psychosocial outcomes because ketone testing is an important sick-day rule and, in the group's experience, some older children and young people with type 1 diabetes are reluctant to test their urine. Urine testing is also difficult for parents with very young children who are still wearing nappies.

6.13.8.2 Consideration of clinical benefits and harms

The limited data available provided some evidence that blood ketone monitoring reduces hospital admissions. The evidence also showed that children and young people using blood ketone testing contacted the diabetes team more frequently. The guideline development group interpreted this finding as meaning that blood ketone testing was more tolerable and resulted in greater adherence to sick-day rules.

In addition, the group felt that blood ketone testing was likely to be more beneficial than urine ketone testing because it provides a measure of ketone levels at the time of testing, whereas a time lag of a few hours is associated with urine testing while the body processes and excretes the ketones. Blood testing is, therefore, more likely to be accurate and allow for more prompt treatment. It also allows for better monitoring of resolution of ketosis. In the group's view blood ketone monitoring was, therefore, more likely to be effective overall in terms of avoiding harm. The group noted that this was particularly relevant for children and young people using continuous subcutaneous insulin infusion (insulin pump therapy) because this regimen does not include the use of long-acting insulin and so children and young people using this regimen are more likely to get ketosis quicker.

The guideline development group acknowledged that some minor harms associated with blood ketone testing do not occur with urine testing. For example, they noted that blood testing strips require contact with a sufficient volume of blood to be effective and some children and young people may find their use difficult or painful. As such there was some potential that tests would need to be repeated. The group felt that this was a comparatively minor concern in relation to other adverse outcomes that might be avoided, such as DKA. Equally they noted that blood ketone testing was preferred by many children and young people in their experience because it can be done at any time and in public and therefore does not involve being separated from peers. Also, some children and young people find the prospect of coming into contact with urine off-putting.

The group also noted that both urine and blood test strips become ineffective beyond their use-by dates and felt that this was a common enough problem that it should be highlighted in the recommendations. They noted that this practical concern was more of an issue for urine testing strips because out-of-date strips convey inaccurate results rather than simply no result. They noted, however, that urine testing strips expire more quickly (after 90 days) than do blood test strips. This is particularly problematic because the strips begin to denature as soon as the packet is opened and the number of strips included in a packet exceeds the number likely to be used in a 90-day timeframe.

For the reasons outlined above, use of ketone testing strips tends to be necessarily higher in children and young people using continuous subcutaneous insulin infusion (insulin pump therapy). The group noted again that this was relatively minor concern compared with potential avoidance of DKA and that blood ketone testing had the additional benefit of being able to indicate whether the pump had failed or whether the bolus dose used by the child or young person may have been too low.

There was also consensus in the group that access to blood ketone testing strips was an issue in practice and therefore it was particularly important that recommendations were included in the 2015 update guideline despite the scarcity of the evidence.

6.13.8.3 Consideration of health benefits and resource use

An economic evaluation undertaken for the guideline update suggested there was a very high probability that blood ketone monitoring was more cost effective than urine ketone monitoring. Although the costs of testing are higher with blood ketone monitoring, this is more than offset by reduced treatment costs for DKA as a result of lower rates of hospitalisation.

6.13.8.4 Quality of evidence

The available evidence was of low quality. The guideline development group felt that it was reasonable to include the single study identified, even though it involved people over the age of 18 years, because: the oldest participants were aged 22 years; the young adults formed only a small proportion of the overall study population; there is little difference between the physiology of a young person aged 18 years and that of a young adult aged 20 years; and because of the paucity of evidence overall.

The group felt that, in most cases, there would be no significant difference in behaviour across the age range reflected in the study. Furthermore, they noted that the risk of ketosis increases with age, making it reasonable to assume that any observed effects would underestimate potential benefits or harms and therefore not be misleading.

The group also concluded that the fact that the investigators knew which method of testing the participants were using was not problematic because the outcomes being measured were not subject to observer bias.

6.13.8.5 Other considerations

The guideline development group noted that advice about ketone testing is given to children and young people with type 1 diabetes as part of a package of sick-day rules and that this was reflected in the wording of the recommendations in the 2004 guideline. However, they also noted that the 2004 recommendations incorporated guidance on short- and rapid-acting insulin analogues, the evidence base for which was not examined in the 2015 update review on ketone monitoring. As such, the guideline development group for the 2015 update decided to retain the existing advice about rapid-acting insulin analogues as a standalone recommendation and to provide new, more detailed guidance on sick-day rules that incorporated their advice on the use of blood ketone testing.

The group decided not to discuss short-acting insulin analogues in the updated recommendations at all because in their experience such preparations can lead to a build-up of insulin and hypoglycaemia.

The guideline development group felt that it was important for guidance on sick-day rules to be delivered in a way that does not discriminate against children and young people with type 1 diabetes and their family members or carers (as appropriate) who have difficulties related to language, literacy or numeracy. As part of this the group felt that it was appropriate that information should be presented both verbally and in written formats.

The group also agreed that it was important to review sick-day rules annually because in their experience written protocols are often lost and need to be re-issued. The group was aware that rules may need to be individualised and they may need to change over time. In the group's experience reiterating rules regularly improves adherence.

The objective of the review question for the 2015 update was to compare the clinical and cost effectiveness of blood ketone monitoring with urine ketone monitoring in the prevention or early detection of DKA in children and young people with type 1 diabetes. As the guideline development group was able to determine that blood ketone monitoring is cost effective compared with urine ketone monitoring the recommendation to monitor blood ketones during intercurrent illness or episodes of hyperglycaemia supersedes the 2004 recommendation for further research on this topic.

6.13.8.6 Key conclusions

The guideline development group recommended that healthcare professionals should offer children and young people with type 1 diabetes blood ketone testing strips and a meter, and advise them and their family members or carers (as appropriate) to test for ketonaemia if they are ill or have hyperglycaemia. The group also recommended that healthcare professionals should explain the importance of ensuring that blood ketone testing strips are not used after the 'use-by' date.

The guideline development group's considerations with regard to delivering guidance on sick-day rules in a way that does not discriminate against children and young people with type 1 diabetes and their family members or carers (as appropriate) who have difficulties related to language, literacy or numeracy is reflected in the overarching recommendations about offering a continuing programme of education for children and young people and their family members or carers (as appropriate), tailoring the programme to take account of issues including age, maturity and cultural considerations, and taking particular care when communicating with and providing information to those who have physical and sensory difficulties or difficulties speaking or reading English (see Section 5.7).

Recommendations specific to provision of oral and written advice for management of type 1 diabetes in children and young people during intercurrent illness (sick-day rules) are presented in Section 8.1.1. These include monitoring and interpreting of blood ketones (beta-hydroxybutyrate) being part of sick-day rules, and revisiting the advice with the child or young person and their family members or carers (as appropriate) at least annually.

6.13.9 Recommendations

The current recommendations can be found at https://www.nice.org.uk/guidance/ng18.

7 Management of type 1 diabetes – hypoglycaemia

7.1 Introduction

Hypoglycaemia is a significant cause of morbidity and mortality in patients with diabetes. The National Paediatric Diabetes audit has estimated that about 4% of children and young people aged under 17 years with type 1 diabetes experience 1 or more episodes of severe hypoglycaemia per year.[1] Although hypoglycaemia does not appear to cause long-term neuropsychological impairment in adults,[102,480] it may do so in children and young people[104] (see Section 9.4). Hypoglycaemia in children and young people should be avoided, particularly in those aged under 5 years.[481]

There is no consistent or agreed definition of hypoglycaemia. In theory, hypoglycaemia is the level of blood glucose at which physiological neurological dysfunction begins. In practice, neurological dysfunction can be symptomatic or asymptomatic, and the level at which it occurs varies between individuals, may vary with time and circumstance, and is affected by antecedent hypoglycaemia or hyperglycaemia. Symptoms usually occur in most people when the blood glucose level is less than 3.0 mmol/l, although for some it may be as low as 2.0 mmol/l or as high as 3.5 mmol/l.

Clinically, hypoglycaemia causes signs and symptoms of:

- autonomic activation (hunger, trembling of hands or legs, palpitations, anxiety, pallor, sweating)
- neuroglycopaenia (impaired thinking, change of mood, irritability, dizziness, headache, tiredness, confusion and, later, convulsions and coma).

The threshold for autonomic (counter-regulatory) activation has been shown to occur at a higher blood glucose level in children and young people than in adults. The threshold varies with level of metabolic control: poor control causes the threshold for autonomic activation to occur at a higher blood glucose level, whereas good control causes the threshold to occur at a lower blood glucose level. Autonomic activation may be lowered by antecedent hypoglycaemia and sleep.

The blood glucose threshold for cognitive impairment is usually between 2.6 and 3.5 mmol/l (plasma glucose 3.1 to 4.0 mmol/l). Neuroglycopaenia may occur before autonomic activation, causing hypoglycaemic unawareness.[15]

The severity of hypoglycaemia may be graded as follows.[15]

- Mild (grade 1): The patient is aware of, responds to and self-treats the hypoglycaemia. Children aged below 5 to 6 years can rarely be classified as having mild hypoglycaemia because they are usually unable to help themselves.
- Moderate (grade 2): The patient cannot respond to hypoglycaemia and requires help from someone else, but oral treatment is successful.
- Severe (grade 3): The patient is semi-conscious or unconscious or in a coma with or without convulsions and may require parenteral therapy (glucagon or intravenous glucose). (Some children and young people present with ‘stroke-like’ symptoms involving one-sided weakness and are unable to eat, drink or speak.)

7.2 What is the optimum treatment of mild to moderate hypoglycaemia in children and young people with type 1 diabetes?

Although mild to moderate hypoglycaemia is a major clinical problem and a major concern to children and young people and their families, there are surprisingly few clinical studies on the management of this condition.

7.2.1 Comparison of 10 g oral glucose, 20 g oral glucose, 1.0 mg subcutaneous glucagon and placebo

An RCT compared administration of 10 g oral glucose, 20 g oral glucose, 1.0 mg subcutaneous glucagon and placebo (n=6 adults). Compared with placebo, 10 g oral glucose, 20 g oral glucose and 1.0 mg subcutaneous glucagon produced significant, but transient, increments in plasma glucose levels; 20 g oral glucose treatment increased the plasma glucose to a significantly higher peak than 10 g oral glucose; 1.0 mg subcutaneous glucagon treatment increased the plasma glucose to a significantly higher peak than 10 g oral glucose or 20 g oral glucose treatment.[482] [evidence level Ib] A second RCT (n=41 adults) compared the correction of blood glucose levels and clinical symptoms of hypoglycaemia of 7 orally administered carbohydrates (glucose solution, glucose tables, glucose gel, sucrose solution, sucrose tablets, hydrolysed polysaccharide solution and orange juice). All carbohydrate types led to raised mean blood glucose levels after 20 minutes compared with baseline; there was some concern that glucose gel and orange juice did not increase plasma glucose as much as the other carbohydrate sources.[483] [evidence level Ib]

Examples of 10 g simple carbohydrate are:

- 55 ml of a high-energy glucose drink
- 100 ml of cola (not diet)
- 150 ml of lemonade (not diet)
- 23 g oral ampoule of Hypostop®
- three glucose tablets
- two teaspoons of sugar.

Milk, unsweetened fruit juice and fun-size chocolate bars are not absorbed as quickly, but they may be used because they are acceptable to children and young people.

Examples of complex long-acting carbohydrate are:

- one to 2 digestive biscuits
- an oat-based cereal bar
- bread and butter or a sandwich
- a bowl of cereal
- a piece of fruit.

7.2.2 Comparison of oral terbutaline sulphate, subcutaneous terbutaline, oral alanine and placebo

A small RCT compared administration of oral terbutaline sulphate, subcutaneous terbutaline, oral alanine and placebo in adults with type 1 diabetes with induced hypoglycaemia (n=6).[482] Compared with placebo, oral terbutaline, subcutaneous terbutaline and oral alanine produced significant sustained increments in plasma glucose levels. Subcutaneous

terbutaline increased plasma glucose to a significantly higher peak than oral terbutaline treatment.[482] [evidence level Ib]

We found no studies that looked at long-term implications.

7.3 What is the optimum treatment of severe hypoglycaemia in children and young people with type 1 diabetes?

A variety of treatments has been suggested for severe hypoglycaemia. These include oral glucose preparations, glucagon (nasal spray or intramuscular injection) and intravenous glucose solutions. Various studies have looked at the efficacy of different approaches.

Intravenous 10% glucose may be given in a dose of 5 ml/kg body weight into a large vein through a large-gauge needle. Care is required since glucose solution at this concentration is an irritant, especially if extravasation occurs. Close monitoring is necessary in the case of an overdose with long-acting insulin because further administration of glucose may be required[133] and electrolytes, particularly potassium, may become disturbed.

Glucagon is a polypeptide hormone produced by the alpha cells of the islets of Langerhans. It increases plasma glucose concentration by mobilising glycogen stored in the liver. It can be injected by any route (intramuscular, subcutaneous or intravenous), but the intramuscular route is preferred in circumstances when an intravenous injection of glucose would be difficult or impossible to administer. Glucagon may be issued to close relatives of insulin-treated patients for emergency use in hypoglycaemic attacks. It is often advisable to prescribe glucagon on an 'if necessary' basis for hospitalised insulin-treated patients, so that it may be given rapidly by nurses during a hypoglycaemic emergency. If not effective in 10 minutes, intravenous glucose should be given. Children and young people over 8 years old (or body weight of 25 kg or more) should be given 1 mg; children under 8 years old (or body weight under 25 kg) should be given 500 µg; if there is no blood glucose response within 10 minutes, intravenous glucose must be given.[133]

Eight RCTs have investigated treatment of severe hypoglycaemia in patients with type 1 diabetes. The studies examined a range of treatments, including intramuscular glucagon, subcutaneous glucagon, intravenous glucagon, intranasal glucagon, intravenous glucose (dextrose monohydrate) and intramuscular epinephrine. The studies are described below.

7.3.1 Intramuscular glucagon compared with intravenous glucose

Two RCTs have compared administration of intramuscular glucagon with intravenous glucose.

The first RCT compared intramuscular administration of 1 mg glucagon with 50 ml 50% intravenous glucose in insulin-treated adult patients with hypoglycaemic coma (n=29).[484] Significantly slower recovery to normal consciousness was observed in the glucagon treatment group compared with the glucose treatment group, and 2 of the glucagon patients required administration of additional intravenous glucose after failure to show signs of clinical recovery within 15 minutes of treatment. [evidence level Ib]

The second RCT compared administration of 1 mg intramuscular glucagon with 50 ml of 50% glucose administered intravenously in adults with severe hypoglycaemia (n=14).[485] Recovery time ranged from 8 to 21 minutes for those receiving intramuscular glucagon and 1 to 3 minutes for those receiving intravenous glucose. [evidence level Ib]

7.3.2 Intravenous glucagon compared with intravenous glucose

An RCT compared intravenous administration of 1 mg glucagon to 50 ml of 50% glucose in insulin-treated adult patients with hypoglycaemic coma (n=49).[486] Significantly slower

recovery to normal consciousness was reported in the glucagon treatment group compared with the glucose treatment group. [evidence level Ib]

The consensus view of healthcare professionals is that 10% is the maximum strength of intravenous glucose that should be given to children and young people.

7.3.3 Intravenous glucagon compared with intramuscular glucagon

Two RCTs have compared administration of intramuscular glucagon with intravenous glucagon.

The first RCT compared administration of 1 mg intramuscular glucagon with 1 mg intravenous glucagon in insulin-treated patients with hypoglycaemia (n=99, including 20 aged under 20 years).[487] No significant difference was seen between the treatment groups in terms of the number of patients who were either awake or sufficiently roused to take oral glucose within 15 minutes of treatment. [evidence level Ib]

The second RCT compared administration of 1 mg intramuscular glucagon with 1 mg intravenous glucagon in adults with induced hypoglycaemia (n=15).[488] There was a significantly higher increase in plasma glucose for the intramuscular group than the intravenous group 20 and 40 minutes after treatment. [evidence level Ib]

7.3.4 Intramuscular glucagon compared with subcutaneous glucagon

An RCT compared administration of intramuscular glucagon to subcutaneous glucagon in children and young people with induced hypoglycaemia (n=30).[489] No difference was found between blood glucose or plasma glucagon concentrations in children and young people treated with intramuscular glucagon or subcutaneous glucagon at 20 µg/kg body weight. [evidence level Ib]

7.3.5 Intranasal glucagon compared with subcutaneous glucagon

Two RCTs have compared administration of intranasal glucagon with subcutaneous glucagon.

The first RCT compared administration of intranasal glucagon to subcutaneous glucagon in children and young people with induced hypoglycaemia (n=12).[490] No significant difference in blood glucose at 15 minutes was seen between the treatment groups. However, by 45 minutes there was a significantly higher increase in plasma glucose in the subcutaneous treatment group than in the intranasal treatment group. This study reported nausea in more than 90% of children and young people receiving subcutaneous treatment and less than 10% of those receiving intranasal treatment. Mild nasal irritation was recorded in four children and young people who received intranasal treatment. [evidence level Ib]

The second RCT compared administration of intranasal glucagon with subcutaneous glucagon in adults with induced hypoglycaemia (n=6).[491] No significant difference in the plasma glucose profile was seen between the 2 treatment groups. [evidence level Ib]

7.3.6 Intranasal glucagon compared with intramuscular glucagon

An RCT compared administration of intranasal glucagon with intramuscular glucagon in adults with metabolic decompensation (n=30).[492] The mean rise of blood glucose levels was greater with intramuscular than intranasal glucagon. [evidence level Ib]

Combined treatment of intravenous glucose and intramuscular glucagon compared with intravenous glucose alone

An RCT compared combined treatment of intravenous glucose and intramuscular glucagon to intravenous glucose alone in adults with hypoglycaemia (n=18).[493] No significant difference in the plasma glucose profile was seen between the 2 treatment groups. [evidence level Ib]

7.3.7 Intramuscular epinephrine compared with intramuscular glucagon

An RCT compared administration of intramuscular epinephrine with intramuscular glucagon in children and young people with induced hypoglycaemia (n=10).[494] [evidence level Ib] Administration of epinephrine was significantly less effective than glucagon in reversing the decrease in plasma glucose. There was a significantly higher peak hypoglycaemia score for epinephrine than glucagon. Nine out of 10 children and young people complained of severe nausea 2 to 6 hours after taking glucagon.

7.3.8 Concentrated oral glucose

Concentrated oral glucose solutions can be administered in the event of a severe hypoglycaemic episode. (Hypostop® is a commercially available solution.) Concern has been raised that administration of such a solution is dangerous in the semi- or fully-unconscious patient, with a possibility of inhalation of glucose solution. No clinical studies have been performed, but the issue has been debated in the medical literature with a strong lobby that Hypostop® appears to be safe in practice.[495] [evidence level IV]

7.4 Long-term effects of hypoglycaemia

Evidence relating to cognitive function following hypoglycaemia is presented in Section 9.4.

7.5 Recommendations

The current recommendations can be found at https://www.nice.org.uk/guidance/ng18

8 Management of type 1 diabetes in special circumstances – during intercurrent illness or surgery

8.1 Intercurrent illness

Illness associated with fever tends to raise blood glucose due to higher levels of stress hormones, gluconeogenesis and insulin resistance. Illness associated with vomiting and diarrhoea (for example, gastroenteritis) may lower blood glucose and possibility cause hypoglycaemia.[15]

We found no studies that evaluated advice for treatment of intercurrent illness in children and young people with type 1 diabetes.

A consensus guideline provided the following guidance regarding management of children and young people with type 1 diabetes during intercurrent illness.[15] [evidence level IV]

The diabetes care team should provide clear guidance on managing diabetes during intercurrent illness to avoid the complications of dehydration, ketoacidosis and hypoglycaemia. Guidance should include the following:

- Never stop insulin.
- Advice should be available on alterations of insulin dose.
- When to contact the diabetes care team, general practitioner or hospital.

More frequent monitoring:

- Frequent blood glucose testing (at least 4 times daily) with appropriate changes to insulin dose facilitates optimal management during illness.
- Urinary ketone tests will guide management.
- Adequate supplies of blood glucose and ketone test strips should be available to avoid complications during intercurrent illness.

Loss of appetite:

- Replace meals with easily digestible food and sugar-containing fluids.

Maintaining hydration:

- Hyperglycaemia, fever and excessive glycosuria increase fluid loss.
- Encourage frequent intake of fluids, for example, water or reduced sugar fluids.

Specific medical advice:

- Treat fever, malaise and headache with antipyretics such as paracetamol.
- Vomiting may be caused by the illness itself (when blood glucose may be low) or lack of insulin (when blood glucose will be high and ketones may develop).
- Consider treatment of vomiting with a single injection of an anti-emetic to help oral intake of carbohydrate.
- Sugar-free medicines for children and young people are advisable but not essential.
- Infection associated with hyperglycaemia with or without ketosis:
- Recommend additional doses of short or rapid-acting insulins with careful monitoring to reduce blood glucose, prevent ketoacidosis and avoid hospital admission.

- The dose and frequency of insulin injections will depend on the age of the child, the level and duration of hyperglycaemia, the severity of ketosis and previous experience with alterations of insulin.
- For example, for a sick child, blood glucose 15 to 20 mmol/l with or without ketosis, advise to take 10 to 20% of total daily insulin dose (or 0.1 units/kg body weight) as short- or rapid-acting insulin analogue every 2 to 4 hours until blood glucose falls to <15 mmol/l. Thereafter any additional doses might be 5 to 10% of the total daily dose.

Infections associated with hypoglycaemia:

- These infections are often associated with nausea and vomiting with or without diarrhoea.
- Advise replacing meals with frequent small volumes of sugary drinks and careful blood glucose monitoring.
- Reduction of insulin dosage by 20 to 50% may be required.
- If hypoglycaemia (and nausea or food refusal) persists, an injection of glucagon may reverse the symptoms of hypoglycaemia and enable oral fluids to be re-established.

In a child or young person with intercurrent illness, urgent specialist medical or nursing advice must be obtained when:

- the diagnosis is unclear
- vomiting is persistent (particularly in children)
- blood glucose continues to rise despite increased insulin requirements
- hypoglycaemia is severe
- ketonuria is heavy and persistent
- the child becomes exhausted or confused, is hyperventilating or dehydrated, or has severe abdominal pain.

When metabolic control is persistently unsatisfactory or if blood glucose monitoring is inadequate or unavailable, intercurrent infections may be more frequent and more severe. In such situations:

- Advise more frequent urinary glucose and ketone testing
- Give clear guidance on alterations of insulin dosage to prevent ketoacidosis.

If sudden repeated episodes of hyperglycaemia with vomiting occur, it should be recognised that this may be due to omission or inadequate administering of insulin.

This section of the 2004 guideline included a recommendation to offer clear guidance and protocols (‘sick day rules’) for children and young people with type 1 diabetes during intercurrent illness. The guideline development group for the 2015 update replaced this recommendation with a more specific recommendation highlighting the need during intercurrent illness and episodes of hyperglycaemia for monitoring of blood glucose and blood ketones (rather than urine ketones as reflected in the guidance reviewed above as part of the 2004 guideline) and for adjustment, if necessary, of insulin and food and fluid intake and when and where to seek further advice or help. This was considered important because such advice could reduce the risk of diabetic ketoacidosis (DKA).

8.1.1 Recommendations

The current recommendations can be found at https://www.nice.org.uk/guidance/ng18

8.2 Surgery

We found no studies that investigated the management of children and young people with type 1 diabetes before, during or after surgery.

A consensus guideline made the following recommendations regarding children and young people with type 1 diabetes who require surgery or fasting.[15] [evidence level IV]

Children and young people with type 1 diabetes who require surgery:

- should be admitted to hospital for general anaesthesia
- require insulin, even if they are fasting, to avoid ketoacidosis
- should receive glucose infusion when fasting before an anaesthetic to prevent hypoglycaemia.

Elective surgery:

- Operations are best scheduled early on the list, preferably in the morning.
- Admit to hospital the afternoon prior to surgery for morning and major operations, or early morning for minor operations later in the day.
- Earlier admission is important if glycaemic control is poor.
- Admission should be to a paediatric diabetes or paediatric surgical ward.

Evening prior to elective surgery:

- Frequent blood glucose monitoring is important especially before meals and snacks and before bedtime (and urinary ketones should be checked).
- The usual evening or bedtime insulin(s) and a bedtime snack should be given.
- Ketosis or severe hypoglycaemia will necessitate correction, preferably by overnight intravenous infusion, and might cause delay in surgery.

Morning operations:

- No solid food from midnight.
- Clear fluids may be allowed up to 4 hours pre-operatively (this should be checked with the anaesthetist).
- Omit usual morning insulin dose.
- Start intravenous fluid and insulin infusion at 6.00 to 7.00 a.m.
- Hourly blood glucose monitoring pre-operatively, then half-hourly during operation and until woken from anaesthetic.
- Hourly blood glucose monitoring 4 hours post-operatively.
- Aim to maintain blood glucose between 5 and 12 mmol/l.
- Continue intravenous infusion until the child or young person tolerates oral fluids and snacks (this may not be until 24 to 48 hours after major surgery).
- Change to usual subcutaneous insulin regimen or short-acting insulin/rapid-acting insulin analogue before the first meal is taken.
- Stop insulin infusion 60 minutes after subcutaneous insulin is given.
- For minor operations it may be possible to discharge from hospital after the evening meal if the child is fully recovered.

Afternoon operations:

- Give one-third of the usual morning insulin dose as short-acting insulin if the operation is after midday.
- Allow a light breakfast.
- Clear fluids may be allowed up to 4 hours preoperatively.
- Start intravenous fluids and insulin infusion at midday at the latest.
- Then as for morning operations (see above).

Emergency surgery:

- Diabetic ketoacidosis may present as ‘acute abdomen’.
- Acute illness may precipitate diabetic ketoacidosis (with severe abdominal pain).
- Nil by mouth.
- Secure intravenous access.
- Check weight, electrolytes, glucose, blood gases and urinary ketones pre-operatively.
- If ketoacidosis is present, follow protocol for diabetic ketoacidosis and delay surgery until circulating volume and electrolyte deficits are corrected.
- If there is no ketoacidosis, start intravenous fluid and insulin infusion as for elective surgery.

Minor procedures requiring fasting:

- For short procedures (with or without sedation or anaesthesia) and when rapid recovery is anticipated, a simplified protocol may be organised by experienced diabetes/anaesthetic personnel and may include either early morning procedures (for example, 8.00 to 9.00 a.m.) with delayed insulin and food until immediately after completion, or reduced usual insulin dose (or give repeated small doses of short/rapid-acting insulin).
- Glucose 5 to 10% infusion and frequent blood glucose monitoring are recommended in all these situations.

8.2.1 Recommendations

The current recommendations can be found at https://www.nice.org.uk/guidance/ng18

9 Psychological and social issues in children and young people with type 1 diabetes

9.1 Introduction

This section was updated in 2015.

This section of the guideline addresses the following psychological and social issues relevant to children and young people with type 1 diabetes:

- emotional and behavioural problems
- anxiety and depression
- eating disorders
- cognitive disorders
- behavioural and conduct disorders
- non-adherence
- psychological interventions
- adolescence
- advice on alcohol, smoking and recreational drugs.

For the 2015 update a specific review question on the effectiveness of psychological interventions to improve outcomes in children and young people with type 1 diabetes was considered. The evidence identified in relation to this review question and the guideline development group's interpretation of the evidence are presented in Section 9.8. This review has replaced and updated the 2004 guideline evidence review that was presented under the heading 'Psychosocial support'. The remaining contents of the 2004 guideline evidence reviews that related to psychological and social issues in children and young people with type 1 diabetes are retained in Section 9.2 to Section 9.7, Section 10.9 and Section 9.10.

The 2004 recommendations related to monitoring for associated conditions and complications, and the recommendations arising from the 2015 update, are presented together in Section 9.11.

9.2 Emotional and behavioural problems

Achieving good metabolic control through insulin injections, blood glucose and dietary monitoring is the cornerstone of diabetes care in preventing both short- and long-term complications. However, optimal care requires appropriate attention to psychological and psychosocial issues that also affect the management and care of type 1 diabetes in children and young people. Conditions such as depression, disordered eating, cognitive and behavioural disorders may pre-date the onset of diabetes or present during the course of illness. There are additional challenges when diabetes develops in children and young people with pre-existing emotional and psychological difficulties, such as severe conduct or attachment difficulties, autism spectrum disorder or family dysfunction. Identification and management of psychological and social issues related to chronic disease care and overall patient wellbeing are best addressed in a partnership between paediatric and child mental health services.

Diagnosis of a chronic condition such as type 1 diabetes may be accompanied by a period of denial followed by gradual acceptance during which feelings of grief, stress and difficulty in

coping may be experienced. Questions pertinent to children and young people with type 1 diabetes and their families are whether the initial emotional response to diagnosis disappears, whether beneficial family dynamics exist (for example, family cohesion), and how age at diagnosis affects children and young people and their families.

Elements of family adaptation to chronic illness include the family system, a stressful event requiring adaptation, familial knowledge, skills and resources, and use of coping strategies.[565] [evidence level IV]

Elements of family environment and glycaemic control were investigated in children and young people (age range 9 to 16 years) and their mothers.[566] [evidence level IIb] Children and young people with the least open and expressive families (as reported by children and young people and their mothers) demonstrated a greater deterioration in glycaemic control ($p \leq 0.01$ as reported by mothers and $p \leq 0.006$ as reported by children and young people). Males from less cohesive families and those with greater conflict showed a decline in HbA1c levels over 4 years compared with females ($p \leq 0.01$).

We found 1 study that addressed the emotional difficulties children and young people experienced in association with controlling diabetes (n=60, age range 9 to 18 years).[567] [evidence level III]

A 10-year follow-up study measured the effect of diabetes on self-esteem in 57 children and young people with diabetes and 54 children and young people with acute illnesses.[568] [evidence level IIb–III] When controlled for sex and socio-economic status there was no difference in self-esteem scores between the children and young people with diabetes and children and young people with acute illnesses after 10 years. However, significant differences in perceived competence, global self-worth and sociability were reported ($p \leq 0.006$).

Two studies have investigated the wellbeing of parents of children and young people with type 1 diabetes. A Swiss study of 38 children and young people revealed that 24% of mothers and 22% of fathers had features of post-traumatic stress syndrome within 6 weeks of their child's diagnosis.[569] [evidence level III] Evidence for an indirect relationship between family support and depressive symptoms in mothers of 52 children and young people with type 1 diabetes (mean duration 2.7 years) was found in a predictive modelling study.[570] [evidence level III]

In children under the age of 3 years who present with type 1 diabetes the high level of dependence on their parents presents an increased psychosocial burden to the family.[571] [evidence level III] Themes relating to stress, coping with the diagnosis, hospitalisations, and long-term management adaptation were common among participating parents. Concerns for their own wellbeing (emotional responses and depression) were expressed.

An evidence-based guideline reported that the following factors contributed to an increased risk of children and young people with type 1 diabetes developing psychological problems:[9] [evidence level IV]

- avoidance of coping strategies
- increased responsibility given to the child
- family dysfunction
- non-effective communication between the family and health professionals
- low socio-economic status
- single parent families
- maternal morbidity (particularly psychological morbidity).

9.3 Anxiety and depression

Depression is a collection of physical, cognitive, affective and attitudinal symptoms that can often go unrecognised when associated with other medical conditions. Depression or depressive episodes could be the cause of, or result from, poor glycaemic control. Psychosocial factors may play a role in the occurrence of depression when patients and their families become overwhelmed by the daily demands of type 1 diabetes management and care.

9.3.1 Prevalence

In 2000, the Office for National Statistics surveyed the prevalence of mental health problems in children and young people aged 5 to 15 years living in Great Britain: 5% had clinically significant conduct disorders and 4% suffered from emotional disorders (anxiety and depression).[572] [evidence level III] In comparison, prevalence of depression among children and young people with type 1 diabetes ranged from 2 to 3 times that of young people without diabetes.[573] Correlates of depression in this population may include age, duration of diabetes and sex.

A cross-sectional study estimated that 14.5% of children and young people aged 9 to 18 years who had had type 1 diabetes for at least 2 years had suffered from depression.[574] [evidence level III]

A cohort study conducted in the USA found increased rates of depression among 14 to 16 year-olds (25%) and among those who had diabetes for at least 10 years (23%), compared with an overall rate of 15.4% among the 97 participants (aged 12 to 20 years) in the study.575 [evidence level IIb] After 2 years of follow-up, 59% of the patients reported a depression rate of 10%. These patients had significantly higher HbA1clevels than patients with no depression symptoms (9.0 ±0.85% versus 8.3 ±1.4%, p=0.03).

Studies based on adults with type 1 diabetes have shown an association between poor glycaemic control and increased risk of depressive disorders.[576,577] [evidence levels III–IV]

Evidence from a small (n=16) descriptive study of young people with type 1 diabetes (age range 15 to 18 years) demonstrated a positive correlation between social support and family emotional health ($r=0.46$, $p<0.05$).[578] [evidence level III] Depression was positively correlated with deteriorating glycaemic control ($r=0.51$, $p<0.05$), and 62.5% of participants reported experiencing moderate to high stress.

These 2 studies recruited patients from hospital clinics and they used different cut-off scores of the Children's Depression Inventory (≥ 15 versus ≥13) to define depression. Although this test was originally devised in Australia and has a small standardisation sample, it is widely used in childhood depression studies.

Another study prospectively followed 85 sequential admissions to a diabetes inpatient clinic for 5 years.[579] [evidence level IIb] Patients were aged 8 to 13 years and 16% had a psychiatric disorder predating the onset of diabetes. Major depressive disorder and/or dysthymia (milder depressive symptoms with longer duration) were reported in 26.1% of the study population. The cumulative probability of any depression occurring during a 10-year period was 27.5%. Diagnosis of depression was based on the Interview Schedule for Children and Adolescents. Maternal depression was also found to be a significant risk factor for depression in children and young people ($r=0.97$, $p=0.02$). Maternal psychopathology was determined by the Beck Depression Inventory using a cut-off score of ≥ 16.

The relationship between suicide ideation (suicidal thoughts) and attempted suicide with the occurrence of depressive symptoms, anxiety and severity of illness at diagnosis has also been investigated.[580] [evidence level IIb] Retrospective ascertainment of suicide ideation among 95 inpatients aged 8 to 13 years yielded an overall prevalence of 21.1%. The initial

prevalence of suicide ideation was 29.5% at study intake, and reached 46% during follow-up. Severity of depression was significantly related to a history of suicide ideation (p<0.004), and those with suicide ideation were less likely to adhere to insulin regimens than other children (p<0.003). Time intervals between assessments varied across patients. The Interview Schedule for Children and Adolescents was used to measure outcomes.

We found evidence that grief and anxiety related to a diagnosis of diabetes reported by children and young people was less marked than that reported by parents (p<0.05).[581] [evidence level IIb] Among children and young people aged ≥ 6 years, maternal stress and reaction increased the odds of poor metabolic control (OR 1.3, p<0.01).

A cross-sectional study found that increased HbA1cat the time of interview was associated with increased stress (rank correlation r=0.554, p<0.001) as perceived by the mother. Family social support was not directly related to HbA1c, but increased levels of support buffered the effects of family-life stress.[582] [evidence level III]

9.3.2 Methods of identifying depression

We found no studies that compared methods of detecting depression or depressive episodes in children and young people with type 1 diabetes.

Instruments used to identify depression are either symptom-based rating scales or diagnostic interviews. The studies which examined prevalence of depression in children and young people with type 1 diabetes used several instruments to measure outcome: criteria based on the Diagnostic Statistical Manual (DSM III or IV), the Children's Depression Inventory, the Interview Schedule for Children and Adolescents, the Beck Depression Inventory, and the Hamilton Depression Rating Scale.

9.3.3 Methods of managing depression

The aim of diabetes management is to maintain glucose levels within the normal range, thus preventing or reducing the severity of associated complications. Co-morbid depressive symptoms or episodes in children and young people with type 1 diabetes may exist, irrespective of glycaemic control, because of the demanding nature of diabetes management on the individual and family.

Methods of managing depression in adults with diabetes have included blood glucose awareness training to improve mood, antidepressant medication (tricyclics and selective serotonin re-uptake inhibitors), patient education and cognitive behavioural therapy.[583–585] [evidence level Ib–IIb] An evidence-based guideline has recommended screening for depression among adults with diabetes, increased awareness among healthcare professionals, and the use of selective serotonin re-uptake inhibitors to treat adults with depression.[9] [evidence level IV] However, the Medicines and Healthcare products Regulatory Agency recently advised that the antidepressants paroxetine and venlafaxine (selective serotonin re-uptake inhibitors) should not be prescribed to people under the age of 18 years; other modern antidepressants are not excluded.

A systematic review investigated the effectiveness of tricyclic antidepressant use in children and young people without diabetes.[586] [evidence level Ia] Thirteen trials with a total of 506 children and young people were included. Compared with placebo, tricyclic antidepressants showed no overall improvement (pooled OR 0.84, 95% CI 0.56 to 1.25, n=454, for 9 studies). The OR for young people was 0.85 (95% CI 0.54 to 1.34), whereas the OR for children was 0.69 (95% CI 0.25 to 1.89). These results indicate marginal evidence of an effect in young people, but not in the treatment of pre-pubertal children. Given the adverse effects of tricyclic antidepressants (cardiotoxicity) and their potential for fatality in overdose, caution in prescribing is warranted, as is encouragement to seek help from a child mental health professional.

We found no studies that measured the effectiveness of cognitive behavioural therapy or antidepressant medication specifically for depression among children and young people with type 1 diabetes. However, cognitive behavioural therapy in populations of depressed children and young people without diabetes (aged 8 to 19 years) has been shown to be effective.[587,588] [evidence level Ia]

In adults, successful treatment of depression includes changes in dietary and exercise habits; this could affect blood glucose monitoring and insulin injections in children and young people with type 1 diabetes. These potential interactions should be considered when choosing medical therapy for children and young people with type 1 diabetes.[576] [evidence level IV]

9.3.4 Suitable professionals to advise on management

We found no studies that identified the specific type of healthcare professional for advising children and young people with type 1 diabetes about managing depression.

A consensus guideline has recommended training for diabetes care teams to aid in the recognition of, and counselling for, psychological problems.[15] [evidence level IV] The guideline states that overt psychological disorders should receive support not only from the diabetes care team, but also from a child mental health professional who has been trained to advise children and young people and their families.

The NICE clinical guideline 28 was published in 2005[e] and is currently scheduled for update with publication due in December 2015.

9.4 Eating disorders

Type 1 diabetes in association with eating disorders can cause acute subsequent long-term physical complications.[589] [evidence level IV]

A systematic review of case–control studies in young people and adults suggested that the prevalence of anorexia nervosa was not increased in people with type 1 diabetes; however, the power of the studies may be insufficient to rule out a higher prevalence.[590] [evidence level III]

Patients with type 1 diabetes and anorexia nervosa have an increased mortality rate compared with patients with type 1 diabetes alone (premature death OR 20.39, 95% CI 6.6 to 38.3, p<0.001, n=510 young women with type 1 diabetes and n=658 young women without type 1 diabetes).[591] [evidence level III]

Bulimia nervosa is over-represented in people with type 1 diabetes. A systematic review of case–control studies of children, young people and female adults with type 1 diabetes compared with those without type 1 diabetes showed an increased prevalence of bulimia nervosa (OR 3.12, 95% CI 1.24 to 7.9, p=0.024, based on 8 studies with n=727 patients with type 1 diabetes and n=1499 without type 1 diabetes), eating disorders not otherwise specified (OR 1.8, 95% CI 1.3 to 2.7, p=0.0009, based on 7 studies with n=686 patients with type 1 diabetes and n=1457 without type 1 diabetes), and sub-threshold eating disorders (OR 1.9, 95% CI 1.3 to 2.6, p=0.0002, based on 4 studies with n=542 patients with type 1 diabetes and n=1307 without type 1 diabetes).[590] [evidence level III]

The rate of bulimia nervosa, established by eating disorders inventory questionnaire, has been shown by an observational study to be no higher in young women than young men with type 1 diabetes (age range 11 to 19 years, male mean rate of bulimia 0.7, SD 1.8, n=65 versus female mean 1.8, SD 3.3, n=79, p<0.16).[592] [evidence level III]

[e] www.nice.org.uk/guidance/CG28

Patients with diabetes may be tempted to restrict insulin intake in order to lose calories. A systematic review of case–control studies in children, young people and adults showed that omission or intentional under-dosing of insulin (so-called 'insulin purging') was increased in patients with type 1 diabetes and eating disorders compared with type 1 diabetes alone (OR 2.6, 95% CI 7.8 to 21.1, n=171 patients with eating disorders and type 1 diabetes and n=560 patients with type 1 diabetes alone). Insulin purging leads to poor glycaemic control and an increased risk of medical complications.[589] [evidence level IV] Another systematic review of studies involving young people and adults found an increased level of retinopathy in patients with type 1 diabetes and eating disorders compared with patients with type 1 diabetes alone (OR 4.8, 95% CI 3.0 to 7.8, p<0.00001, n=171 patients with eating disorders and type 1 diabetes and n=560 patients with type 1 diabetes alone).[590] [evidence level III]

A study in young people has shown an association between eating disorders and deteriorating glycaemic control. A multiple regression analysis showed an association between bulimia score and HbA1c (regression coefficient β=0.19, t=1.70, p=0.09, n=152).[592] [evidence level III] However, a second study involving adults found no significant difference in glycaemic control between patients with type 1 diabetes and eating disorders (n=18) and patients with type 1 diabetes alone (n=341). This may have been due to the small number of patients with type 1 diabetes and eating disorders.[593] [evidence level III]

The co-existence of type 1 diabetes and eating disorders presents challenges not only for physical management but also for psychological treatment. One of the goals of cognitive behavioural therapy for bulimia nervosa is to relax control over eating and this can conflict with the nutritional advice given to people with diabetes.[594] [evidence level III] On the other hand it is most important that these patients are helped to overcome their eating disorders, given the associated physical complications.[589] [evidence level IV]

An RCT compared psycho-education with 'standard care' for people with type 1 diabetes and bulimia nervosa. Eighty-five young women who attended a paediatric diabetes clinic and who showed evidence of disturbed eating attitudes or behaviour were randomised to psycho-education or standard care (aged 12 to 19 years). Assessments were conducted before and after treatment, and after 6 months of follow-up. An intention-to-treat, group by time multivariate analysis of variance indicated significant reductions following psycho-education on the Restraint and Eating Concern subscale of the Eating Disorder Examination, and on the Drive for Thinness and Body Dissatisfaction subscales of the Eating Disorder Inventory, but no improvement in frequency of purging by insulin omission (mean 2.0, SD 5.0 insulin omission days at baseline and mean 1.3, SD 5.6 at 6 months follow-up) or HbA1c levels (mean at baseline 9.2%, SD 1.6% and 9.3%, SD 1.7% at 6 months follow-up). Psycho-education was associated with a reduction in eating disturbance, but not with improved metabolic control.[595] [evidence level Ib]

The NICE clinical guideline 9, Eating disorders: Core interventions in the treatment and management of anorexia nervosa, bulimia nervosa and related eating disorders complements this guideline.[589]

9.4.1 Summary

Young women with type 1 diabetes have an increased risk of bulimia nervosa and other eating disorders, and poor adherence to insulin treatment is common. The co-existence of type 1 diabetes and eating disorders complicates psychological interventions. Psycho-education may have a limited benefit on eating disorder symptoms, but not on glycaemic control. In the management of people with type 1 diabetes and bulimia nervosa, close liaison and a shared knowledge-base between the eating disorder and diabetes teams is essential.[589] [evidence level IV]

9.5 Cognitive disorders

Patient-related characteristics and fluctuations in glycaemic control may cause cognitive impairment in children and young people with type 1 diabetes. Some studies have shown that subtle neurocognitive dysfunction may occur if diabetes onset occurs before the age of 5 years, or if a child suffers from hypoglycaemia-induced seizures.[596–600] [evidence level IIb–III]

A case–control study compared academic achievement in children with type 1 diabetes (n=244, mean age 14.8 ±3.2 years), a sibling control group (n=110) and a matched classmate control group (n=209).[601] [evidence level III] The study found that current academic performance among children and young people with type 1 diabetes was at least as good as those among siblings and matched classmates. Children and young people with type 1 diabetes performed better than their siblings on mathematics (mean standardised achievement score 115.0 versus 111.1, p<0.02) and reading, language and mathematics combined (mean standardised achievement score 113.9 versus 110.5, p<0.04) and better than their matched classmates on reading (mean standardised achievement score 108.9 versus 106.8, p<0.04). The study found lower achievement in children and young people with type 1 diabetes who had poor metabolic control than those with average control.[602] [evidence level III] Socio-economic status and parent-reported ratings of behavioural problems were correlated with academic achievement, whereas HbA1clevels, hospitalisations for hypoglycaemia and hospitalisations for hyperglycaemia were not strong predictors of academic achievement.

Evidence from an early cross-sectional study showed that median intelligence quotient (IQ) scores were significantly lower among children and young people with early onset of diabetes (age <7 years) and a longer duration (≥5 years) of diabetes (p<0.05).[596] [evidence level III]

An Oxford-based study compared cognitive processing and mood among 29 children and young people who suffered from 1 nocturnal hypoglycaemic episode.[603] [evidence level III] No significant differences in cognitive processing were found among the 17 children and young people who experienced 1 night with hypoglycaemia and 1 night without. However, median scores for mood (Children's Depression Inventory) were higher after 1 night of hypoglycaemia (median 5, range 2 to 8.5 versus median 3, range 1.5 to 6.5, p=0.03).

A Finnish study found significantly lower scores for phonological and memory processes in children with a history of hypoglycaemia compared with children with no history of hypoglycaemia (p<0.05 and p<0.01, respectively). Scores relating to attention processes were significantly lower in children who did not experience hypoglycaemia (p<0.05). However, multiple comparisons were made between children with type 1 diabetes and at least 1 episode of severe hypoglycaemia (n=11), children with type 1 diabetes, but no history of hypoglycaemia (n=10) and children without type 1 diabetes (n=10).[599] [evidence level III]

The studies conducted in Oxford and Finland produced conflicting results. Both studies were small, and the sources of children for comparison were children of hospital staff or friends/siblings of children with a history of hypoglycaemia. Also, ORs were not estimated, and comparisons were made within groups of children with a history of hypoglycaemia, rather than between these groups and the children with no history of hypoglycaemia.

The DCCT examined the cognitive abilities of patients who had no hypoglycaemic episodes compared with patients who had 5 or more hypoglycaemic episodes since the start of the study. No significant difference was seen in the cognitive score for general ability, or in separate cognitive scores for spatial ability, processing speed, verbal ability, memory and finger tapping.[604] [evidence level III]

A case–control study in children and young people with type 1 diabetes found no association between severe hypoglycaemia and cognitive function (n=142, age range 6 to 15 years).[605] [evidence level III]

A case–control study in California in children with type 1 diabetes (n=55, age range 5 to 10 years) found no association between neurocognitive test scores and hypoglycaemia, but subjects with a history of hypoglycaemic seizures had lower scores on tests assessing memory skills, including short-term memory ($p<0.03$).[606] [evidence level III]

A case–control study in Norway compared children and young people with type 1 diabetes (n=15, age range 9 to 16 years) to healthy children and young people matched for age, gender and social background. The study found no difference in cognitive performance between the 2 groups. However, among children and young people who had experienced an episode of severe hypoglycaemia, those with onset of diabetes before the age of 5 years had lower psychomotor efficiency scores than those with onset of diabetes after the age of 5 years.[607] [evidence level III]

A case–control study in Indianapolis of children with type 1 diabetes (n=23, age 5.9 ±1.8 years) found no association between hypoglycaemia and results of the Stanford–Binet Intelligence Scale. However, the relative frequency of asymptomatic hypoglycaemia correlated with scores on the abstract/visual reasoning scale.[608] [evidence level III]

A cross-sectional study of 28 children and young people (mean age 12.6 years) examined age at onset of diabetes, duration of diabetes and metabolic control in relation to cognitive function.[597] [evidence level III] Increasing chronological age was associated with decreasing full-scale IQ ($p<0.004$), arithmetic and verbal fluency ($p<0.005$), and block design ($p<0.01$), implying that longer duration of diabetes carried an increased risk of cognitive dysfunction.

Vocabulary aspects of cognition were found to differ significantly between diagnosis and 1-year follow-up among 63 children and young people with diabetes (mean age 7.3 years, $p<0.05$).[609] [evidence level IIb–III] Two years after the onset of diabetes, 116 children and young people aged 3 to 14 years showed significantly lower scores in vocabulary ($p<0.01$), block design ($p<0.05$), auditory verbal learning ($p<0.01$) and speed of processing tasks ($p<0.05$) compared with 112 children and young people without type 1 diabetes.[610] [evidence level IIb–III] These results suggest that smaller cognitive developmental gains occur in children and young people with type 1 diabetes.

Verbal IQ, adjusted for age, declined significantly among 16 children who experienced hypoglycaemic seizures (67%) compared with those who did not (14%).[598] [evidence level IIb–III] Children with a history of seizures also scored significantly lower than children without type 1 diabetes in cognitive aspects of perception, fine motor skills, visuomotor, visual memory and attention ($p<0.01$). Deterioration in age-adjusted verbal IQ over the first 7 years of diabetes was not associated with hyperglycaemia, early age at onset or family background factors.

A small crossover RCT assessed the effects of hyperglycaemia on cognitive function.[611] [evidence level Ib] Twelve children and young people (mean age 12.4 years) were randomised to a euglycaemic state and then to a hyperglycaemic state with a 6-month interval. Two-thirds of the children and young people showed a decrease in IQ performance while they were hyperglycaemic ($p<0.05$).

We found no studies that examined the risks of diabetic ketoacidosis on cognitive function in children and young people with type 1 diabetes.

9.6 Behavioural and conduct disorders

In 2000, the Office for National Statistics surveyed the prevalence of mental health problems in children and young people aged 5 to 15 years living in Great Britain: 5% had clinically significant conduct disorders.[572] [evidence level III] Conduct disorders commonly present as oppositional-defiant disorders in younger children and are far more common in males than females. Behavioural and conduct disorders can, therefore, influence the effectiveness of diabetes care in children and young people. Evidence from case–control studies suggests

that children and young people with diabetes have more parent-reported behavioural problems compared with children and young people of the same age and sex without diabetes.[612–614] [evidence level III] Negative events and acting-out were associated with developing diabetes among 67 children and young people with diabetes and 61 children and young people without diabetes under the age of 15 years. Interviews were conducted with parents 2 months after initial diagnosis, a time when children and young people and their families are coming to terms with the diagnosis and its ramifications on lifestyle.[612] [evidence level III]

There is a need for parents and healthcare professionals to distinguish whether an increased prevalence of behaviour disorders in this population is evident and establish whether optimal diabetes care is compromised. Identifying precipitating factors for behavioural disturbances may help to prevent complications such as hypoglycaemia and diabetic ketoacidosis. However, it is difficult to determine whether higher levels of attention problems and aggressive and delinquent behaviour are predictive of higher levels of HbA1c or vice versa.

A survey of 28 children and young people, their mothers and teachers found that children and young people with better glycaemic control made significantly more internal, stable and global attributions for negative events, even when controlled for age and sex. According to their teachers, children and young people with later onset of diabetes experienced more externalising behavioural symptoms ($p<0.001$).[615] [evidence level III]

Another study in which 70 children and young people with type 1 diabetes were compared with 70 children and young people without type 1 diabetes found no differences in teacher-reported behaviour.[616] [evidence level III] However, significantly more children and young people with type 1 diabetes were at least 2 years behind chronological age in reading ability ($p<0.01$).

Children and young people hospitalised with recurrent diabetic ketoacidosis (n=25) suffered more from anxiety, affective and disruptive behaviour disorders (attention deficit hyperactivity disorder and conduct disorder) compared with 25 children and young people without recurrent diabetic ketoacidosis ($p<0.001$). The children and young people with diabetic ketoacidosis were in poor control at diagnosis and at study entry as reflected by mean number of hospital admissions and emergency hospital visits ($p<0.001$).[614] [evidence level III]

A survey of 231 young people aged 11 to 18 years attending treatment centres found that those with self-reported attention problems were more likely to have HbA1clevels >9% (OR 2.3, 95% CI 1.2 to 4.3, $p<0.01$).[617] [evidence level III] A combination of aggressive and delinquent behaviour was also more likely to occur in those with elevated glycosylated haemoglobin levels (OR 2.41, 95% CI 1.35 to 4.30, $p<0.003$).

We found no studies that directly assessed the effectiveness of interventions aimed at improving behavioural disorders in children and young people with type 1 diabetes. Difficulties arise in conducting and interpreting studies that assess the relationship between conduct and behavioural disorders and type 1 diabetes. Research is often conducted after children and young people and their families have been living with diabetes, and this could influence their perception and recall of events.

9.7 Non-adherence

Diabetes care encompasses a complex regimen of insulin administration, blood glucose monitoring, diet and lifestyle changes. Studies have assessed non-adherence by self-reports from children and young people and their parents by surrogate markers such as HbA1c and fasting blood glucose levels. Factors such as age, family structure, education and personality traits can affect various domains of non-adherence in children with type 1 diabetes.[618] Adherence to insulin therapy is affected less than adherence to self-monitoring of blood glucose and dietary management.[619–621] [evidence level III]

Adherence to diabetes care is good in children and young people aged 6 to 12 years.[622] [evidence level IIb] Cohort studies have found that young people are less likely to comply with prescribed care, with associated poor glycaemic control.[501,622–624] [evidence level IIb] A study in Scotland found that people aged 10 to 20 years had significantly higher levels of HbA1c($p=0.01$) and lower adherence to insulin ($p<0.001$) compared with children aged <10 years and young adults aged >20 years (n=89).[501] [evidence level IIb] Diabetic ketoacidosis was strongly associated with poor long-term adherence to insulin therapy.[501] [evidence level IIb]

Aspects of family functioning are associated with the level of adherence to treatment by children and young people with type 1 diabetes and their parents. One study that investigated adherence, cohesion and adaptability in families compared 150 children and young people with type 1 diabetes aged 7 to 13 years and their parents with children and young people without type 1 diabetes and their parents. More of the families with a child or young person with type 1 diabetes showed disengagement with low levels of cohesion than did families with no child or young person with type 1 diabetes ($p<0.05$). Families with a child or young person with type 1 diabetes had more rigid family functioning with low levels of adaptability than families with no child or young person with type 1 diabetes ($p<0.0001$).[625] [evidence level III] Family adaptability in children and young people with type 1 diabetes was positively correlated with the parents' educational level (mother, $r=0.37$, $p<0.001$; father, $r=0.24$, $p<0.01$). Lower family cohesion scores correlated with parents' adherence to diet ($r=0.19$, $p<0.05$) and episodes of hypoglycaemia ($p<0.01$).[625] [evidence level III]

Higher levels of education in young people with type 1 diabetes and parents of children and young people with type 1 diabetes are associated with improved adherence.[625,626] [evidence level IIb–III]

Characteristics of personality, such as motivation, attitudes and self-efficacy, have been shown to influence adherence.[627,628] [evidence level III] Motivation can be improved by support and encouragement from parents. Perceptions of parental and healthcare professionals' actions in relation to adherence have also been investigated.[629] [evidence level III]

A theoretical model of adherence to therapy based on interviews with 51 young people and observed behaviour in 18 of the participants revealed that motivation, results of care, a sense of normality, adequate energy and willpower for care were attributes that could improve adherence.[630] [evidence level III]

We found no systematic reviews that examined methods of improving adherence in children and young people with type 1 diabetes. Studies have investigated interventions such as hypnosis, goal setting and behavioural and educational programmes that aim to reduce non-adherence.[631,632] A quasi-experimental study evaluated the effects of a behavioural programme aimed at improving adherence and stress management in 37 young people; no effect on diet, exercise or blood glucose monitoring was found between young people who took part in the behavioural programme and those who did not.[633] [evidence level IIb]

9.7.1 Brittle diabetes

The term 'brittle diabetes' has been used to describe people who present with frequent episodes of diabetic ketoacidosis over a relatively short time, often with poor glycaemic control and frequently hypoglycaemic. Brittle diabetes is very often, but not exclusively, seen in young women with type 1 diabetes. There is a high degree of covert disruption of diabetes management, underpinned by specific psychological and psychiatric problems.

Two studies that related to insulin misuse in young people with type 1 diabetes found that insulin misuse occurred in combination with psychiatric disorders. One case study described a young person who injected extra doses of short-acting insulin several times per day to induce hypoglycaemia.[634] [evidence level IV] A second case series identified 6 young people

taking additional insulin: this was believed to represent suicidal behaviour in 2 patients and to represent symptom substitution in the other patients when other health-threatening behaviour such as recurrent ketoacidosis was made increasingly difficult through appropriate intervention.[635] [evidence level IV]

9.8 Psychological interventions

This section was updated in 2015.

9.8.1 Review question

What is the effectiveness of psychological interventions to improve outcomes in children and young people with type 1 diabetes?

9.8.2 Introduction

The objective of this review question is to determine the effectiveness of psychological interventions in improving outcomes for children and young people with type 1 diabetes. The question is sufficiently broad to cover interventions aimed at families and healthcare professionals as well as those aimed at the child or young person. The guideline development group prioritised the following interventions for consideration.

- Motivational interviewing – this can be delivered either one-to-one or in a group setting. It focuses on a general exploration of ambivalence around maladaptive behaviours and of the person's motivation and actual needs. It is intended to help the individual to develop insight into their maladaptive behaviour in order to change it.
- Cognitive behavioural therapy (CBT) – this can be delivered either one-to-one or in a group setting. CBT focuses on recognising specific triggers for maladaptive behaviour and on bringing about changes to that behaviour.
- Counselling – this is delivered one-to-one and encompasses a variety of approaches in terms of the content of the interventions used.
- Family therapy – this is behavioural intervention therapy delivered to the family as a unit, but the therapy can include separate sessions with 1 or more members of the family.
    - Family-based teamwork is an approach in which the intervention promotes working together within the family. The child or young person and other members of the family share or take responsibility for different tasks while working together towards a common goal. The approach specifically identifies key tasks that need attention and fosters the family-based approach, promoting communication and team-work in the family.
    - Behavioural family systems therapy (BFST) uses an intensive approach and targets the specific needs of the individual family. In this context the term 'systems' refers to the use of a systematic approach to addressing specific maladaptive behaviours within the individual family.
    - Multi-systemic therapy refers to intensive family therapy using intensive evidence-based interventions and involving other agencies such as schools.
- Mentoring – this can be delivered one-to-one or in a group context. It involves a supportive relationship in which a more experienced or expert individual guides a less experienced or less expert individual to achieve their goals. The mentor is often in a position of authority, for example being older than the person or in a position of influence relative to the patient.
- Peer support – this can be delivered one-to-one or in a group setting. It involves people of similar age to the patient providing peer support.

Outcomes prioritised for inclusion in the review were:

- glycaemic control:
  - HbA1c (glycated haemoglobin; minimum follow-up 6 months after completion of the primary intervention)
- adherence to diabetes management (including self-management)
- adverse events (for example severe hypoglycaemic episodes, diabetic ketoacidosis [DKA] or self-harm)
- health-related quality of life
- satisfaction of children, young people and families with the intervention
- anxiety or depression
- school performance or attendance
- risk-taking behaviours (such as smoking).

Studies included in the evidence reviews related to psychological and social issues in the 2004 guideline (Section 9.2 to Section 9.7, and the evidence review for psychosocial interventions to enhance support, which this 2015 update review updates and replaces) have been considered for inclusion in the 2015 update review, but only systematic reviews and randomised controlled trials (RCTs) were eligible for inclusion.

9.8.3 Description of included studies

Fifteen publications reporting 13 studies (all RCTs) were identified for inclusion for this review question (Anderson 1999; Channon 2007; de Wit 2008; Ellis 2004; Ellis 2005; Graue 2005; Laffel 2003; Nansel 2007; Nansel 2009; Robling 2012; Wang 2010; Wysocki 2000; Wysocki 2001; Wysocki 2006; Wysocki 2007).

Six of the studies (all RCTs) covered the following forms of psychological intervention aimed at the child or young person with diabetes:

- motivational interviewing (Channon 2007; Robling 2012; Wang 2010)
- CBT focussed on quality of life (de Wit 2008)
- other forms of CBT (Nansel 2007)
- counselling (Graue 2005).

The remaining 7 publications (all RCTs) covered the following forms of psychological interventions focused on the family:

- family-based teamwork (Anderson 1999; Laffel 2003)
- other forms of family-based psychological intervention (Nansel 2009; Wysocki 2000; Wysocki 2001; Wysocki 2006; Wysocki 2007)
- multi-systemic therapy, including BFST (Ellis 2004; Ellis 2005; Wysocki 2000; Wysocki 2001; Wysocki 2006; Wysocki 2007).

Wysocki (2000) and Wysocki (2001) reported the same study, as did Wysocki (2006) and Wysocki (2007), with the first article in each pair reporting the methods and the second reporting relevant outcomes for the guideline review.

No evidence was identified for inclusion with regard to mentoring or peer support.

9.8.3.1 Interventions focused on the child or young person

9.8.3.1.1 Motivational interviewing versus support visits

A single RCT (Channon 2007) conducted in the UK included 66 children and young people with type 1 diabetes of whom 34 (51.5%) were female. At baseline, the mean age was

15.3±1.1 years and mean HbA1c was 9.2%±1.9%. Mean body mass index (BMI) was not reported and all participants were injecting insulin 2 to 4 times per day. Reported outcomes included HbA1c, health-related quality of life at 12 months and depression at 12 months from baseline. The other a priori specified outcomes – adherence to diabetes management, incidence of anxiety, depression or adverse events, satisfaction with the intervention, school performance or attendance and risk-taking behaviour – were not reported.

9.8.3.1.2 Motivational interviewing versus no psychological intervention

A single RCT (Robling 2012) conducted in the UK included 689 children and young people with type 1 diabetes of whom 347 (50.4%) were female. At baseline, the mean age was 10.5±2.8 years, mean HbA1c was 9.3%±1.8 and mean BMI was 19.4±3.2 kg/m^2. Insulin regimens used were not reported. This study employed a motivational interview therapy programme delivered by diabetes healthcare professionals who had first undergone a programme of specific skills training (see Table 35 for details of the therapy and training programmes). The participants in the intervention arm of the study were compared with children and young people who were awaiting treatment with the same intervention (on a waiting list). Reported outcomes included HbA1c, adherence to diabetes management and health-related quality of life at 12 months from baseline. The other a priori specified outcomes – incidence of anxiety, depression or adverse events, satisfaction with the intervention, school performance or attendance and risk-taking behaviour – were not reported.

9.8.3.1.3 Motivational interviewing versus structured education

A single RCT (Wang 2010) conducted in the USA included 44 children and young people with type 1 diabetes of whom 22 (50%) were female. At baseline, the mean age was 15.4±1.56 years and mean HbA1c was 11.0±1.6%. Neither mean BMI nor insulin regimen were reported. Reported outcomes included HbA1c, health-related quality of life and depression at 6 months from baseline. The other a priori specified outcomes – adherence to diabetes management, incidence of anxiety, depression or adverse events, satisfaction with the intervention, school performance or attendance and risk-taking behaviour – were not reported.

9.8.3.1.4 Cognitive behavioural therapy focused on quality of life versus standard care

A single RCT (de Wit 2008) conducted in the Netherlands included 91 children and young people with type 1 diabetes of whom 41 (45.1%) were female. At baseline, the mean age was 14.8±1.04 years, mean HbA1c was 8.7±1.3% and mean BMI was 21.1±3.3 kg/m^2. Thirty-nine (42.8%) of the participants were on 2 to 3 injections per day, 30 (33.0%) were on 4 or more injections per day and the remaining 12 (13.2%) were using insulin pump therapy. Reported outcomes included HbA1c at 12 months from baseline, health-related quality of life at 12 months and depression at 12 months. The other a priori specified outcomes – adherence to diabetes management, incidence of anxiety, depression or adverse events, satisfaction with the intervention, school performance or attendance and risk-taking behaviour – were not reported.

9.8.3.1.5 Cognitive behavioural therapy versus standard care

A single RCT (Nansel 2007) conducted in the USA included 81 children and young people with type 1 diabetes of whom 45 (55.6%) were female. At baseline, the mean age was 13.8±1.7 years. The mean HbA1c and mean BMI were not reported. Thirty (37%) of the participants were on multiple injections per day and the remaining 51 (63%) were using insulin pump therapy. Reported outcomes included adherence to diabetes management and health-related quality of life at 12 months following baseline. The other a priori specified outcomes – HbA1c, incidence of anxiety, depression or adverse events, satisfaction with the intervention, school performance or attendance and risk-taking behaviour – were not reported.

9.8.3.1.6 Counselling versus standard care

A single RCT (Graue 2005) conducted in Norway included 101 children and young people with type 1 diabetes of whom 47 (46.5%) were female. At baseline, the mean age was 14.4±1.60 years, mean HbA1c was 9.5±1.5% and mean BMI was 20.6±3.1 kg/m^2. Fifty (49.5%) of the participants were on 3 injections per day, 47 (46.5%) on 4 or more injections per day and the remaining 4 (4.0%) were using insulin pump therapy. Reported outcomes included HbA1c, incidence of adverse events and health-related quality of life at 15 months from baseline. The other a priori specified outcomes – adherence to diabetes management, incidence of anxiety, depression or adverse events, satisfaction with the intervention, school performance or attendance and risk-taking behaviour – were not reported.

9.8.3.2 Family-focused interventions

9.8.3.2.1 Family-based teamwork intervention versus standard care

Two RCTs (Anderson 1999; Laffel 2003) conducted in the USA included 185 children and young people with type 1 diabetes of whom 47 (48.0%) were female. At baseline, the mean age was 12.1±2.3 years, mean HbA1c was 8.4±1.2% and mean BMI was 20.5±3.6 kg/m^2, while the participants in the second study had a mean age of 12.6 years and mean HbA1c of 8.5% but mean BMI was not reported. Ninety-four (94.0 %) of the participants in the first study were on 2 to 3 injections per day and 6 (6.0%) were on 4 or more injections per day; none were using insulin pump therapy. In the other study, 19.5% and 69.5% of participants were on 2 or 3 injections per day, respectively. Reported outcomes included HbA1c and health-related quality of life at 12 months from baseline. The other a priori specified outcomes – adherence to diabetes management, incidence of anxiety, depression or adverse events, satisfaction with the intervention, school performance or attendance and risk-taking behaviour – were not reported.

Three RCTs (Nansel 2009; Wysocki 2000 and Wysocki 2001; Wysocki 2006 and Wysocki 2007) conducted in the USA included 345 children and young people with type 1 diabetes, of whom 47 (45.2%) were female in 1 study, gender was not specified in the second study and 58% of participants were female in the third study. Two studies (Wysocki 2000 and Wysocki 2001; Wysocki 2006 and Wysocki 2007) included 3 study arms: behavioural family systems therapy; educational support; and standard care. This comparison within the review used the data from the education support arm. The mean ages were 11.5 years, 14.2 years and 14.3 years, respectively. The mean HbA1c was 8.4±1.3% in the first study, 14.2% in the second and 9.6% in the third. The mean BMI was not reported in any of the studies. Sixteen (23.5%) of the participants in 1 study (Wysocki 2006) were using insulin pump therapy; the remainder of the participants in the study arms included in the guideline review were on insulin injections although the frequency was not reported. Insulin regimen was not reported in the other study (Nansel 2009).

9.8.3.2.2 Multi-systemic therapy versus standard care (including behavioural family systems therapy)

Four RCTs (Ellis 2004; Ellis 2005; Wysocki 2000 and Wysocki 2001; Wysocki 2006 and Wysocki 2007) conducted in the USA included 277 children and young people with type 1 diabetes of whom 152 (54.8%) were female. Two studies (Wysocki 2000 and Wysocki 2001; Wysocki 2006 and Wysocki 2007) included 3 study arms: behavioural family systems therapy; educational support; and standard care. This comparison within the review used the data from the behavioural family systems therapy arm. The mean age of the participantswas 13.6±1.6 years in Ellis (2004), 13.8±1.7 years in Ellis (2005), 14.4 years in Wysocki (2001) and 14.05 years in Wysocki (2006). Mean HbA1c was 11.4±2.2% in the first study, 13.2%±3.5% in the second, 11.8% for the 2 relevant arms of the third study and 9.7% for the fourth study. The mean BMI was not reported in any of the studies. In 1 study (Ellis 2005) the majority of participants, 114 (89.8%), were on 2 to 3 injections per day while a single

participant (0.8%) was on 4 or more injections per day and 4 (3.1%) were using insulin pump therapy. In the other study, all the participants were on 2 to 3 injections per day. The number of daily injections was not reported for the third or fourth study. Reported outcomes included HbA1c and adherence to diabetes management. The other a priori specified outcomes – incidence of anxiety, depression or adverse events, health-related quality of life, satisfaction with the intervention, school performance or attendance and risk-taking behaviour – were not reported at the relevant time points.

Table 34: Summary of psychological interventions evaluated in randomised controlled trials involving children and young people with type 1 diabetes

This section was updated in 2015.

Study	Intervention and comparator	Session duration	Number of sessions	Frequency	Provider	Details of intervention or comparator
Anderson 1999	Teamwork	30-minute intervention prior to routine appointment	4	Every 3 to 4 months	Routine clinical care plus research assistant	Focused on common conflicts or issues that may interfere with parent-adolescent team-work around diabetes management. Module topics were: • effects of growth and puberty on diabetes management; • need for parental involvement during this period; • coping with common conflicts around blood glucose monitoring; • preventing conflicts around food; • parental support for exercise. Parents and child negotiated a responsibility-sharing plan at end of each session.
	Attention control	30-minute intervention prior to routine appointment	4	Every 3 to 4 months	Routine clinical care plus research assistant	Families received time and attention from the research assistant equivalent to that provided to families in the teamwork group. Didactic 'traditional' diabetes education was provided.
	Standard care	Not reported	Not reported	Every 3 to 4 months	Routine clinical care	Routine clinical care from the diabetes team every 3 to 4 months over the 12-month study period.
Channon 2007	Motivational interviewing	Not reported	Not reported	As requested by the patient	Trainee health psychologist	A menu of strategies was used, including: • awareness building • alternatives • problem-solving • making choices • goal-setting • avoidance of confrontation.
	Support visits	Not reported	Not reported	Not reported	Therapist with a nursing background	Non-directive psychological support.

Study	Intervention and comparator	Session duration	Number of sessions	Frequency	Provider	Details of intervention or comparator
Robling 2012	Motivational interviewing delivered by diabetes healthcare professionals with specific training	1.5 hours	2 team sessions	NA	NA	Diabetes healthcare professionals were trained to deliver a motivational interviewing programme of therapy using more constructive consultations about behaviour change by putting patients at the centre of their own consultation and enhancing engagement with their healthcare. Training emphasised shared setting of agendas and a guiding communication style, plus discrete strategies and skills drawn from motivational interviewing practice. Role play interactions modelled how the strategies could be applied flexibly in routine consultations. Practitioners were able to report consultations online and to receive feedback from the trainer team. The training programme was constructed around 3 case studies representing common clinical challenges in paediatric diabetes care. Practitioners were expected to modify consultations with patients for the remainder of the study as part of otherwise routine care.
	No psychological intervention	NA	NA	NA	NA	Participants in the control group were held on a waiting list for the duration of the trial.
Wang 2010	Motivational interviewing-based education	Not reported	Up to 3 intervention sessions and 2 telephone follow-ups	First session at enrolment and second session 1 to 2 months later. Third session if HbA1c remained ≥9%	Diabetes educators trained in motivational interviewing	Education programme based on motivational interviewing and delivered using a manual.
	Structured diabetes education	Not reported	Up to 3 intervention sessions and 2 telephone follow-ups	First session at enrolment and second session 1 to 2 months later. Third session if HbA1c remained ≥9%	Diabetes educators with no additional training	Education programme delivered using a comprehensive checklist compiled by the American Diabetes Association and covering medication, monitoring, acute complications and lifestyle.
de Wit 2008	CBT focused on health-related quality of life	Not reported	3	Quarterly	Paediatricians	Monitoring health-related quality of life before each appointment with the paediatrician and discussing health-related quality of life scores with the young person during the appointment.
	Standard care	Not reported	3	Quarterly	Usual carer	Usual care plus completion of a lifestyle questionnaire (rather than a health-related quality of life questionnaire).
	Conventional insulin therapy only	Not reported	3 to 4	3- to 4-monthly	Multidisciplinary team	Not reported

Study	Intervention and comparator	Session duration	Number of sessions	Frequency	Provider	Details of intervention or comparator
Graue 2005	Counselling with structured education	3 hours for a group session 45 minutes for an individual session	6 (3 group sessions and 3 individual sessions)	Frequency not reported Duration 15 months	Group sessions with various professionals Individual sessions with diabetes nurse specialist	Separate group sessions for young people and parents: • Young people: active participation, impact of disease in daily life, problem-solving skills, sharing of personal experiences. • Parents: meeting with other parents faced with similar situations, discuss parental involvement and control in daily diabetes management, supportive communication, physiological and psychological changes during puberty, and areas of conflict in parent-adolescent relationships. • Individual sessions for young people involved review of their knowledge, skills and motivation for diabetes care and self-management.
	Standard care	Not reported	Not reported	Not reported	Usual carer	Not reported
Ellis 2004	Multi-systemic therapy	Not reported	48 to 72	2 or 3 per week Duration 6 months	Trained therapist	Sessions supported by a manual and targeted adherence-based problems with the family system, peer network and broader community system. Intervention techniques included CBT, parent training and BFST.
	Standard care	Not reported	Not reported	Not reported	Not reported	Not reported
Ellis 2005	Multi-systemic therapy	Not reported	48 to 72	2 or 3 per week Duration 6 months	Trained therapist	Sessions supported by a manual and targeted adherence-based problems with the family system, peer network and broader community system. Intervention techniques included CBT, parent training and BFST.
	Standard care	Not reported	Not reported	Not reported	Not reported	Not reported

Study	Intervention and comparator	Session duration	Number of sessions	Frequency	Provider	Details of intervention or comparator
Laffel 2003	Family-focused teamwork	Not reported	Not reported	Not reported	Research assistant	Family-focused teamwork intervention consisted of 4 modules delivered by a research assistant and emphasised the importance of parent and child sharing responsibility for diabetes tasks and ways to avoid conflict that undermines teamwork. The modules addressed the following areas: • communication about diabetes (including discussion of blood glucose results within the family) • meaning of HbA1c and explaining the need for the parent-child teamwork during the adolescence • response to blood glucose and avoiding the 'blame and shame cycle' • sharing the burden of diabetes tasks with family members and using a logbook to trouble-shooting of extreme blood glucose values. Written materials were provided highlighting: • the multiple causes of low and high blood glucose levels during childhood and adolescence • the need for realistic expectations for blood glucose levels and behaviours • the importance of maintaining parent involvement with insulin injections and blood glucose monitoring.
	Standard care	Not reported	Not reported	Not reported	Research assistant	Standard care consisted of usual clinic visits but the research assistant did not engage patients and families in discussion about family teamwork. Families received the same education materials as the teamwork group after completion of the study. Both treatment groups received equal attention in terms of scheduling appointments, contact between study visits, and encouragement around routine diabetes management.

Study	Intervention and comparator	Session duration	Number of sessions	Frequency	Provider	Details of intervention or comparator
Nansel 2009	Family-focused psychological intervention	Not reported	3	Not reported	Specially trained college graduates (health advisers)	Intervention base on WE-CAN structure: • W: work together to set goals • E: explore barriers and solutions • C: choose best solutions • A: act on the plan • N: note results. Intervention aimed at: • improving diabetes management and problem-solving • improving parent-child co-operation and communication, and reducing conflict • facilitating appropriate sharing of disease management responsibility.
	Standard care	Not reported	Not reported	Not reported	Health advisers and usual carers	Families received standard medical care, participated in measurement, received clinic preparation, administrative assistance and attention from health advisers (for example clinic reminders).
Wysocki 2000 and Wysocki 2001	BFST for diabetes	Not reported	10	Not reported	Licensed psychologist with 150 hours of training and supervised BFST experience who was certified as proficient	10 sessions of Robin and Foster's (1989) BFST. The session was taped and rated by Dr Robin or 1 of the project psychologists and feedback from ratings was provided in weekly conference calls. Therapy contained 4 treatment components: • problem-solving training • communication skills training • cognitive restructuring • functional and structural family therapy. Families received an individualised BFST treatment plan Families were paid $100 ($50 each for parent and young person) upon completing each evaluation. The educational support and BFST families could earn another $100 if they completed all 10 treatment sessions.
	Educational support (diabetes education and social support)	90 minutes	10	10 sessions in 12 weeks	A masters-level social worker with extensive diabetes experience and a masters-level health educator as group facilitator	10 family group meetings in the first 12 weeks designed to emulate a common mental health service for families of chronically ill young people and to serve as a 'best alternative therapy' comparison. Content was organised around the chapters of the American Diabetes Support Groups for Young Adults: A Facilitators' manual (1990). Each session included a 45-minute educational presentation by a diabetes professional on 1 of 10 topics, followed by 45 minutes of family interaction about that topic led by the facilitator.

Study	Intervention and comparator	Session duration	Number of sessions	Frequency	Provider	Details of intervention or comparator
	Current therapy	Not reported	Not reported	Three or more times annually	As directed by a physician	• Standard therapy for type 1 diabetes as directed by their physician and GHb assay 3 or more times annually • 2 or more daily injections of mixed intermediate and short-acting insulins • home blood glucose monitoring and recording of test results • diabetes self-management training • a prescribed diet • physical exercise • annual evaluation for long-term diabetic complications.
Wysocki 2006 and Wysocki 2007	BFST for diabetes	90 minutes	12	Frequency not reported Duration 6 months	Psychologists or licensed clinical social workers trained and certified as proficient in BFST for diabetes	BFST-D consisted of 4 components: • problem-solving training • communication skills training • cognitive restructuring methods targeted at family members • functional and structural family therapy interventions targeted at anomalous family systemic characteristics.
	Educational support (diabetes education and social support)	90 minutes	12	Frequency not reported Duration 6 months	Experienced diabetes nurses who received extensive training	Session content followed an American Diabetes Association curriculum for teenagers. Sessions did not cover family communication and conflict resolution skills (these were covered by BFST for diabetes).
	Standard care	Not reported	2	Quarterly	Paediatric endocrinologist or other qualified healthcare professional	Usual clinical practice at each site.
Nansel 2007	Diabetes personal trainer	Not reported	6	Frequency not reported Duration 2 months	Personal trainer with a health-related degree and training in the programme, but not a healthcare professional	Joint session for young people and parents followed by sessions for young people only. Semi-structured sessions involving diabetes management, motivational interviewing, applied behaviour analysis, parent-child issues, safety, ethics and activities. Supplemented by telephone calls from the personal trainer.
	Educational intervention	Not reported	Not reported	Not reported	NA	Received the same assessments as the intervention group and an educational booklet about blood glucose monitoring based on materials used in an effective psycho-educational intervention.

BFST behavioural family systems therapy, CBT cognitive behavioural therapy, NA not applicable

9.8.4 Evidence profile

The evidence profiles for this review question (psychological interventions for type 1 diabetes) are presented in Table 35 to Table 43.

Table 35: Evidence profile for effectiveness of motivational interviewing versus support visits in children and young people with type 1 diabetes

Number of studies	Number of children and young people		Effect		Quality
	Motivational interviewing	Support visits	Relative (95% confidence interval)	Absolute (95% confidence interval)	
HbA1c at 12 months from baseline					
1 (Channon 2007)	35	25	NA	MD 0.5 lower (1.43 lower to 0.43 higher)	Moderate
Depression (wellbeing questionnaire) at 12 months from baseline (lower scores indicate better outcomes)					
1 (Channon 2007)	35	25	NA	MD 1.77 lower (2.80 lower to 0.74 lower)	High
Health-related quality of life (Diabetes Quality of Life for Youths, impact) at 12 months from baseline (lower scores indicate better outcomes)					
1 (Channon 2007)	35	25	NA	MD 10.56 lower (17.81 lower to 3.31 lower)	High

MD mean difference, NA not applicable

Table 36: Evidence profile for effectiveness of motivational interviewing skills training versus awaiting treatment with the same intervention (placing patients on a waiting list)in children and young people with type 1 diabetes

Number of studies	Number of children and young people		Effect		Quality
	Motivational interviewing delivered by trained HCPs	No motivational interviewing (waiting list)	Relative (95% confidence interval)	Absolute (95% confidence interval)	
HbA1c at 15 months from baseline					
1 (Robling 2012)	342	318	NA	MD 0.2 higher (0.06 lower to 0.46 higher)	High
Adherence to diabetes management (measured with Diabetes Mismanagement Questionnaire) at 15 months from baseline (lower scores indicate better outcomes)					
1 (Robling 2012)	186	163	NA	MD 4.6 lower (8.04 lower to 1.16 lower)	High
Health-related quality of life (measured with Diabetes Quality of Life Questionnaire, impact subscale) at 15 months from baseline(higher scores indicate better outcomes)					
1 (Robling 2012)	167	166	NA	MD 5.8 lower (9.85 lower to 1.75 lower)	High

MD mean difference, NA not applicable

Table 37: Evidence profile for effectiveness of motivational interviewing versus structured education in children and young people with type 1 diabetes

Number of studies	Number of children and young people		Effect		Quality
	Motivational interviewing	Structured education	Relative (95% confidence interval)	Absolute (95% confidence interval)	
HbA1c at 6 months from baseline					
1 (Wang 2010)	21	23	NA	MD 1.1 higher (0.27 higher to 1.93 higher)	Low
Depression (CES-D) at 6 months from baseline (lower scores indicate better outcomes)					
1 (Wang 2010)	21	23	NA	MD 0.07 higher (1.53 lower to 1.67 higher)	Moderate
Health-related quality of life (EDIC-QoLY, lifestyle subscale) at 6 months from baseline (lower scores indicate better outcomes)					
1 (Wang 2010)	21	23	NA	MD 0.01 lower (1.61 lower to 1.59 higher)	Moderate

MD mean difference, NA not applicable

Table 38: Evidence profile for effectiveness of cognitive behavioural therapy focused on quality of life versus standard care in children and young people with type 1 diabetes

Number of studies	Number of children and young people		Effect		Quality
	Cognitive behavioural therapy focused on quality of life	Standard care	Relative (95% confidence interval)	Absolute (95% confidence interval)	
HbA1c at 12 months from baseline					
1 (de Wit 2008)	41	40	NA	MD 0.1 higher (0.53 lower to 0.73 higher)	Moderate
Depression (CES-D) at 12 months from baseline (lower scores indicate better outcomes)					
1 (de Wit 2008)	41	40	NA	MD 1.04 higher (1.26 lower to 3.34 higher)	High
Health-related quality of life from baseline (CHQ-CF87, global health subscale) at 12 months (higher scores indicate better outcomes)					
1 (de Wit 2008)	41	40	NA	MD 10.08 higher (2.16 higher to 18 higher)	High

MD mean difference, NA not applicable

Table 39: Evidence profile for effectiveness of cognitive behavioural therapy not specifically focused on quality of life versus standard care in children and young people with type 1 diabetes

Number of studies	Number of children and young people		Effect		Quality
	Cognitive behavioural therapy	Standard care	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Adherence to diabetes management (measured with Diabetes Self- Management Profile, child domain) at 12 months from baseline					
1 (Nansel 2007)	40	41	NA	MD 0.01 lower (0.07 lower to 0.05 higher)	High
Health-related quality of life (measured with Diabetes Quality of Life for Youth, impact subscale) at 15 months from baseline (higher scores indicate better outcomes)					
1 (Nansel 2007)	40	41	NA	MD 3.67 higher (3.1 higher to 4.24 higher)	High

MD mean difference, NA not applicable

Table 40: Evidence profile for effectiveness of counselling versus standard care in children and young people with type 1 diabetes

Number of studies	Number of children and young people		Effect		Quality
	Counselling	Standard care	Relative (95% confidence interval)	Absolute (95% confidence interval)	
HbA1c at 15 months from baseline					
1 (Graue 2005)	45	38	NA	MD 0.44 lower (1.04 lower to 0.16 higher)	Moderate
Adverse events (severe hypoglycaemic episodes at 15 months from baseline)					
1 (Graue 2005)	7/45 -15.60%	5/38 -13.20%	RR 1.18 (0.41 to 3.42)	24 more per 1000 (from 78 fewer to 318 more)	Low

Number of studies	Number of children and young people		Effect		Quality
	Counselling	Standard care	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Health-related quality of life (measured with Diabetes Quality of Life Questionnaire, impact subscale) at 15 months from baseline (higher scores indicates better outcomes)					
1 (Graue 2005)	45	38	NA	MD 4.3 higher (0.16 higher to 8.44 higher)	High

MD mean difference, NA not applicable, RR relative risk

Table 41: Evidence profile for effectiveness of multi-systemic therapy (including behavioural family systems therapy) versus standard care in children and young people with type 1 diabetes

Number of studies	Number of children and young people		Effect		Quality
	Multi-systemic therapy	Standard care	Relative (95% confidence interval)	Absolute (95% confidence interval)	
HbA1c at 6 to 7 months' from baseline					
1 (Ellis 2004)	13	15	NR	MD 1.9 lower (4.24 lower to 0.44 higher)	Low
1 (Ellis 2005)	64	63	NR	MD 0.77 lower (1.35 to 0.19 lower)	Moderate
HbA1c at 6 months' post-intervention					
1 (Wysocki 2001)	36	40	NR	MD 0.4 lower (not reported)	Very low
1 (Wysocki 2007)[a]	36	32	NR	MD 0.7 lower (1.42 lower to 0.02 higher)	Low
HbA1c at 12 months' post-intervention					
1 (Wysocki 2001)	36	40	NR	MD 0.2 lower (not reported)	Very low
1 (Wysocki 2007)	36	32	NR	MD 0.8 lower (1.57 lower to 0.03 lower)	Low
Adherence to diabetes treatment at 6 to 7 months' from baseline					
1 (Ellis 2004)	16	15	NR	MD 0.17 higher (0.53 lower to 0.87 higher)	Low
1 (Ellis 2005)	64	63	NR	MD 0.87 higher (0.46 to 1.28 higher)	Moderate
Adherence to diabetes (measured with self-care inventory) at 6 months' post-treatment (higher scores indicate better adherence)					
1 (Wysocki 2001)	36	40	NR	MD 4.4 higher (not reported)	Very low
1 (Wysocki 2007)	36	32	NR	MD 6.6 higher (1.77 to 11.43 higher)	Moderate
Adherence to diabetes (measured with self-care inventory) at 12 months' post-treatment (higher scores indicate better adherence)					
1 (Wysocki 2001)	34	38	NR	MD 8.7 higher (not reported)	Very low
1 (Wysocki 2006)	28	29	NR	MD 6.6 higher (1.37 to 11.83 higher)	Moderate
1 (Wysocki 2007)	36	32	NR	MD 4 higher (1.08 lower to 9.08 higher)	Moderate

MD mean difference, NR not reported
a. Behavioural family systems therapy (BFST) intervention versus standard care

Table 42: Evidence profile for effectiveness of family-based teamwork intervention versus standard care in children and young people with type 1 diabetes

This section was updated in 2015

Number of studies	Number of children and young people		Effect		Quality
	Family-based teamwork intervention	Standard care	Relative (95% confidence interval)	Absolute (95% confidence interval)	
HbA1c at 12 months from baseline					
1 (Laffel 2003)	50	50	NA	MD 0.5 lower (1.02 lower to 0.02 higher)	Moderate
1 (Anderson 1999)	28	27	NA	MD 0.2 higher (not reported)	Very low
Health-related quality of life (PedsQL) at 12 months from baseline (higher scores indicate better outcomes)					
1 (Laffel 2003)	50	50	NA	MD 0.4 higher (3.91 lower to 4.71 higher)	High

MD mean difference, NA not applicable

Table 43: Evidence profile for effectiveness of family-based behavioural intervention not specifically based on teamwork versus standard care in children and young people with type 1 diabetes

This section was updated in 2015

Number of studies	Number of children and young people		Effect		Quality
	Family-based behavioural intervention	Standard care	Relative (95% confidence interval)	Absolute (95% confidence interval)	
HbA1c at 6 months					
1 (Wysocki 2001)[a]	37	40	NR	MD 0.1 lower (not reported)	Very low
1 (Wysocki 2006/2007)[a]	36	32	NR	MD 0.3 lower (not reported)	Very low
HbA1c at 12 months					
1 (Nansel 2009)	58	58	NR	MD 0.2 higher (0.38 lower to 0.78 higher)	Very low
1 (Anderson 1999)[b]	30	27	NA	MD 0.0 (not reported)	Very low
1 (Wysocki 2001)[a]	36	38	NR	MD 0.8 lower (not reported)	Very low
1 (Wysocki 2007)[a]	36	32	NR	MD 0.1 lower (not reported)	Very low
Adherence to diabetes management (measured with Diabetes Self-Management Profile) at 12 months from baseline (higher scores indicate better outcomes)					
1 (Nansel 2009)	58	58	NR	MD 0.2 higher (3.45 lower to 3.85 higher)	Very low
Adherence to diabetes (measured with Self-care inventory) at 6 months post-intervention (higher scores indicate better adherence)					
1 (Wysocki 2001)[a]	37	40	NR	MD 2.3 higher (not reported)	Very low
1 (Wysocki 2007)[a]	36	32	NR	MD 4 higher (1.4 lower to 9.4 higher)	Very low
Adherence to diabetes (measured with Self-care inventory) at 12 months post-intervention (higher scores indicate better adherence)					

1 (Wysocki 2001)[a]	36	38	NR	MD 4.2 higher (not reported)	Very low
1 (Wysocki 2007)[a]	36	32	NR	MD 2 higher (3.26 lower to 7.26 higher)	Very low

MD mean difference, NR not reported
a. Education plus support versus conventional treatment or standard care
b. Attention control versus standard care

9.8.5 Evidence statements

Overall, the evidence obtained from the included studies demonstrated that psychological interventions had varying degrees of effect on HbA1c, incidence of anxiety, depression and adverse events, adherence to diabetes management and health-related quality of life. Further details related to this evidence are presented below.

None of the included studies reported evidence related to satisfaction with the psychological intervention among children and young people or their parents and carers, school performance or attendance, or risk-taking behaviours.

9.8.5.1 Motivational interviewing versus support visits

9.8.5.1.1 HbA1c

The evidence from 1 study (total 60 participants) did not demonstrate that either motivational interviewing or support visits was more effective than the other at 12 months. The quality of the evidence for this finding was moderate.

9.8.5.1.2 Depression

The evidence from 1 study (total 60 participants) showed that motivational interviewing was less likely to be associated with depression than were support visits. The quality of the evidence for this finding was high.

9.8.5.1.3 Health-related quality of life

The evidence from 1 study (total 60 participants) demonstrated that motivational interviewing was associated with better quality of life scores than were support visits at 12 months. The quality of the evidence for this finding was high.

9.8.5.2 Motivational interviewing versus awaiting treatment with the same intervention (placing patients on a waiting list)

9.8.5.2.1 HbA1c

The evidence from 1 study (total 660 participants) did not demonstrate that motivational interviewing delivered by diabetes healthcare professionals with specific training in the intervention was more effective than awaiting treatment with the same intervention (placing patients on a waiting list) at 15 months. The quality of the evidence for this finding was high.

9.8.5.2.2 Adherence to diabetes management

The evidence from 1 study (total 349 participants) demonstrated that motivational interviewing delivered by diabetes healthcare professionals with specific training in the intervention was associated with improved adherence to diabetes management compared with awaiting treatment with the same intervention (placing patients on a waiting list) at 15 months. The quality of the evidence for this finding was high.

9.8.5.2.3 Health-related quality of life

The evidence from 1 study (total 333 participants) demonstrated that motivational interviewing delivered by diabetes healthcare professionals with specific training in the intervention was associated with worse quality of life than was awaiting treatment with the same intervention (placing patients on a waiting list) at 15 months. The quality of the evidence for this finding was high.

9.8.5.3 Motivational interviewing versus structured education

This section was updated in 2015

9.8.5.3.1 HbA1c

The evidence from 1 study (total participants 44) demonstrated that motivational interviewing was associated with higher HbA1c than was structured education at 6 months. The quality of the evidence for this finding was low.

9.8.5.3.2 Depression

The evidence from 1 study (total participants 24) did not demonstrate a difference in depression scores at 6 months. The quality of the evidence for this finding was moderate.

9.8.5.3.3 Health-related quality of life

The evidence from 1 study (total 44 participants) did not demonstrate a difference in health-related quality of life at 6 months. The quality of the evidence for this finding was moderate.

9.8.5.4 Cognitive behavioural therapy focused on quality of life versus standard care

9.8.5.4.1 HbA1c

The evidence from 1 study (total 81 participants) did not demonstrate that CBT focused on quality of life was more effective than standard care at 12 months. The quality of the evidence for this finding was moderate.

9.8.5.4.2 Depression

The evidence from 1 study (total 81 participants) did not demonstrate that CBT focused on quality of life was more effective than standard care at 12 months. The quality of the evidence for this finding was high.

9.8.5.4.3 Health-related quality of life

The evidence from 1 study (total 81 participants) demonstrated that CBT focused on quality of life was more effective than standard care at 12 months. The quality of the evidence for this finding was high.

9.8.5.5 Cognitive behavioural therapy versus standard care

9.8.5.5.1 Adherence to diabetes management

The evidence from 1 study (total 81 participants) did not demonstrate a difference between CBT and standard care in adherence to diabetes management at 12 months. The quality of the evidence for this finding was high.

9.8.5.5.2 Health-related quality of life

The evidence from 1 study (total 81 participants) demonstrated that CBT was associated with better health-related quality of life than was standard care at 12 months. The quality of the evidence for this finding was high.

9.8.5.6 Counselling versus standard care

This section was updated in 2015

9.8.5.6.1 HbA1c

The evidence from 1 study (total 83 participants) did not demonstrate that counselling was more effective than standard care at 15 months. The quality of the evidence for this finding was moderate.

9.8.5.6.2 Adverse events (severe hypoglycaemic episodes)

The evidence from 1 study (total 83 participants) did not demonstrate that counselling was more effective than standard care at 15 months. The quality of the evidence for this finding was low.

9.8.5.6.3 Health-related quality of life

The evidence from 1 study (total 83 participants) demonstrated that counselling was associated with better health-related quality of life than was standard care at 15 months. The quality of the evidence for this finding was high.

9.8.5.7 Family-based teamwork versus standard care

9.8.5.7.1 HbA1c

The evidence from 1 study (total 100 participants) did not demonstrate that family-based teamwork was more effective than standard care at 12 months. The quality of the evidence for this finding was moderate.

The evidence from 1 study (total 55 participants) demonstrated a numerically better HbA1c at 12 months for family-based teamwork compared with standard care, but no measure of precision was reported. The quality of the evidence for this finding was very low.

9.8.5.7.2 Health-related quality of life

The evidence from 1 study (total 100 participants) did not demonstrate that family-based teamwork was more effective than standard care at 12 months. The quality of the evidence for this finding was high.

9.8.5.8 Family-based psychological intervention not specifically based on teamwork versus standard care

9.8.5.8.1 HbA1c

The evidence from 2 studies (total 145 participants) demonstrated that family-based psychological intervention was associated with lower HbA1c than standard care at 6 months follow-up from baseline, but no measure of precision was reported in either study. The quality of the evidence for this finding was very low.

The evidence from 2 studies (total 173 participants) did not demonstrate that family-based psychological intervention was more effective than standard care at 12 months. One study did not report a measure of precision. The quality of the evidence for this finding was very low.

The evidence from 2 studies (total 142 participants) did not demonstrate that family-based psychological intervention was more effective than standard care at 12 months follow-up, although the effect was numerically in favour of family-based interventions. No measure of precision was reported in in either study. The quality of the evidence for this finding was very low.

9.8.5.8.2 Adherence to diabetes treatment

This section was updated in 2015

The evidence from 2 studies (total 173 participants) did not demonstrate a difference in adherence to diabetes treatment at 12 months. The quality of evidence for this finding was very low.

The evidence from 2 studies (total 145 participants) demonstrated an improvement in adherence associated with family-based psychological interventions compared with standard care as measured by the self-care inventory at 6 or 12 months follow-up, but a measure of precision was not reported for 1 study. The quality of the evidence for this finding from both studies was very low.

9.8.5.9 Multi-systemic therapy (including behavioural family systems therapy) versus standard care

9.8.5.9.1 HbA1c

The evidence from 2 studies (total 155 participants) demonstrated that multi-systemic therapy (including CBT and BFST) was associated with lower HbA1c at 6 to 7 months' follow-up than was standard care. The quality of the evidence for this finding was moderate.

The evidence from 1 study (total 76 participants) demonstrated multi-systemic therapy (BFST) was associated with lower HbA1c at 6 months and 12 months following intervention compared with standard care, but no measure of precision was reported. The quality of the evidence for this finding was very low.

The evidence from 1 study (total 68 participants) demonstrated multi-systemic therapy (BFST) was associated with lower HbA1c at 6 months and 12 months following intervention compared with standard care. The quality of the evidence for this finding was low.

9.8.5.9.2 Adherence to diabetes management (frequency of blood glucose testing per day)

The evidence from 2 studies (total 158 participants) demonstrated that multi-systemic therapy (including CBT and BFST) was associated with better adherence to diabetes management than was standard care. The quality of the evidence for this finding was moderate or low.

9.8.5.9.3 Adherence to diabetes (self-care inventory)

The evidence from 1 study (total 76 participants) demonstrated that multi-systemic therapy (BFST) was associated with greater adherence (as demonstrated by higher self-care inventory scores) at 6 months and 12 months following the intervention compared with standard care, but no measure of precision was reported. The quality of the evidence for this finding was very low.

The evidence from 1 study (total 68 participants) demonstrated that multi-systemic therapy (BFST) was associated with greater adherence (as demonstrated by higher self-care inventory scores) at 6 months and 12 months following intervention compared with standard care. The quality of evidence for this finding was moderate.

9.8.6 Health economics profile

A systematic literature search identified a single US study which compared the cost of multisystemic therapy with standard care to reduce DKA-related admissions to hospital in young people with poorly controlled blood glucose (Ellis 2007). Calculations undertaken for this guideline on the results reported in that article suggest that multisystemic therapy was more expensive than standard care. This study is described in detail in Section 19.2.1.

This question was not prioritised for health economic analysis as the guideline development group considered structured education a higher priority for health economic analysis. Furthermore, the clinical effectiveness data on which to base any modelling were limited.

9.8.7 Health economics evidence statement

On indirectly applicable cost-analysis with potentially major limitations suggested that multisystemic therapy was more expensive than standard care.

9.8.8 Evidence to recommendations

9.8.8.1 Relative value placed on the outcomes considered

The guideline development group agreed that HbA1c value was the highest priority outcome because, in their view, if the use of a particular psychological intervention resulted in a reduction in HbA1c by near to or greater than 0.5 percentage points (or 5.5 mmol/mol) then this would represent an important clinical benefit to a child or young person with type 1 diabetes. This decision was underpinned by the group's knowledge of research in adults with type 1 diabetes (The Diabetes Control and Complications Trial Research Group 1993) which showed that a 1 percentage point decease in HbA1c halved the risk of diabetes-related complications, including retinopathy and nephropathy. The guideline development group considered that this result could be meaningfully extrapolated to cover the population of children and young people with type 1 diabetes of relevance in this question.

Psychosocial symptoms (for example anxiety or depression) were also considered high priority outcomes for this review question. The association between affective disorders, including depression, in adults with chronic physical health problems is recognised (see the guideline on depression in adults with a chronic physical health problem). The guideline development group also recognised this as an important association in children, young people and their family members.

The group prioritised adherence to diabetes management as an outcome for inclusion because this is often a specified focus of psychological interventions and the guideline development group's understanding was that better adherence should help improve glycaemic control.

Changes in health-related quality of life and in the satisfaction of children, young people and families with the psychological intervention were also considered to be important outcomes of interest.The guideline development group also believed that severe hypoglycaemic episodes and episodes of DKA were important outcomes for consideration in determining the safety of overall care as they were indicators of either too stringent or too relaxed HbA1c targets for children and young people with type 1 diabetes.

9.8.8.2 Consideration of clinical benefits and harms

The guideline development group recognised that the evidence included in the guideline review was sometimes inconsistent in its findings.

There was no evidence in relation to any of the psychological interventions for children and young people with type 1 diabetes (motivational interviewing, CBT focused on quality of life,

CBT more generally, counselling, peer support or mentoring) in terms of benefit from a reduction in HbA1c or in the frequency of episodes of DKA or hypoglycaemia. However, counselling, CBT generally and CBT focused specifically on quality of life all had a beneficial effect on quality of life. Motivational interviewing was associated with improved quality of life in 1 study, but worse health-related quality of life in another.

Motivational interviewing reduced depression in 1 study and improved adherence in another. A third study that evaluated the effectiveness of motivational interviewing was not considered relevant to current practice in this area (see Quality of evidence below) and was not considered further by the guideline development group.

There was no convincing evidence of benefit in terms of reducing anxiety or depression or frequency of episodes of DKA or hypoglycaemia for any of the psychological interventions focused on the family as a whole (multi-systemic therapy, family-based teamwork and family-based psychological interventions). Multi-systemic therapy showed a statistically significant reduction in HbA1c but there was uncertainty about the clinical importance of the effect size. Similarly, family-based teamwork was associated with a reduction in HbA1c that was almost statistically significant, but there was great uncertainty about the clinical importance of the effect size. Multi-systemic therapy also improved adherence to diabetes management which the guideline development group considered to be a plausible mechanism by which the reported improvement in HbA1c might have come about.

In light of the evidence the guideline development group did not consider that there was sufficient justification to recommend routine use of any form of psychological intervention for all children and young people with type 1 diabetes. The group did, however, conclude that there was evidence to support recommendations to consider the use of specific interventions for children and young people with particular difficulties (for example difficulties with treatment adherence). The group was aware that depression was an important problem for many children and young people with type 1 diabetes in that type 1 diabetes is a risk factor for depression as well as being a cause of social stigma and isolation. The group found evidence that motivational interviewing improved the outcome of depression in such children and young people, but referred to the treatment strategies outlined in the existing NICE guideline depression in children and young people.

The guideline development group was persuaded that the limited evidence for multi-systemic therapy improving HbA1c in children and young people with type 1 diabetes who have poor glycaemic control provided justification that the intervention should be considered in this group of children and young people. Family therapy, with involvement, where appropriate, of other agencies such as schools, would be a rational approach in such situations. A practical example might be the involvement of the school to facilitate insulin injections.

The group also felt that the evidence included in the guideline review supported consideration of other psychological interventions (motivational interviewing, CBT and counselling) to improve health-related quality of life or adherence to diabetes care.

As no evidence relevant to mentoring or peer support was identified for inclusion, the guideline development group did not feel that they should completely remove the existing recommendations about the use of these interventions, but it was appropriate to alter them to reflect the lack of specific supportive evidence regarding benefits in terms of glycaemic control, and to take account of the group's consensus views regarding these treatments.

The guideline development group retained an existing recommendation on the use of behavioural family systems therapy for diabetes-specific conflict because in the 2015 update review diabetes-specific conflict was not a prioritised outcome and so any new evidence on this topic was not available to the group. The group did not make any new recommendations on other family-focused psychological interventions due to the lack of evidence of benefit.

The guideline development group noted that psychological interventions may be considered be inconvenient or even burdensome for some children, young people and their families; for example they might impact on school attendance and require additional healthcare appointments. The group agreed that this should be kept in mind when discussing whether or not to proceed with the treatment, but should not influence the decision on whether to offer the treatment in the first place.

Reflecting on psychological interventions generally, the guideline development group believed that the individual person delivering the intervention might have a significant impact on the effectiveness of the intervention, but they also felt that training and experience would be expected to improve the ability of individuals to successfully deliver such interventions. The group was aware of data from a pilot study predating the included trial on motivational interviewing delivered by diabetes healthcare professionals with specific training (Robling 2012) which indirectly supported this assertion. Consequently, they recommended that psychological interventions should be delivered by appropriately skilled personnel who have an understanding of diabetes. This may include, but is not limited to, professionals such as clinical psychologists, family therapists, counsellors and/or psychiatrists.

9.8.8.3 Consideration of health benefits and resource use

The guideline development group acknowledged that psychological interventions could be costly and the cost would be affected by:

- the number of sessions required
- the setting in which the intervention is delivered
- the level of training or expertise needed to become appropriately skilled in delivering the intervention
- whether the intervention is delivered in a one-to-one setting or to groups.

Nevertheless, the guideline development group felt that overall their recommendations would a represent a cost-effective use of NHS resources in the specific groups and circumstances identified as this would be a highly targeted intervention in those with a large capacity to benefit.

9.8.8.4 Quality of evidence

The guideline development group noted that despite the use of similar terminology in the trials that evaluated the effectiveness of motivational interviewing, the content of the interventions delivered were very different. The group was of the view that the intervention evaluated by Wang (2010) did not reflect the form of motivational interviewing most often used in current clinical practice and they therefore chose to exclude this study from their deliberations when considering the evidence on motivational interviewing. The group noted that the skills and professional training of the individuals delivering the interventions also differed in these studies. The group reflected on the role and level of skill of the person delivering the intervention (see the section on Consideration of clinical benefits and harms above).

The group also noted that overall the evidence was quite limited with regard to several key outcomes, that for the outcomes that were reported the quality was very varied, and that the majority of the included studies were very small.

9.8.8.5 Other considerations

The Paediatric diabetes Best Practice Tariff criteria set by the Department of Health state that psychology should be integral to the multidisciplinary team and that each patient should have an annual assessment by their multidisciplinary team as to whether input to their care

by a psychologist is needed. The guideline development group believe that their recommendations are complementary to the Best Practice Tariff criteria.

9.8.8.6 Key conclusions

The guideline development group concluded that a weak recommendation to consider a programme of psychological intervention therapy (behavioural intervention therapy or behavioural techniques) for children and young people with type 1 diabetes in whom there are concerns about psychological wellbeing was warranted. The guideline development group specified the improvements that should be sought through psychological intervention therapy, and provided examples of specific forms of therapy that would be useful in those situations. Specifically, the group recommended that healthcare professionals should consider a programme of psychological interventions for children and young people with type 1 diabetes in whom there are concerns about psychological wellbeing in order to improve:

- health-related quality of life – for example counselling or CBT, including CBT focused on quality of life
- adherence to diabetes treatment – for example motivational interviewing or multi-systemic therapy
- blood glucose control in children and young people with high HbA1c levels (HbA1c above 69 mmol/mol [above 8.5%]) – for example multi-systemic therapy.

The guideline development group also recommended that healthcare professionals should offer specific family-based psychological interventions, such as behavioural family systems therapy, if there are difficulties with diabetes-related family conflict.

9.9 Adolescence

Adolescence is a major period of change physically, emotionally and socially. The hormonal changes associated with puberty will tend to increase insulin resistance and therefore changes to the diet and insulin treatment may be appropriate.

Young people cope with the demands of diabetes care and management differently from children who are still dependent on parental aid. The teenage years are a time when young people struggle for independence from their caregivers and worry about gaining acceptance from their peers, whilst trying to construct a new identity. There is a need to assist young people with type 1 diabetes in maintaining a sense of competence and self-esteem and to provide reassurance that they have not lost control of their life or body during this critical period of change.[657]

Major risks to young people with type 1 diabetes include persistent or progressively worse glycaemic control, risk-taking behaviour, recurrent diabetic ketoacidosis, accelerated microvascular complications and failure to attend clinic while shifting to adult-based care.[15] [evidence level IV]

The management aims of young people with type 1 diabetes are many and include the maintenance of blood glucose levels, normal growth and development, normal lifestyle and the prevention or minimisation of chronic complications.[658]

Young people aged 11 to 18 years were interviewed about the effects of psychological status, behaviour and self-esteem on glycaemic control; this was repeated about 8 years later (n=73).[659] [evidence level IIb] Behavioural problems in adolescence were significantly associated with higher mean HbA1c levels in the subsequent 8 years (regression coefficient β=0.15, 95% CI 0.07 to 0.24), but not to emotional state (β=0.06, 95% CI −0.002 to 0.13). Recurrent admission for diabetic ketoacidosis was a significant predictor of psychological state at follow-up (t=4.4, 95% CI 0.4 to 1.1).

An intervention study randomised 53 young people into a control group or a 6-week problem solving diabetes education programme to examine the effect on behaviour and glycaemic control.[660] [evidence level Ib] No significant differences were found between the groups 6 months later.

A small RCT (n=14) of young people with HbA1c levels >9.0% randomised participants to standard care or stress management training.[661] [evidence level Ib] Outcomes reported were stress, anxiety, use of coping strategies and glycaemic control. No significant differences were found between the 2 groups, but differences were detected within the intervention group. A controlled treatment outcome study of 19 patients produced similar results.[662] [evidence level IIa]

When 27 young people were stratified by level of glycaemic control (good, fair or poor), no differences in anxiety or stress were found between groups. Coping mechanisms differed between groups: young people with poor control (mean HbA1c 13.3%) used more wishful thinking ($p<0.01$) and avoidance/help-seeking measures ($p<0.03$) than did those with good control (mean HbA1c 8.4%).[663] [evidence level III] Good adherence to insulin regimen was predicted by high family knowledge about type 1 diabetes, positive family relations and younger age at adolescence.[664] [evidence level III]

A cohort of 42 children and young people (mean age of 12.9 years) was followed over 4 years to examine whether pubertal development had an effect on family environment and adjustment to diabetes.[665] [evidence level IIb–III] Overall adjustment to diabetes was correlated with family cohesion ($r=0.38$, $p<0.01$). Pre-pubertal young people had higher correlations for family cohesion factors with respect to overall adjustment, peer relations ($p=0.008$), attitude to diabetes ($p=0.03$) and body image concerns ($p=0.05$) when compared with other young people.

In summary, an extensive literature has described the association of type 1 diabetes in children and young people and abnormal psychological outcome and social dysfunction. Limited specific behavioural intervention strategies appear to improve psychological wellbeing and glycaemic control, particularly in young people using intensive insulin regimens. However, further evidence on the effectiveness of psychological and social interventions is required in the UK.

Other aspects of care that may impact on diabetes management in young people are discussed in Section 18 (transition from paediatric to adult care).

9.10 Advice on alcohol, smoking and recreational drugs for children and young people with type 1 diabetes

9.10.1 Alcohol

It is illegal for people under the age of 18 years to buy alcohol. However, it is recognised that the consumption of alcohol in young people with type 1 diabetes can be a problem.

We found no studies investigating the effects of alcohol consumption in young people with type 1 diabetes.

It has been widely reported in discussion articles that drinking alcohol can cause an increased risk of hypoglycaemia in patients with type 1 diabetes. However, we found no strong evidence to support this view.

One small study in adult males compared blood glucose levels and hypoglycaemia occurrence after drinking 0.75 g alcohol/kg body weight in an evening compared with a different evening when only mineral water was consumed (n=6). The study reported no change in evening or overnight blood glucose levels. However, morning fasting and

postprandial blood glucose levels were significantly lower after consumption of alcohol, with 5 out of 6 patients requiring treatment for hypoglycaemia.[453] [evidence level IIa]

Two small studies in adults found no change in blood glucose or hypoglycaemia after consuming alcohol in the evening. One of the studies investigated blood glucose levels after the administration of 0.5 g alcohol/kg body weight, compared with saline solution. No change was found in the initial rates of fall of blood glucose, the lowest blood glucose level, or the rate of blood glucose recovery (n=9).[454] [evidence level IIa] The second study investigated diurnal glucose profile and hypoglycaemia after the administration of 1 g alcohol/kg body weight compared with water. No differences were found in blood glucose levels (measured until 10 a.m. the following morning) and no patients in either group experienced hypoglycaemia (n=10).[455] [evidence level IIa]

In an early case series, 5 adult patients were reported to have presented in hospital with severe hypoglycaemia after ingesting alcohol.[456] [evidence level IV]

The effects of consuming alcohol at higher concentrations, in 'binge' drinking and in young people may be different from those discussed above.

It has been suggested that drinking alcohol reduces hypoglycaemia awareness. One small study investigated the perception of blood glucose levels after drinking 0.7 g alcohol/kg body weight in the evening in adults with type 1 diabetes (n=9). No difference in perceived blood glucose levels was found.[457] [evidence level IIa] A second small study investigated the effect of alcohol on hypoglycaemia awareness in men with type 1 diabetes (n=7). The study found that heart rate and sweat production were increased and finger tremors were less marked during hypoglycaemia after taking alcohol compared with placebo. Reaction time during hypoglycaemia was slower after alcohol than placebo ($p<0.05$).[458] [evidence level IIa]

One study investigated the prevalence of retinopathy in relation to alcohol consumption in people treated with insulin who had been diagnosed with diabetes before the age of 30 years (n=891, age range 21 to 78 years). The study found that the average alcohol consumption for the previous year (as determined by a questionnaire) was inversely associated with the prevalence of proliferative diabetic retinopathy (OR 0.49, 95% CI 0.27 to 0.92). Analysis of drinking history showed that ex-drinkers had the highest prevalence of proliferative diabetic retinopathy, although the prevalence was not significantly different from that in non-drinkers (43.8% versus 40.7%, OR 1.47, 95% CI 0.46 to 4.70; current drinkers OR 1.01, 95% CI 0.35 to 2.89 compared with non-drinkers).[459] [evidence level IIb]

A survey of male patients with diabetes found that greater alcohol consumption was associated with poorer adherence to prescribed insulin injection ($p<0.01$, n=154); however, no association was found between alcohol consumption and HbA1clevels.[460] [evidence level III]

We found no evidence relating to a recommended safe intake of alcohol in young people with or without type 1 diabetes. Consensus recommendations suggest that for adults with diabetes, as with the rest of the general adult population, men should consume no more than 21 units/week and women should consume no more than 14 units/week.[461] [evidence level III] However, the effects of alcohol may be greater in young people with type 1 diabetes because they have smaller body mass.

Previous consensus recommendations relating to alcohol consumption include the following.[15,461] [evidence level III]

- Alcohol consumption makes hypoglycaemia more likely to occur. However, as long as precautions are taken and diabetes is well controlled, moderate amounts of alcohol can be consumed before, during or soon after a meal without affecting short-term blood glucose control.
- Hypoglycaemia can occur up to 16 hours after drinking. To reduce the risk of hypoglycaemia, keep blood glucose levels within the recommended range by eating food

containing carbohydrate while drinking, eating a snack containing carbohydrate before bedtime and regular meals containing carbohydrate the following day (including breakfast), by maintaining good hydration and by closely monitoring blood glucose levels during and after consuming alcohol.

- Avoid consuming alcohol on an 'empty stomach' because the alcohol will be absorbed into the blood stream more quickly.
- Avoid substituting usual meals or snacks with alcoholic drinks because this may lead to hypoglycaemia.
- Avoid the consumption of large quantities of alcohol and binge drinking because these increase the risks of severe hypoglycaemia, vomiting, aspiration and diabetic ketoacidosis.
- Alcohol consumption may decrease awareness of hypoglycaemia symptoms. People with type 1 diabetes should be advised to wear some form of diabetes identification because hypoglycaemia may be confused with intoxication.
- If hypoglycaemia is caused by alcohol or fasting, glucagon will have little or no effect in restoring blood glucose levels.
- Excessive drinking over a period of time can lead to raised blood pressure and liver damage.

9.10.2 Smoking

Smoking has been shown to cause excess morbidity and mortality.[462] [evidence level IIb] The risk of morbidity and mortality among smokers with type 1 diabetes is greater than would be expected from simply combining the risks of smoking and type 1 diabetes.[463] [evidence level III]

Macrovascular complications have been shown to be increased in young adults (aged <43 years) with type 1 diabetes who smoke compared with those who do not (n=100).[464] [evidence level IIb]

One study investigated the prevalence of smoking in teenagers with type 1 diabetes (age range 11 to 18 years) in 2 paediatric clinics in Liverpool (n=77). The study identified 9% as probable smokers, who were all aged 15 years or more.[465] [evidence level III] A similar study in patients at a young adult clinic in Liverpool (age range 15 to 18 years) found a 48% prevalence of smoking (n=99).[466] [evidence level III] This suggests that teenagers become regular smokers after leaving paediatric clinics, which in turn suggests that it is important for health education to be targeted at this group.[465] [evidence level III]

A survey of young people (age range 10 to 20 years) in the USA found that 34% had smoked in the past and 27% had smoked in the previous year (n=155).[467] [evidence level III]

A survey of adults with type 1 diabetes in Australia found that 56% of smokers indicated that they would expect to receive no more than a little encouragement from friends and family members to quit. Approximately one-third of respondents felt that concerns about weight gain and dietary adherence were barriers to quitting smoking (n=223).[468] [evidence level III]

We found 1 study that looked at interventions to help people with diabetes stop smoking. The study involved patients under the age of 40 years (n=60) and compared intensive smoking cessation advice with routine advice. The study showed no difference in concentrations of end tidal carbon monoxide or urinary cotinine (a metabolite of nicotine) between the 2 treatment groups after 6 months. At the end of 6 months, none of the patients in the intensive advice group had successfully given up smoking and only 1 patient in the routine advice group had given up (and this was only after a myocardial infarction).[469] [evidence level Ib]

We found no studies that investigated optimum methods for preventing uptake of smoking or smoking cessation therapies in children and young people with type 1 diabetes.

9.10.3 Recreational drugs

The effects of substance misuse in the general population are well known.[133] There is little published information on substance misuse and the consequences in children and young people with type 1 diabetes. There has been 1 case report of ecstasy (3,4-methylenedioxymethamphetamine) use in a young person with type 1 diabetes; ecstasy in combination with insulin omission and sustained exercise caused dehydration with marked ketonuria and glycosuria.[470] [evidence level IV]

A survey of young people (age range 10 to 20 years) in the USA found that 10% had used a recreational drug in the past and 8% had used a recreational drug in the previous year (n=155).[467] [evidence level III].

We found no specific evidence relating to the effects of substance misuse on glycaemic control in people with diabetes or educational advice on substance use that should be given to young people with type 1 diabetes. A leaflet designed by a group of young people with type 1 diabetes is available from Diabetes UK.

Healthcare professionals may find it useful to refer to the recommendations in Section 5 (education) when offering information about smoking, alcohol and recreational drugs.

9.11 Recommendations

The current recommendations can be found at https://www.nice.org.uk/guidance/ng18

9.12 Research recommendations

This section was updated in 2015.

13. **[2004] Further research is needed to evaluate the effects of persistent hypoglycaemia and recurrent diabetic ketoacidosis on neurocognitive function.**

14. **[2004] Further studies are needed to evaluate the effectiveness of behavioural and social interventions on anxiety and depression, eating disorders, behavioural and conduct disorders, and adherence to therapy in children and young people with type 1 diabetes, especially in adolescence, from diagnosis and in established diabetes.**

10 Monitoring for associated conditions and complications of type 1 diabetes

10.1 Introduction

This section was updated in 2015.

This section of the guideline addresses conditions associated with type 1 diabetes in children and young people (including coeliac disease and hypothyroidism) and complications of type 1 diabetes (including retinopathy, nephropathy, hypertension, dyslipidaemia and neuropathy). The recommendations in the 2004 guideline related to screening for coeliac disease were updated in the interval between publication of the 2004 guideline and development of the 2015 update. The 2004 evidence reviews related to screening for coeliac disease and hypothyroidism have been retained in Section 10.2 and modified to note the changes made with regard to screening for coeliac disease, although these changes did not form part of the 2015 update. The 2004 evidence reviews related to other medical conditions associated with type 1 diabetes in children and young people have been retained in Section 10.3.

The evidence reviews in the 2004 guideline related to screening for microvascular and other complications covered:

- retinopathy
- nephropathy
- initial management and treatment
- blood pressure
- lipids
- neuropathy (including foot care and peripheral vascular disease)
- dental care
- growth and puberty.

For the 2015 update specific review questions on optimal monitoring strategies for identifying retinopathy and nephropathy in children and young people with type 1 diabetes were considered. The evidence identified in relation to these review questions and the guideline development group's interpretation of the evidence are presented in Section 10.4.1 and Section 10.4.2, respectively. The 2004 guideline evidence reviews that related to screening for complications other than retinopathy and nephropathy are retained in Section 10.4.3 to Section 10.4.8.

The 2004 recommendations related to monitoring for associated conditions and complications, and the recommendations arising from the 2015 update, are presented together in Section 10.5.

10.2 Screening for coeliac disease and hypothyroidism

Children and young people with type 1 diabetes have a higher prevalence of autoimmune disorders such as coeliac disease and thyroid disease compared with children and young people without type 1 diabetes.[9] [evidence level III] Active surveillance for these conditions in children and young people with type 1 diabetes will help minimise adverse sequelae. Healthcare professionals who care for children and young people with type 1 diabetes should be made aware of indications and methods of screening for coeliac disease and thyroid disease. If diagnosed, appropriate care and referral should be provided.

An evidence-based guideline suggested screening for coeliac and thyroid disease at the onset of diabetes and at intervals thereafter.[9] [evidence level III] The frequency of screening tests was not specified for either condition.

10.2.1 Coeliac disease

A consensus guideline for the management of children and young people with type 1 diabetes stated that healthcare professionals should be alert to the possible diagnosis of coeliac disease when children and young people with type 1 diabetes present with unexplained poor growth, anaemia or gastrointestinal symptoms.[15] [evidence level IV] However, the majority of children and young people present with minimal or no symptoms and then coeliac disease is detected by antibody screening. Anti-endomysial immunoglobulin A (IgA) antibody combined with total IgA levels is considered the most specific test for coeliac disease. It should be performed close to diagnosis and as necessary thereafter. Definitive diagnosis is made by jejunal biopsy. Effective treatment consists of a gluten-free diet, which may or may not alter insulin requirements or metabolic control.

We found no RCTs or systematic reviews that addressed screening for coeliac disease in children and young people with type 1 diabetes. However, we found several studies that investigated screening tools for coeliac disease in children and young people with type 1 diabetes. A prospective cohort study with 3 years of follow-up screened 157 children and young people with type 1 diabetes for coeliac disease with endomysial antibodies.[527] [evidence level IIb] Positive endomysial antibodies were found in 10.2% of patients (n=16), 5 detected at onset and 11 seroconverted during the course of diabetes (mean duration: 33.6 months). The prevalence of biopsy-proven coeliac disease was 5.1% and 8 children and young people showed no clinical signs of disease. Another study diagnosed coeliac disease retrospectively by positive serum gliadin/reticulin antibodies and jejunal biopsy. In this study, 50% of people who were diagnosed with coeliac disease were antibody-positive at initial diagnosis of diabetes.[528] [evidence level IIb]

Studies from various countries have reported prevalence rates of coeliac disease ranging from 2.9% to 5% in children and young people with type 1 diabetes as detected by positive antibodies and confirmed jejunal biopsy.[529–531] [evidence level IIb–III]

A systematic review of the test characteristics of auto-antibody tests for coeliac disease in symptomatic patient populations, or populations at a higher risk of developing coeliac disease, has been conducted. The review concluded that IgA endomysial antibody (using indirect immunofluorescence) was the most accurate test for coeliac disease. If ELISA (which may be more suitable for screening purposes because it can be semi-automated) is required, then testing combined with confirmatory biopsy is most cost effective, whilst combinations of tests add little or no further value. There is limited information regarding test accuracy in people with diabetes, and there is uncertainty about whether test characteristics would remain the same, particularly as there may be a role for screening in silent coeliac disease, and regarding long-term outcomes and complications of untreated coeliac disease.[532]

Following the development of 'Coeliac disease: recognition and assessment of coeliac disease' (NICE clinical guideline 86, 2009) NICE updated its guidance on screening for coeliac disease in children and young people with type 1 diabetes. Specifically, the recommendation to re-test for coeliac disease at least every 3 years after diagnosis was removed.

10.2.2 Thyroid disease

A study investigating routine screening for thyroid disease in 247 children and young people with type 1 diabetes identified thyroid disease in 11/247 children and young people (4.5%). All patients were asymptomatic at the time of diagnosis of thyroid disease. Four patients were diagnosed at or before diagnosis of type 1 diabetes and in the other 7 patients thyroid

disease was identified 2.0 to 10.7 years after diagnosis of type 1 diabetes.[533] [evidence level III]

One review summarised recommendations for thyroid function test screening in young people and adults with type 1 and type 2 diabetes.[534] [evidence level IV] The recommendations included offering screening tests to patients with newly diagnosed diabetes, at annual review and to those with symptoms suggestive of thyroid disease.

A consensus guideline for the management of children and young people with type 1 diabetes stated that thyroid function tests should be performed at diagnosis of type 1 diabetes and at annual assessments thereafter.[15] [evidence level IV] Autoimmune disorders such as hypothyroidism occur more frequently than hyperthyroidism (thyrotoxicosis) in children and young people with type 1 diabetes.[15] [evidence level IV]

Thyroid auto-antibodies, particularly peroxisomal antibodies, are present in 20 to 30% of children and young people with type 1 diabetes. In addition, 10 to 20% may have a palpable or visible goitre. However, the absence of thyroid auto-antibodies does not rule out subsequent thyroid disease.[15] [evidence level IV]

A consensus guideline for the management of children and young people with type 1 diabetes defined hypothyroidism as low total (or free) thyroxine and/or raised thyroid stimulating hormone.[15] [evidence level IV] The prevalence of overt hypothyroidism ranged from 1% to 5% in children and young people with type 1 diabetes. The clinical symptoms of hypothyroidism are goitre, weight gain, decreased growth rate and fatigue, but with screening most children and young people with hypothyroidism can be detected before symptoms arise.

A systematic review investigated the test characteristics of thyroid auto-antibody tests relative to thyroid function tests as a reference standard. The review found poor predictive value of auto-antibody tests relative to thyroid function tests, which appears to rule out their use as a screening test.[532]

10.3 Other medical conditions

A variety of other medical conditions has been described in association with type 1 diabetes in children and young people. These include:

- necrobiosis lipoidica
- Addison’s disease
- rheumatoid arthritis.

Another condition that arises as a result of therapy is lipohypertrophy. Case reports relate insulin injection into an area of lipohypertrophy to poor glycaemic control.[535] [evidence level III]

No systematic evidence is available on the screening for, or management of, these conditions, but they should be considered in clinical reviews of all children and young people with type 1 diabetes.

10.4 Screening for microvascular and other complications

Screening for microvascular and other complications aims to detect early abnormalities that can potentially be reversed by improved glycaemic control. An RCT has confirmed that tight glycaemic control helps to prevent long-term microvascular complications among young people.[83] [evidence level Ib] Management strategies for children and young people with type 1 diabetes should therefore include early detection and ongoing treatment of microvascular and other complications.

Long-term macrovascular complications (such as myocardial infarction resulting from atherosclerosis) are a significant cause of mortality and morbidity in adults with diabetes. Although large-vessel disease processes begin in childhood, macrovascular complications are not chief concerns for children and young people with type 1 diabetes. However, screening for associated risk factors may help to prevent severe long-term macrovascular complications. Dyslipidaemia and sustained hypertension are proxy surveillance measures for macrovascular disease. In addition, smoking cessation and physical activity programmes should be promoted to further reduce the risk of macrovascular disease.

10.4.1 Retinopathy

10.4.1.1 Review question

This section was updated in 2015.

What is the optimal monitoring strategy for identifying retinopathy in children and young people with type 1 diabetes?

10.4.1.2 Introduction

The aim of this review was to determine when screening for retinopathy should start and how frequently it should be repeated in children and young people with type 1 diabetes. The search covered cross-sectional studies which reported prevalence of retinopathy, as well as longitudinal studies which reported incidence of new retinopathy over time. Both the age of the children and young people affected and the duration of diabetes were to be considered when assessing the prevalence and incidence of retinopathy. Only studies that identified retinopathy using retinal photography were included.

All studies reporting prevalence of retinopathy for an entire population of children and young people (with no stratification according to age or duration of diabetes) were excluded. Studies were included if they reported data for participants aged over 18 years provided that data for children and young people aged 18 years and under were reported separately. Studies were also included if the mean age of participants was less than 18 years or if more than 50% of participants were aged under 18 years.

Outcomes prioritised for inclusion in the review were:

- prevalence of retinopathy at different time points after diagnosis
- incidence of retinopathy over time.

10.4.1.3 Description of included studies

Eighteen studies were identified for inclusion in this review question (Cerutti 1989; Cheung 2008; Cho 2011; Diabetes Control and Complications Trial Research Group 1994; Donaghue 1999; Flack 1996; Frank 1982; Goldstein 1993; Johansen 1994; Joner 1992; Kernell 1997; Klein 1984; Klein 1989; Klein 1997; Lobefalo 1997; Massin 2007; Murphy 1990; Olsen 2004). Nine of the studies were cross-sectional surveys assessing the prevalence of retinopathy (Donaghue 1999; Frank 1982; Johansen 1994; Joner 1992; Kernell 1997; Klein 1984; Lobefalo 1997; Massin 2007; Murphy 1990) and 8 were prospective cohort studies (Cerutti 1989; Cheung 2008; Cho 2011; Flack 1996; Goldstein 1993; Klein 1989; Klein 1997; Olsen 2004). The remaining study (Diabetes Control and Complications Trial Research Group 1994) reported the results of a randomised controlled trial (RCT).

The different studies reported prevalence of retinopathy at a variety of time points in terms of age or duration of diabetes (for example age 7 to 11 years, age 9 to 10 years, age 10 to 14 years). For this reason it was not possible to pool the data; instead, the range of prevalence

estimates at a given age is reported. In the example given above, children aged 10 years are included in each of the studies, and so the corresponding evidence profiles show the range of prevalence estimates from each study, but assuming that prevalence of retinopathy is related to age then studies reporting lower age ranges (for example 7 to 11 years) are likely to report lower prevalence than those reporting older ranges (for example 10 to 14 years). Thus some of the reported prevalence ranges are necessarily wide.

Almost all the studies reported only presence or absence of retinopathy as the outcome of interest. However, 'background retinopathy' would not usually warrant referral to an ophthalmologist or treatment (although it might be useful to inform the person that they should tighten their diabetic control). The dichotomous form of reporting may explain the relatively high prevalence of retinopathy even at very young ages (that is, less than 12 years, which was the starting point for screening in the 2004 guideline recommendations). Where an article indicates whether the participants have retinopathy that warrants further investigation or treatment this is noted in the evidence tables, but it was not possible to quantify this in the accompanying evidence profiles.

10.4.1.3.1 Cross-sectional surveys

Donaghue (1999) conducted an observational study between 1990 and 1997 to determine the prevalence of retinopathy in children and young people with type 1 diabetes. This study was conducted in Australia. The prevalence of retinopathy was reported for 110 children and young people aged 6 to 11 years (young people older than 11 years were also included in the study, but their data are also reported in another included study; Cho 2011).

Frank (1982) reported prevalence and severity of retinopathy in children and young people with type 1 diabetes aged 6 to 23 years (mean 13.2 years). The prevalence of retinopathy for children and young people of different ages and for different durations of diabetes was reported. This study was conducted in the USA and there were 173 participants.

Johansen (1994) conducted a population-based cross-sectional survey in a single county in Denmark which included 42 children and young people (age range 7 to 15 years, median 11 years). The prevalence of retinopathy was reported and could be calculated for different age groups. The median duration of diabetes was 4 years (range 1 to 12 years).

Joner (1992) reported on a nationwide cross-sectional study conducted in Norway, which aimed to assess the prevalence of retinopathy in children and young adults with type 1 diabetes. Although the mean age of participants was 18.3 years, the prevalence of retinopathy in children aged under 13 years was reported separately. The study included 371 participants, 45 of whom were under 13 years. Data for the children and young people aged under 13 years were used for the guideline review.

Kernell (1997) conducted a population-based cross-sectional study to assess the prevalence of retinopathy in children and young people with type 1 diabetes in Sweden. The study included 557 participants and prevalence was assessed according to both the age of participants and the duration of diabetes. The median age of participants was 14.6 years, with an interquartile range of 12.2 to 17.0 years.

Klein (1984) reported the prevalence of retinopathy in participants diagnosed with type 1 diabetes who enrolled in a prospective longitudinal study. All participants were diagnosed before the age of 30 years. This study was conducted in the USA and included 1210 participants. However, the majority of participants were adults (mean age 29.4 years). Nonetheless, data for 272 children and young people aged 19 years and under were available for analysis of prevalence of retinopathy according to age and have been used in the guideline review.

Lobefalo (1997) reported the prevalence of retinopathy in 246 children and young people with type 1 diabetes (mean age 16.2 years, range 6 months to 26.9 years). This study was

conducted in Italy. No data were reported regarding the prevalence of retinopathy at different ages, but the study did assess prevalence of retinopathy according to duration of diabetes.

Massin (2007) conducted a cross-sectional survey at summer camps for French children and young people with type 1 diabetes, with a mean age of 13.2 years (age range not reported). Prevalence of retinopathy in 504 participants was reported, expressed according to the participant's age and the duration of diabetes.

Murphy (1990) reported the prevalence of retinopathy in a group of 70 children and young people with type 1 diabetes (mean age 13.8 years, range 6.2 to 22.9 years). This study was conducted in the USA and reported prevalence according to duration of diabetes, but not according to age.

10.4.1.3.2 Prospective cohort studies

Cerutti (1989) conducted a prospective cohort study of children and young people with type 1 diabetes from January 1978 to December 1987. The prevalence of retinopathy at the conclusion of the study was reported (as cross-sectional data) according to duration of diabetes and age of the participants. This study was conducted in Italy and there were 112 participants, with a mean age of 15 years at the end of the study (age range 6 to 18 years).

Cheung (2008) reported the incidence of retinopathy in participants with type 1 diabetes who were retinopathy-free at baseline examination. The 650 participants were enrolled between 1990 and 2002 and were followed up for a median of 2.5 years. This study was conducted in Australia and included children and young people aged 12 to 20 years.

Cho (2011) reported the prevalence of retinopathy in children and young people aged 11 to 17 years, all of whom had been diagnosed with type 1 diabetes 2 to 5 years previously. There were 819 participants and they were assessed between 1990 and 2006. This study was conducted in the same hospital as that of Donaghue (1999) and Cheung (2008) and is, therefore, likely to include data on the participants aged over 11 years in the Donaghue (1999).

Flack (1996) conducted a prospective cohort study in Sweden between 1989 and 1993. The participants were 182 children and young people and results were reported for children and young people aged younger than 13 years, 13 to 14.9 years, 15 to 16.9 years and 17 to 18.9 years. The prevalence of retinopathy at the conclusion of the study was reported (according to age and duration of diabetes) as well as the incidence of retinopathy over the 2.5-year follow-up period.

Goldstein (1993) reported longitudinal follow-up of 420 children and young people with type 1 diabetes. The mean age of participants was 15.9 years (range 2.5 to 30.9 years). The prevalence of retinopathy after specific durations of diabetes was reported. This study was conducted in the USA.

Klein (1989) reported 4-year follow-up data for 891 participants recruited for the Klein (1984) cross-sectional study described above. Again, although the mean age of participants was 28.3 years, the study reported the incidence of retinopathy over a 4-year period for children and young people of different ages (0 to 9 years, 10 to 12 years and 13 to 14 years at baseline). The study was conducted in the USA.

Klein 1997) reported on a second cohort of individuals with type 1 diabetes in the USA. Participants were enrolled between 1987 and 1992, and followed up for 4 years. All participants were aged between 4 and 30 years, but data for those aged less than 10 years and those aged 10 to 14 years were presented separately and used in the guideline review. The study authors reported the incidence of retinopathy during the 4-year follow-up period.

Olsen (2004) conducted a nationwide prospective cohort study of Danish children, young people and young adults with type 1 diabetes. The mean age of participants at the

conclusion of the study was 20.9 years, but data for young people aged 12 to 15 years were presented separately and therefore could be used in the guideline review. The prevalence of retinopathy at the conclusion of the study (1995) was reported according to the age of the participants.

10.4.1.3.3 Randomised controlled trials

The only RCT identified for inclusion (Diabetes Control and Complications Trial Research Group 1994) was conducted in the USA. The aim of the trial was to assess the effect of intensive blood glucose control on complications of diabetes in young people aged 13 to 17 years at trial entry. There were 125 participants (all retinopathy-free at baseline). The study reported incidence of any retinopathy over the 4 to 9 year follow-up period, defined as evidence of retinopathy on 2 consecutive fundus photographs taken 6 months apart. The incidence of 'clinically important' retinopathy was also reported; this was defined as a worsening of at least 3 steps on the retinopathy scale sustained for at least 6 months.

10.4.1.4 Evidence profile

The evidence profiles for this review question (monitoring for retinopathy) are presented in Table 44 to Table 46.

Table 44: Evidence profile for prevalence of retinopathy according to age

Number of studies	Number of children and young people	Range of prevalence, % (median, %)	Quality
Age <9 years			
8 (Cerutti 1989, Donaghue 1999, Flack 1996, Frank 1982, Johansen 1994, Joner 1992, Kernell 1997, Klein 1984)	NC	0.0 to 9.0 (4.5)	Moderate
Age 9 years			
8 (Cerutti 1989, Donaghue 1999, Flack 1996, Frank 1982, Joner 1992, Johansen 1994, Klein 1984, Kernell 1997)	NC	0.0 to 9.0 (4.5)	Moderate
Age 10 years			
9 (Cerutti 1989, Donaghue 1999, Flack 1996, Frank 1982, Johansen 1994, Joner 1992, Kernell 1997, Klein 1984, Massin 2007)	NC	0.0 to 15.0 (6.7)	Low[a]
Age 11 years			
8 (Cerutti 1989, Cho 2011, Flack 1996, Frank 1982, Johansen I 1994, Joner 1992, Klein 1984, Massin 2007)	NC	0.0 to 15.0 (6.4)	Low[a]
Age 12 years			
9 (Cerutti 1989, Cho 2011, Flack 1996, Frank 1982, Johansen 1994, Joner 1992, Klein 1984, Massin 2007, Olsen I 2004)	NC	1.0 to 19.0 (7.7)	Low[a]
Age 13 years			
8 (Cerutti 1989, Cho 2011, Flack 1996, Frank 1982, Johansen 1994, Klein 1984, Massin 2007, Olsen 2004)	NC	1.0 to 25.0 (13.0)	Low[a]
Age 14 years			
8 (Cerutti 1989, Cho 2011, Flack 1996, Frank 1982, Johansen 1994, Klein 1984, Massin 2007, Olsen 2004)	NC	5.8 to 44.0 (13.0)	Very low[b]
Age 15 years			
8 (Cerutti 1989, Cho 2011, Flack 1996, Frank 1982, Johansen 1994, Klein 1984, Massin 2007, Olsen 2004)	NC	5.8 to 54.0 (28.7)	Very low[b]

Number of studies	Number of children and young people	Range of prevalence, % (median, %)	Quality
Age 16 years			
6 (Cerutti 1989, Cho 2011, Flack 1996, Frank 1982, Klein 1984, Massin 2007)	NC	11.0 to 54.0 (42.8)	Very low[b]
Age 17 years			
5 (Cerutti 1989, Flack 1996, Frank 1982, Klein 1984, Massin 2007)	NC	17.7 to 54.0 (45.7)	Very low[b]
Age 18 years			
5 (Cerutti 1989, Flack 1996, Frank 1982, Klein 1984, Massin 2007)	NC	17.7 to 60.0 (48.0)	Very low[b]

NC not calculable
a. Serious inconsistency between point estimates
b. Very serious inconsistency between point estimates

Table 45: Evidence profile for prevalence of retinopathy according to duration of diabetes

Number of studies	Number of children and young people	Range of prevalence, % (median, %)	Quality
Duration <2 years			
6 (Flack 1996, Frank 1982, Kernell 1997, Lobefalo 1997, Massin 2007, Murphy 1990)	NC	1.0 to 21.0 (7.9)	Low[a]
Duration 2 years			
6 (Cho 2011, Flack 1996, Frank 1982, Lobefalo 1997, Massin 2007, Murphy 1990)	NC	1.0 to 21.0 (10.9)	Low[a]
Duration 3 years			
7 (Cerutti 1989, Cho 2011, Flack 1996, Frank 1982, Lobefalo 1997, Massin 2007, Murphy 1990,)	NC	1.0 to 23.0 (10.5)	Very low[b]
Duration 4 years			
7 (Cerutti 1989, Cho 2011, Flack 1996, Frank 1982, Lobefalo 1997, Massin 2007, Murphy 1990)	NC	1.0 to 23.0 (10.5)	Very low[b]
Duration 5 years			
7 (Cerutti 1989, Cho 2011, Flack 1996, Frank 1982, Lobefalo 1997, Massin 2007, Murphy 1990)	NC	6.2 to 50.0 (13.6)	Very low[b]
Duration 6 years			
6 (Cerutti 1989, Flack 1996, Frank 1982, Lobefalo 1997, Massin 2007, Murphy 1990)	NC	6.2 to 50.0 (19.3)	Very low[b]
Duration 7 years			
6 (Cerutti 1989, Flack 1996, Frank 1982, Lobefalo 1997, Massin 2007, Murphy 1990)	NC	6.2 to 50.0 (22.9)	Very low[b]
Duration 8 years			
7 (Cerutti 1989, Flack 1996, Frank 1982, Joner 1992, Lobefalo 1997, Massin 2007, Murphy 1990)	NC	6.2 to 50.0 (20.7)	Very low[b]
Duration 9 years			
6 (Goldstein 1993, Flack 1996, Frank 1982, Lobefalo 1997, Massin 2007, Murphy 1990)	NC	6.2 to 59.0 (37.0)	Very low[b]

Number of studies	Number of children and young people	Range of prevalence, % (median, %)	Quality
Duration 10 years			
6 (Flack 1996, Frank 1982, Kernell 1997, Lobefalo 1997, Massin 2007, Murphy 1990)	NC	6.2 to 67.0 (41.0)	Very low[b]
Duration 11 years			
7 (Cerutti 1989, Flack 1996, Frank 1982, Kernell 1997, Lobefalo 1997, Massin 2007, Murphy 1990)	NC	13.0 to 75.0 (57.5)	Very low[b]
Duration 12 years			
7 (Cerutti 1989, Flack 1996, Frank 1982, Kernell 1997, Lobefalo 1997, Massin 2007, Murphy 1990)	NC	13.0 to 75.0 (57.1)	Very low[b]
Duration 13 years			
6 (Cerutti 1989, Flack 1996, Frank 1982 1990, Lobefalo 1997, Massin 2007)	NC	13.0 to 75.0 (57.3)	Very low[b]
Duration 14 years			
6 (Cerutti 1989, Flack 1996, Joner 1992, Lobefalo 1997, Massin 2007, Murphy 1990)	NC	13.0 to 75.0 (53.1)	Very low[b]
Duration 15 years			
7 (Cerutti 1989, Flack 1996, Frank 1982, Goldstein 1993, Lobefalo 1997, Massin 2007, Murphy 1990)	NC	13.0 to 92.0 (57.5)	Very low[b]
Duration 16 years			
6 (Cerutti 1989, Flack 1996, Frank 1982, Lobefalo 1997, Massin 2007, Murphy 1990)	NC	13.0 to 75.0 (57.3)	Very low[b]
Duration 17 years			
5 (Cerutti 1989, Flack 1996, Lobefalo 1997, Massin 2007, Murphy 1990)	NC	13.0 to 75.0 (57.1)	Very low[b]
Duration 18 years			
4 (Flack 1996, Lobefalo 1997, Massin 2007, Murphy 1990)	NC	13.0 to 75.0 (38.9)	Very low[b]

NC not calculable
a.Serious inconsistency between point estimates
b. Very serious inconsistency between point estimates

Table 46: Evidence profile for incidence of retinopathy

Number of studies	Number of children and young people	Incidence per 100 person years	Quality
Any sustained retinopathy			
1 (DCCT Research Group 1994)	55	18	High
1 (DCCT Research Group 1994)	70	23	High
≥ 3 step worsening of retinopathy			
1 (DCCT Research Group 1994)	55	3.2	High
1 (DCCT Research Group 1994)	70	6.3	High
Any retinopathy			
1 (Cheung 2008)	645	14.8	Moderate

Number of studies	Number of children and young people	Incidence per 100 person years	Quality
1 (Flack 1996)	182	7	Moderate
Any retinopathy in age group 0 to 9 years			
1 (Klein 1989)	26	3.85	Moderate
1 (Klein 1997)	14	0	Moderate
Any retinopathy in age group 10 to 12 years			
1 (Klein 1989)	42	13.7	Moderate
Any retinopathy in age group 13 to 14 years			
1 (Klein 1989)	25	12	Moderate
Any retinopathy in age group 10 to 14 years			
1 (Klein 1997)	47	1.08	Moderate

DCCT Diabetes Control and Complications Trial

10.4.1.5 Evidence statements

An asterisk (*) indicates that the total number of participants analysed for each outcome could not be calculated from the published data.

Prevalence of retinopathy according to age

One study* estimated the prevalence of diabetic retinopathy in children and young people aged 9 years or younger to be between 0% and 9% (median 4.5%). The evidence for this finding was of moderate quality.

One study* estimated the prevalence of diabetic retinopathy in children and young people aged 10 years to be between 0% and 15% (median 6.7%). The evidence for this finding was of low quality.

One study* estimated the prevalence of diabetic retinopathy in children and young people aged 11 to be between 0% and 15% (median 6.4%). The evidence for this finding was of low quality.

One study* estimated the prevalence of diabetic retinopathy in children and young people aged 12 to be between 1% and 19% (median 7.7%). The evidence for this finding was of low quality.

One study* estimated the prevalence of diabetic retinopathy in children and young people aged 13 to be between 1% and 25% (median 13%). The evidence for this finding was of low quality.

The evidence for all of the remaining findings was of very low quality.

One study* estimated the prevalence of diabetic retinopathy in children and young people aged 14 to be between 5.8% and 44% (median 13%).

One study* estimated the prevalence of diabetic retinopathy in children and young people aged 15 to be between 5.8% and 54% (median 28.7%).

One study* estimated the prevalence of diabetic retinopathy in children and young people aged 16 to be between 11% and 54% (median 42.8%).

One study* estimated the prevalence of diabetic retinopathy in children and young people aged 17 to be between 17.7% and 54% (median 45.7%).

One study* estimated the prevalence of diabetic retinopathy in children and young people aged 18 to be between 17.7% and 60% (median 48%).

Prevalence of retinopathy according to duration of diabetes

One study* estimated the prevalence of diabetic retinopathy in children and young people who have been diagnosed with type 1 diabetes for less than 2 years to be between 1% and 21% (median 7.9%). The evidence for this finding was of low quality.

One study* estimated the prevalence of diabetic retinopathy in children and young people who have been diagnosed with type 1 diabetes for 2 years to be between 1% and 21% (median 10.9%). The evidence for this finding was of low quality.

The evidence for all the remaining findings was of very low quality.

One study* estimated the prevalence of diabetic retinopathy in children and young people who have been diagnosed with type 1 diabetes for 3 or 4 years to be between 1% and 23% (median 10.5%).

One study* estimated the prevalence of diabetic retinopathy in children and young people who have been diagnosed with type 1 diabetes for 5 years to be between 6.2% and 50% (median 13.6%).

One study* estimated the prevalence of diabetic retinopathy in children and young people who have been diagnosed with type 1 diabetes for 6 years to be between 6.2% and 50% (median 19.3%).

One study* estimated the prevalence of diabetic retinopathy in children and young people who have been diagnosed with type 1 diabetes for 7 years to be between 6.2% and 50% (median 22.9%).

One study* estimated the prevalence of diabetic retinopathy in children and young people who have been diagnosed with type 1 diabetes for 8 years to be between 6.2% and 50% (median 20.7%).

One study* estimated the prevalence of diabetic retinopathy in children and young people who have been diagnosed with type 1 diabetes for 9 years to be between 6.2% and 59% (median 37%).

One study* estimated the prevalence of diabetic retinopathy in children and young people who have been diagnosed with type 1 diabetes for 10 years to be between 6.2% and 67% (median 41%).

One study* estimated the prevalence of diabetic retinopathy in children and young people who have been diagnosed with type 1 diabetes for 11 years to be between 13% and 75% (median 57.5%).

One study* estimated the prevalence of diabetic retinopathy in children and young people who have been diagnosed with type 1 diabetes for 12 years to be between 13% and 75% (median 57.1%).

One study* estimated the prevalence of diabetic retinopathy in children and young people who have been diagnosed with type 1 diabetes for 13 years to be between 13% and 75% (median 57.3%).

One study* estimated the prevalence of diabetic retinopathy in children and young people who have been diagnosed with type 1 diabetes for 14 years to be between 13% and 75% (median 53.1%).

One study* estimated the prevalence of diabetic retinopathy in children and young people who have been diagnosed with type 1 diabetes for 15 years to be between 13% and 75% (median 57.5%).

One study* estimated the prevalence of diabetic retinopathy in children and young people who have been diagnosed with type 1 diabetes for 16 years to be between 13% and 75% (median 57.3%).

One study* estimated the prevalence of diabetic retinopathy in children and young people who have been diagnosed with type 1 diabetes for 17 years to be between 13% and 75% (median 57.1%).

One study* estimated the prevalence of diabetic retinopathy in children and young people who have been diagnosed with type 1 diabetes for 18 years to be between 13% and 75% (median 38.9%).

Incidence of retinopathy

Two studies (total 125 participants) estimated the incidence of sustained retinopathy (over a 6-month period) in children and young people with type 1 diabetes to be between 18 and 23 per 100 person years. The evidence for this finding was of high quality.

Two studies (total 125 participants) estimated the incidence of a more than 3-step worsening of retinopathy (that is, development of clinically important retinopathy) in children and young people with type 1 diabetes to be between 3.2 and 6.3 per 100 person years. The evidence for this finding was of high quality.

Two studies (total 827 participants) estimated the incidence of retinopathy in children and young people of all ages with type 1 diabetes to be between 7 and 14.8 per 100 person years. The evidence for this finding was of moderate quality.

Two studies (total 40 participants) estimated the incidence of retinopathy in children and young people aged 0 to 9 years with type 1 diabetes to be between 0 and 3.85 per 100 person years. The evidence for this finding was of moderate quality.

Two studies (total 89 participants) estimated the incidence of retinopathy in children and young people aged 10 to 12 years with type 1 diabetes to be between 1.08 and 13.7 per 100 person years. The evidence for this finding was of moderate quality.

Two studies (total 72 participants) estimated the incidence of retinopathy in children and young people aged 13 to 14 years with type 1 diabetes to be between 1.08 and 12 per 100 person years. The evidence for this finding was of moderate quality.

10.4.1.6 Health economics profile

A systematic literature search did not identify any relevant economic evaluations addressing the optimal monitoring strategy for identifying retinopathy in children and young people with type 1 diabetes.

This question was not prioritised for health economic analysis. It was anticipated that the number of children and young people who might be affected by a change in the recommendations for this topic was relatively small and therefore any cost impact arising was not expected to be very important. Furthermore, the clinical evidence review did not address the effectiveness of screening technologies, or treatment or management decisions

that may follow from the screening results. Such evidence would be required for economic modelling.

10.4.1.7 Evidence to recommendations

10.4.1.7.1 Relative value placed on the outcomes considered

The guideline development group considered the main aim of retinal screening in children and young people with diabetes to be the identification of retinopathy that requires treatment (that is, more advanced stages of retinopathy than background retinopathy). Nevertheless the group felt that there may be some benefit from the identification of minor (background) retinopathy because, in their experience, awareness of this can encourage children and young people to improve their blood glucose control. However, the group noted that the incidence of microaneurysms in people of this age who do not have diabetes is unknown and it is difficult, therefore, to ascertain whether the identification of background retinopathy is specifically associated with diabetes.

The 2004 guideline recommended annual retinopathy screening based on age criteria alone. The guideline development group felt that there remained some clinical uncertainty as to whether the screening strategy should also take account of duration of diabetes. For this reason the group prioritised prevalence and incidence in children and young people with diabetes as outcomes of interest in the 2015 update review so that they could gain an understanding of both the number of cases of retinopathy in different age groups and also the rate at which new cases occurred in relation to time from diagnosis.

The guideline development group noted that studies commonly reported only the presence or absence of retinopathy, with little emphasis on severity. Therefore, it was difficult for the group to determine the prevalence of retinopathy requiring treatment at any given age.

Of the studies which commented on severity of retinopathy at different ages, 5 reported no incidence of proliferative retinopathy in children and young people under the age of 13 years (Cerutti 1989; Frank 1982; Goldstein 1993; Johansen 1994; Klein 1989). This was consistent with the clinical experience of the guideline development group, which was that retinopathy requiring treatment is extremely rare in children and young people under the age of 12 years.

10.4.1.7.2 Consideration of clinical benefits and harms

The guideline development group was aware that the identification of clinically significant retinopathy (retinopathy requiring treatment) is relevant to reduce the risk of long-term impairment of vision. However, the group felt that the identification of retinopathy may cause distress to the child or young person or their family members or carers (as appropriate), even if this retinopathy is not felt to pose a serious risk to their sight or to require any treatment.

The group noted that background retinopathy is commonly found in children and young people with diabetes (even despite good glycaemic control). Furthermore, it was agreed that background retinopathy may fluctuate, rather than being a persistent feature. Therefore, while attention should be paid to optimising diabetes control, retinopathy does not usually progress to a stage requiring treatment or pose a risk to sight during childhood or adolescence.

10.4.1.7.3 Consideration of health benefits and resource use

The current national screening programme includes all people with diabetes from the age of 12 years. Therefore no change would be made to current practice by continuing to recommend screening from this age.

10.4.1.7.4 Quality of evidence

The guideline development group was aware that much of the data identified for inclusion in the guideline review was obtained from studies conducted in the 1980s and 1990s. At that time, treatment of diabetes was less intensive and glycaemic control was suboptimal. This may have led to over-estimation of the prevalence of retinopathy when compared with children and young people with type 1 diabetes at present.

Due to the nature of reporting in the included studies it was impossible to obtain specific data for the prevalence of retinopathy at individual ages or following a specific duration of diabetes. Individual studies subdivided their populations into particular age ranges, or ranges of diabetes duration, and the approach taken varied between studies. Therefore the prevalence estimates obtained for a specific age or duration of diabetes summarise estimates from studies considering a range of ages or durations of diabetes. This is likely to have contributed to the wide ranges of prevalence estimates reported in the included studies.

The guideline development group noted that almost all of the evidence identified was of very low or low quality. This was due in part to the inability to assess the precision of the prevalence estimates and the degree of heterogeneity between studies.

10.4.1.7.5 Other considerations

There were no other considerations.

10.4.1.7.6 Key conclusions

The guideline development group agreed that the consensus recommendation in the 2004 guideline advising children and young people with type 1 diabetes to have an eye examination by an optician every 2 years was still considered good practice and they found that there was no evidence to direct a change from the previous recommendation. The group felt that there was likely to be added benefit to be gained in terms of improving glycaemic control by providing information about background retinopathy and the risks of clinically significant retinopathy.

To mitigate against risk of distress to the child or young person and their family members or carers (as appropriate), the group also felt that it was important to explain the rarity of clinically significant retinopathy in children and young people with type 1 diabetes, the importance of regular screening from the age of 12 years and the fact that early treatment of retinopathy improves outcomes. The group therefore recommended that healthcare professionals should offer children and young people with type 1 diabetes screening for diabetic retinopathy annually from the age of 12 years. They also recommended that healthcare professionals should explain to children and young people with type 1 diabetes and their family members or carers (as appropriate) the importance of annual screening from the age of 12 years for diabetic retinopathy and that:

- screening begins at the age of 12 years because diabetic retinopathy that needs treatment is extremely rare in people under 12
- background retinopathy is often found through screening, and improving blood glucose control will reduce the risk of this progressing to significant diabetic retinopathy
- annual screening from the age of 12 years is important because if significant diabetic retinopathy is found, early treatment will improve the outcome.

The recommendations related to the optimal monitoring strategy for retinopathy in children and young people with type 1 diabetes use the terminology ‘monitoring’ rather than ‘screening’.

10.4.2 Nephropathy

10.4.2.1 Review question

This section was updated in 2015.

What is the optimal monitoring strategy for identifying nephropathy in children and young people with type 1 diabetes?

10.4.2.2 Introduction

The objective of this review question was to determine when monitoring for nephropathy should start following diagnosis of type 1 diabetes and how frequently it should be repeated. A raised albumin excretion rate (termed low-level albuminuria or microalbuminuria) is a risk factor for developing nephropathy and therefore cross-sectional studies that report prevalence of low-level albuminuria or longitudinal studies that estimate incidence of new cases of low-level albuminuria over time were identified and assessed for inclusion. In order to assess at what age or duration of diabetes monitoring should start in children and young people with type 1 diabetes, and how frequently it should be repeated, only studies that reported low-level albuminuria prevalence or incidence stratified by age or duration of diabetes were considered. Low-level albuminuria was measured by either albumin excretion rate (AER) in micrograms per minute or albumin:creatinine ratio (ACR) in micrograms per milligram across studies. In accordance with usual nephropathy screening practice in the UK (ACR measured in mg/mmol), AERs expressed in microgram/minute and ACRs expressed in microgram/mg were converted to ACRs expressed in mg/mmol using linear regression equations (Schultz 1999) and interconversion equations (Chavan 2011) used in previous studies, respectively. Studies testing for low-level albuminuria (defined as measured or converted ACR larger than 2.5 mg/mmol in males or 3.5 mg/mmol in females) on at least 2 out of 3 urine collections were included.

10.4.2.3 Description of included studies

Thirteen published studies were identified for inclusion for this review question (Bognetti 1997; Cho 2011; Daniels 2013; Donaghue 1999; dos Santos 2002; Dunger 2014; Gallego 2006; Galler 2012; Karavanaki 1999; Kong 2005; Nicoloff 2001; Olsen 2004; Rudberg 1993; Yoo 2004). Additionally, unpublished data from the Oxford Regional Prospective Study obtained through personal communication were also included (Dunger 2014). Seven of the studies were cross-sectional in design (Bognetti 1997; Cho 2011; Daniels 2013; Donaghue 1999; dos Santos 2002; Kong 2005; Yoo 2004) and 7 were prospective studies (Dunger 2014; Gallego 2006; Galler 2012; Karavanaki 1999; Nicoloff 2001; Olsen 2004; Rudberg 1993).

Four studies were undertaken in Australia (Cho 2011; Donaghue 1997; Gallego 2006; Kong 2005), 2 in the UK (Dunger 2014; Karavanaki 1999) and 1 each in the USA (Daniels 2013), Denmark (Olsen 2004), Sweden (Rudberg 1993), Germany and Austria (Galler 2012), Italy (Bognetti 1997), Bulgaria (Nicoloff 2001), Brazil (dos Santos 2002) and Korea (Yoo 2004). Sample sizes ranged from 28 to 955, and the age of participants ranged from 0 to 18 years across studies.

Low-level albuminuria prevalence stratified by age (ranging from less than 10 to 18 years) was estimated and reported across 11 studies (Bognetti 1997; Cho 2011; Daniels 2013; Donaghue 1999; dos Santos 2002; Dunger 2014; Gallego 2006; Galler 2012; Karavanaki 1999; Olsen 2004; Yoo 2004). Low-level albuminuria prevalence stratified by duration of diabetes (ranging from less than 2 years to 15 years) was estimated and reported across 8 studies (Bognetti 1997; Daniels 2013; Donaghue 1999; dos Santos 2002; Dunger 2014; Kong 2005; Nicoloff 2001; Yoo 2004). Incidence of low-level albuminuria stratified by

duration of diabetes (ranging from 0 to 9 years) was reported in 1 longitudinal study (Rudberg 1993). None of the studies reported low-level albuminuria incidence by age.

Observational studies were the appropriate study design to addressing this question, so were initially assigned moderate quality and downgraded based on potential sources of bias.

10.4.2.4 Evidence profile

The evidence profiles for this review question (monitoring for nephropathy in children and young people with type 1 diabetes) are presented in Table 47 to Table 50.

Table 47: Evidence profile for prevalence of low-level albuminuria by age (albumin:creatinine ratio ranging from more than 3.39 mg/mmol to more than 3.5 mg/mmol in males and from more than 3.39 mg/mmol to more than 4.0 mg/mmol in females, in at least 2 out of 3 urine collections)

Number of studies	Number of children and young people	Range of prevalence, % (median, %)	Quality
Age <10 years			
5 (Daniels 2013; Donaghue 1999; Dunger 2014 dos Santos 2002; Yoo 2004)	NC	0 to 66.7 (0)	Very low
Age 10 years			
8 (Bognetti 1997; Daniels 2013; Donaghue 1999; dos Santos 2002; Dunger 2014; Gallego 2006; Galler 2012; Yoo 2004)	NC	0 to 9 (0)	Very low
Age 11 years			
5 (Cho 2011; Daniels 2013; Donaghue 1999; Dunger 2014; dos Santos 2002)	NC	0 to 10 (2.4)	Very low
Age 12 years			
6 (Cho 2011; Daniels 2013; Donaghue 1999; Dunger 2014; dos Santos 2002; Olsen 2004)	NC	0 to 15.4 (2.2)	Very low
Age 13 years			
6 (Cho 2011; Daniels 2013; Donaghue 1999; Dunger 2014; dos Santos 2002; Olsen 2004)	NC	0 to 67 (5)	Very low
Age 14 years			
6 (Cho 2011; Daniels 2013; Donaghue 1999; Dunger 2014; dos Santos 2002; Olsen 2004)	NC	0 to 67 (4.7)	Very low
Age 15 years			
7 (Cho 2011; Daniels 2013; Donaghue 1999; Dunger 2014; Dos Santos 2002; Galler 2012; Olsen 2004)	NC	0 to 75 (5)	Very low
Age 16 years			
6 (Cho 2011; Daniels 2013; Donaghue 1999; Dunger 2014 dos Santos 2002; Olsen 2004)	NC	3 to 75 (9.9)	Very low
Age 17 years			
5 (Daniels 2013; Donaghue 1999; Dunger 2014; dos Santos 2002; Olsen 2004)	NC	5 to 67 (14)	Very low
Age 18 years			
5 (Daniels 2013; Donaghue 1999; Dunger 2014; Dos Santos 2002; Olsen 2004)	NC	5 to 67 (14)	Very low

NC not calculable

Table 48: Evidence profile for prevalence of low-level albuminuria by age (albumin:creatinine ratio more than 4.59 mg/mmol in males, and more than 5.24 mg/mmol in females, in at least 2 out of 3 urine collections)

Number of studies	Number of children and young people	Range of prevalence, % (median, %)	Quality
Age ≤ 10 years			
1 (Karavanaki 1999)	NC	0 to 0 (0)	Low

NC not calculable

Table 49: Evidence profile for prevalence of low-level albuminuria by duration of diabetes (albumin:creatinine ratio ranging from more than 3.39 mg/mmol to more than 3.5 mg/mmol in males and from more than 3.39 mg/mmol to more than 4.0 mg/mmol in females, in at least 2 out of 3 urine collections)

Number of studies	Number of children and young people	Range of prevalence, % (median, %)	Quality
Duration <2 years			
5 (Donaghue 1999; dos Santos 2002; Dunger 2014; Nicoloff 2001; Yoo 2004)	NC	0 to 0 (0)	Very low
Duration 2 years			
5 (Donaghue 1999; dos Santos 2002; Dunger 2014; Nicoloff 2001; Yoo 2004)	NC	0 to 16.7 (1)	Very low
Duration 3 years			
4 (Donaghue 1999; Dos Santos 2002; Dunger 2014; Nicoloff 2001)	NC	0 to 2 (0)	Very low
Duration 4 years			
5 (Daniels 2013; Donaghue 1999; dos Santos 2002; Dunger 2014; Nicoloff 2001)	NC	0 to 16.7 (2)	Very low
Duration 5 years			
6 (Daniels 2013; Donaghue 1999; dos Santos 2002; Dunger 2014; Kong 2005; Nicoloff 2001)	NC	0 to 25 (2.8)	Very low
Duration 6 years			
6 (Bognetti 1997; Daniels 2013; Donaghue 1999; dos Santos 2002; Dunger 2014; Kong 2005)	NC	0 to 50 (4.4)	Very low
Duration 7 years			
5 (Daniels 2013; Donaghue 1999; dos Santos 2002; Dunger 2014; Kong 2005)	NC	1.9 to 26.1 (5)	Very low
Duration 8 years			
5 (Daniels 2013; Donaghue 1999; dos Santos 2002; Kong 2005)	NC	1.9 to 22.2 (5)	Very low
Duration 9 years			
5 (Daniels 2013; Donaghue 1999; dos Santos 2002; Dunger 2014; Kong 2005)	NC	1.9 to 29 (5)	Very low
Duration 10 years			
5 (Daniels 2013; Donaghue 1999; dos Santos 2002; Dunger 2014; Kong 2005)	NC	1.9 to 31.8 (6.9)	Very low

Number of studies	Number of children and young people	Range of prevalence, % (median, %)	Quality
Duration 11 years			
4 (Donaghue 1999; dos Santos 2002; Dunger 2014; Kong 2005)	NC	1 to 28.3 (20.2)	Very low
Duration 12 years			
2 (Dunger 2014; Kong 2005)	NC	1 to 16.3 (8.66)	Low
Duration 13 years			
2 (Dunger 2014; Kong 2005)	NC	1 to 31.9 (16.5)	Low
Duration 14 years			
2 (Dunger 2014; Kong 2005)	NC	1 to 35.9 (18.5)	Low
Duration 15 years			
2 (Dunger 2014; Kong 2005)	NC	1 to 20 (10.5)	Low

NC not calculable

Table 50: Evidence profile for incidence of low-level albuminuria by duration of diabetes (albumin:creatinine ratio more than 3.5 mg/mmol in males and more than 4.0 mg/mmol in females, in at least 2 out of 3 urine collections)

Number of studies	Number of children and young people	Range of incidence, % (median, %)	Quality
Duration <1 year			
1 (Rudberg 1993)	NC	8 (NA)	Low
Duration 1 year			
1 (Rudberg 1993)	NC	8 (NA)	Low
Duration 2 years			
1 (Rudberg 1993)	NC	8 (NA)	Low
Duration 3 years			
1 (Rudberg 1993)	NC	8 (NA)	Low
Duration 4 years			
1 (Rudberg 1993)	NC	8 (NA)	Low
Duration 5 years			
1 (Rudberg 1993)	NC	14 (NA)	Low
Duration 6 years			
1 (Rudberg 1993)	NC	14 (NA)	Low
Duration 7 years			
1 (Rudberg 1993)	NC	14 (NA)	Low
Duration 8 years			
1 (Rudberg 1993)	NC	14 (NA)	Low
Duration 9 years			
1 (Rudberg 1993)	NC	14 (NA)	Low

NA not applicable, NC not calculable

10.4.2.5 Evidence statements

Where indicated by an asterisk (*) the total number of participants analysed for each outcome could not be calculated from the published data.

Prevalence of low-level albuminuria by age (albumin:creatinine ratio ranging from more than 3.39 mg/mmol to more than 3.5 mg/mmol in males, and from more than 3.39 mg/mmol to more than 4.0 mg/mmol in females, in at least 2 out of 3 urine collections)

The evidence for the following findings was of very low quality.

Age less than 10 years

Five studies* estimated the prevalence of low-level albuminuria in children and young people with type 1 diabetes aged less than 10 years to be between 0% and 66.7%.

Age 10 years

Eight studies* estimated the prevalence of low-level albuminuria in children and young people with type 1 diabetes aged 10 years to be between 0% and 9%.

Age 11 years

Five studies* estimated the prevalence of low-level albuminuria in children and young people with type 1 diabetes aged 11 years to be between 0% and 10%.

Age 12 years

Six studies* estimated the prevalence of low-level albuminuria in children and young people with type 1 diabetes aged 12 years to be between 0% and 15%.

Age 13 years

Six studies* estimated the prevalence of low-level albuminuria in children and young people with type 1 diabetes aged 13 years to be between 0% and 67%.

Age 14 years

Six studies* estimated the prevalence of low-level albuminuria in children and young people with type 1 diabetes aged 14 years to be between 0% and 67%.

Age 15 years

Seven studies* estimated the prevalence of low-level albuminuria in children and young people with type 1 diabetes aged 15 years to be between 0% and 75%.

Age 16 years

Six studies* estimated the prevalence of low-level albuminuria in children and young people with type 1 diabetes aged 16 years to be between 3% and 75%.

Age 17 years

Five studies* estimated the prevalence of low-level albuminuria in children and young people with type 1 diabetes aged 17 years to be between 5% and 67%.

Age 18 years

Five studies* estimated the prevalence of low-level albuminuria in children and young people with type 1 diabetes aged 18 years to be between 5% and 67%.

Prevalence of low-level albuminuria by age (albumin:creatinine ratio more than 4.59 mg/mmol in males, and more than 5.24 mg/mmol in females, in at least 2 out of 3 urine collections)

Age less than or equal to 10 years

One study* estimated the prevalence of low-level albuminuria in children and young people with type 1 diabetes aged less than or 10 years to be 0%. The evidence for this finding was of very low quality.

Prevalence of low-level albuminuria by duration of diabetes (albumin:creatinine ratio ranging from more than 3.39 mg/mmol to more than 3.5 mg/mmol in males, and from more than 3.39 mg/mmol to more than 4.0 mg/mmol in females, in at least 2 out of 3 urine collections)

Unless indicated otherwise, the evidence for the following findings was of very low quality.

Duration less than 2 years

Five studies* estimated the prevalence of low-level albuminuria in children and young people with type 1 diabetes of less than 2 years' duration to be 0%.

Duration 2 years

Five studies* estimated the prevalence of low-level albuminuria in children and young people with type 1 diabetes of 2 years' duration to be between 0% and 17%.

Duration 3 years

Four studies* estimated the prevalence of low-level albuminuria in children and young people with type 1 diabetes of 3 years' duration to be between 0% and 2%.

Duration 4 years

Five studies* estimated the prevalence of low-level albuminuria in children and young people with type 1 diabetes of 4 years' duration to be between 0% and 17%.

Duration 5 years

Six studies* estimated the prevalence of low-level albuminuria in children and young people with type 1 diabetes of 5 years' duration to be between 0% and 25%.

Duration 6 years

Six studies* estimated the prevalence of low-level albuminuria in children and young people with type 1 diabetes of 6 years' duration to be between 0% and 50%.

Duration 7 years

Five studies* estimated the prevalence of low-level albuminuria in children and young people with type 1 diabetes of 7 years' duration to be between 1.9% and 26%.

Duration 8 years

Five studies* estimated the prevalence of low-level albuminuria in children and young people with type 1 diabetes of 8 years' duration to be between 1.9% and 22%.

Duration 9 years

Five studies* estimated the prevalence of low-level albuminuria in children and young people with type 1 diabetes of 9 years' duration to be between 1.9% and 29%.

Duration 10 years

Five studies* estimated the prevalence of low-level albuminuria in children and young people with type 1 diabetes of 10 years' duration to be between 1.9% and 32%.

Duration 11 years

Four studies* estimated the prevalence of low-level albuminuria in children and young people with type 1 diabetes of 11 years' duration to be between 1% and 28%.

Duration 12 years

Two studies* estimated the prevalence of low-level albuminuria in children and young people with type 1 diabetes of 12 years' duration to be between 1% and 16%. The evidence for this finding was of low quality.

Duration 13 years

Two studies* estimated the prevalence of low-level albuminuria in children and young people with type 1 diabetes of 13 years' duration to be between 1% and 32%. The evidence for this finding was of low quality.

Duration 14 years

Two studies* estimated the prevalence of low-level albuminuria in children and young people with type 1 diabetes of 14 years' duration to be between 1% and 36%. The evidence for this finding was of low quality.

Duration 15 years

Two studies* estimated the prevalence of low-level albuminuria in children and young people with type 1 diabetes of 15 years' duration to be between 1% and 20%. The evidence for this finding was of low quality.

Incidence of low-level albuminuria by duration of diabetes (albumin:creatinine ratio more than 3.5 mg/mmol in males and more than 4.0 mg/mmol in females, in at least 2 out of 3 urine collections)

The evidence for the following findings was of low quality.

Duration less than 1 year

One study* estimated the incidence of low-level albuminuria in children and young people with type 1 diabetes of less than 1 years' duration to be 8%.

Duration 1 to 5 years

One study* estimated the incidence of low-level albuminuria in children and young people with type 1 diabetes of 1 to 5 years' duration to be 8%.

Duration 6 to 9 years

One study* estimated the incidence of low-level albuminuria in children and young people with type 1 diabetes of 6 to 9 years' duration to be 14%.

10.4.2.6 Health economics profile

A systematic literature search did not identify any relevant economic evaluations addressing the optimal monitoring strategy for identifying nephropathy in children and young people with type 1 diabetes.

This question was not prioritised for health economic analysis. It was anticipated that the number of children and young people who might be affected by a change in the recommendations for this topic was relatively small and therefore any cost impact arising was not expected to be very important. Furthermore, the clinical evidence review did not address the effectiveness of screening technologies, or treatment or management decisions that may follow from the screening results. Such evidence would be required for economic modelling.

10.4.2.7 Evidence to recommendations

10.4.2.7.1 Relative value placed on the outcomes considered

The guideline development group felt that there was some clinical uncertainty as to whether the strategy for monitoring for nephropathy should take account of duration of diabetes as well as (or instead of) age. For this reason the group prioritised measures of prevalence and incidence in all children and young people with type 1 diabetes as outcomes of interest in the update review so that they could gain an understanding of both the number of cases of nephropathy in different age groups and also the rate at which new cases occurred in relation to time from diagnosis.

10.4.2.7.2 Consideration of clinical benefits and harms

The guideline development group considered that the early identification of low-level albuminuria (as a risk factor for nephropathy) presented an important clinical benefit because it can prompt early intervention with angiotensin converting enzyme (ACE) inhibitors which alter disease progression and reduce the risk of chronic kidney disease and ultimately mortality.

The group recognised that, as with all diagnostic tests, false positive results presented a potential harm in terms of exposing people who receive such results to unnecessary treatment and anxiety. Overall the group felt that the benefits of testing outweighed this potential harm but felt that it was appropriate to recommend a specific approach to testing to maximise potential for accurate results being obtained, namely using the first urine sample of the day (‘early morning urine’) for the test and confirming positive initial test results by repeating the test.

The group concluded that the evidence supported the recommendation from the 2004 guideline that young people should be tested for low-level albuminuria from the age of 12 years because prevalence increased markedly between the ages of 12 and 13 years in the studies included in the guideline review. The group concluded that the existing stipulation that monitoring should occur annually remained relevant.

The guideline development group noted that the review question was not designed to provide evidence about when treatment should be undertaken based on test results. However, they felt that it was important to provide guidance as to what should be considered a positive result in terms of determining the need for repeat confirmatory testing. The group felt that it was both practical and clinically relevant to base this guidance on the thresholds for treatment outlined in the guideline on type 1 diabetes in adults.

10.4.2.7.3 Consideration of health benefits and resource use

Testing for low-level albuminuria from the age of 12 years is already routine practice due to it being recommended in the 2004 guideline. The group noted that the thresholds for

albumin:creatinine ratio specified in the guideline on type 1 diabetes in adults were different to those used to define low-level albuminuria in the included studies (the studies used different thresholds for males and females). The guideline development group recognised that specifying a single threshold for both sexes in the recommendations might result in a slightly higher number of girls and young women undergoing repeat testing than previously. Again, the group felt that any uplift in resource use due to this would be marginal and justified by the likely health benefits.

The group noted that false positive test results have implications for resource use and this provided further support for the decision to recommend a specific approach to testing. The group also noted that in some settings it is common practice to carry out 3 tests from the outset and so the recommendations in the 2015 update may result in fewer unnecessary tests being done.

10.4.2.7.4 Quality of evidence

The group noted that the evidence identified for inclusion was of very low to low quality. They concurred with the judgements that had been made regarding the limitations of the studies which had led to these quality ratings being assigned through the GRADE quality appraisal process. Nevertheless the group felt that the evidence was broadly relevant and, given that the results affirmed their clinical experience, provided enough information on which to base decisions regarding recommendations. For this reason the group agreed that it was appropriate to make a strong recommendation even though the evidence was of low quality.

As indicated above, the group noted that most of the included studies used a higher albumin:creatinine ratio threshold to determine the presence of low-level albuminuria to the one used in UK practice and therefore the results may underestimate the prevalence and incidence of nephropathy in children and young people with type 1 diabetes.

The group also noted that some of the evidence identified for inclusion was unpublished, but that this evidence was broadly in keeping with the published evidence and did not alter the group's recommendations.

10.4.2.7.5 Other considerations

The guideline development group considered that the first urine sample of the day (early morning urine) should be used for the screening albumin:creatinine ratio test. If the first urine sample of the day is not available, healthcare professionals should use a random sample, but be aware that this is associated with an increased risk of false positive results. The group noted that young people are often reluctant to provide urine samples and this supported the decision to recommend the use of a random urine sample (which could be collected in clinic) if the first urine sample of the day (early morning urine) is not available.

The group decided that if the initial albumin:creatinine ratio is above 3 mg/mmol but below 30 mg/mmol (low-level albuminuria), the result should be confirmed by repeating the test on 2 further occasions using first urine samples of the day (early morning urine) before starting further investigation and therapy. The group considered that healthcare professionals should investigate further if the initial albumin:creatinine ratio is 30 mg/mmol or more (proteinuria). The threshold triggering further investigation (30 mg/mmol) is the same as that used in adults with type 1 diabetes and the terminology and definition of low-level albuminuria is the same as that used in the NICE guideline on chronic kidney disease.

10.4.2.7.6 Key conclusions

The guideline development group did not identify any evidence to direct a change in the recommendation in the 2004 guideline and so they concluded that children and young people with type 1 diabetes should be offered testing for low-level albuminuria from the age of 12 years and annually thereafter.

The group therefore recommended that healthcare professionals should offer children and young people with type 1 diabetes screening for low-level albuminuria (to detect diabetic kidney disease) annually from the age of 12 years. They also recommended that healthcare professionals should explain to children and young people with type 1 diabetes and their family members or carers (as appropriate) the importance of annual screening from the age of 12 years for diabetic kidney disease and that:

- screening begins at the age of 12 years because diabetic kidney disease in people under 12 years old is extremely rare
- using the first urine sample of the day (early morning urine) to screen for low-level albuminuria is important, as this reduces the risk of false positive results
- if low-level albuminuria is detected, improving blood glucose control will reduce the risk of this progressing to clinically significant diabetic kidney disease
- annual screening from the age of 12 years is important because if diabetic kidney disease is found, early treatment will improve the outcome.

The recommendations related to the optimal monitoring strategy for low-level albuminuria in children and young people with type 1 diabetes use the terminology ‘monitoring’ rather than ‘screening’. In the recommendations the terminology ‘low-level albuminuria’ is replaced by ‘moderately increased albuminuria (ACR 3–30 mg/mmol; ‘microalbuminuria’).

10.4.3 Initial management and treatment

This section was updated in 2015.

A consensus-based guideline has recommended that measures to prevent persistent microalbuminuria, such as optimal blood glucose control, smoking cessation, participation in physical activity, a low-protein diet and blood pressure control, should be promoted.[15] [evidence level IV]

Adults with type 1 diabetes and persistent, progressive microalbuminuria show improvement when treated with angiotensin-converting enzyme inhibitors. In young people with microalbuminuria, the use of angiotensin-converting enzyme inhibitors may delay the onset of nephropathy, but no evidence shows their usefulness in long-term protection.[15] [evidence level IV] Previous guidelines have recommended that if persistent microalbuminuria is found, careful consideration be given before commencing treatment with angiotensin-converting enzyme inhibitors, together with appropriate monitoring of renal function because of potential adverse effects. In addition, if hypertension is present and does not respond to angiotensin-converting enzyme inhibitors it should be treated appropriately.

10.4.4 Blood pressure

Hypertension has been shown to be associated with retinopathy.[549,550] [evidence level III] Diastolic blood pressure has been shown to be associated with morphometric kidney abnormalities.[551] [evidence level III]

Blood pressure may be significantly elevated in young people with type 1 diabetes. An evidence-based guideline stated that measurements should be taken annually, starting at the age of 12 years.[9] [evidence level IV] A review of screening for complications in children and young people with type 1 diabetes recommended blood pressure screening every 3 to 6 months, but did not specify a starting age.[539] [evidence level III-IV]

10.4.5 Lipids

We found no robust evidence that examined lipid screening in children and young people with type 1 diabetes. However, 3 non-systematic reviews addressed blood lipid profile monitoring. A review article based on American and Canadian clinical practice

recommendations advised that normal results of serum high-density lipoprotein, low-density lipoprotein, total cholesterol and triglyceride levels be checked within 6 months of diagnosis and retested at mid-puberty.[539] [evidence level III-IV] Abnormal results indicate screening for familial hyperlipidaemia.

Arguments against global childhood cholesterol screening have been based on studies and clinical opinion.[552] [evidence level III–IV] Reasons against screening for lipids in children and young people are that management by diet carries additional burdens for children and young people with type 1 diabetes and their families; screening in adulthood may be just as effective in preventing cardiovascular events; and problems of adherence. Some of these considerations may or may not be appropriate when considering screening in children and young people with type 1 diabetes.

10.4.6 Neuropathy (including foot care and peripheral vascular disease)

Clinical neuropathy is rare in children and young people with good glycaemic control.[15] [evidence level IV] A case–control study demonstrated that sub-clinical neuropathy, as measured by vibration perception threshold at the medial malleolus and great toe, was significantly higher in 307 children and young people with diabetes compared with 232 children and young people without diabetes.[553] [evidence level III] We found no evidence to support routine screening for neuropathy in children and young people with type 1 diabetes.

Good foot hygiene should be a component of routine healthcare for all children and young people with type 1 diabetes. Adults with type 1 diabetes are advised to have annual foot surveillance consisting of inspection and examination, with educational and risk perception issues adequately addressed. Parents' knowledge and education about foot care for their children and young people with type 1 diabetes was shown to be poor by a small (n=30) cross-sectional survey at a London clinic.[554] [evidence level III] The mean age of the children and young people was 11 years, and in most children and young people the diagnosis of diabetes had been made 4 to 6 years before the survey.

10.4.7 Dental care

Good dental hygiene should be a component of routine healthcare for all children and young people. Studies have shown a higher prevalence of peridontitis among children and young people with type 1 diabetes compared with children and young people without diabetes.[555,556] [evidence III–IV] Other studies have shown an association between poor glycaemic control (high HbA1c) and increased incidence of dental caries in children and young people with type 1 diabetes.[557,558] [evidence level III] We found no evidence that determined the frequency of routine dental examinations for children and young people with type 1 diabetes. A consensus guideline has advised that regular dental examinations form an important part of general healthcare.[15] [evidence level IV]

A non-systematic review of studies concerning oral hygiene in children and young people with type 1 diabetes recommended: regular plaque removal by a dentist twice a year; correct teeth brushing twice a day; and maintenance of a healthy diet and glycaemic control.[559] [evidence level IV]

Please refer also to Dental recall: Recall interval between routine dental examinations, NICE clinical guideline 19 (2004)[f].

10.4.8 Growth and puberty

The measurement of height and weight is an integral part of diabetes care. Children and young people with optimal blood glucose control will grow and develop normally. There is

[f] www.nice.org.uk/Guidance/CG19

evidence to suggest that obesity is an emerging problem in older children and young people with type 1 diabetes, particularly among females.[560,561] [evidence level III] An international survey of 2873 children and young people found that females on 4 or more insulin injections/day had a significantly higher body mass index than those on twice-daily insulin regimens ($p<0.01$).[562] [evidence level III]

We found no RCTs that investigated growth and puberty among children and young people with type 1 diabetes. However, 1 cohort study reported evidence of decreased linear growth associated with HbA1clevels above 16% (normalised change in growth rate after adjusting for age and sex −0.07 ±0.03).[563] [evidence level IIb] The level of growth suppression was dependent on pubertal status.

Several growth chart formats are available commercially and revised reference values for curves of stature and weight for the UK were introduced in 1990.[564] [evidence level III]

The young people's consultation day organised for this guideline in collaboration with the NCB found that young people with type 1 diabetes, particularly young women, were sensitive about body weight and wanted weighing to be carried out in a private room.[38] [evidence level IV]

10.5 Recommendations

The current recommendations can be found at https://www.nice.org.uk/guidance/ng18.

10.6 Research recommendation

This section was updated in 2015.

15. [2004] Further research is needed to evaluate the effectiveness of screening for cardiovascular risk factors in children and young people with type 1 diabetes.

11 Education for children and young people with type 2 diabetes

This section was updated in 2015.

11.1 Review question

What is the effectiveness of structured education programmes in improving clinical and patient outcomes in children and young people with type 2 diabetes?

11.2 Introduction

This was an entirely new topic covered by the 2015 update scope. The purpose of this review question was to evaluate the effectiveness of structured education programmes in terms of improving outcomes in children and young people with type 2 diabetes. The review covered educational interventions directed at children and young people or their families, but not those directed at healthcare professionals. The search was limited to systematic reviews or randomised controlled trials (RCTs). It was agreed by the guideline development group that if no such studies were identified then systematic reviews of comparative observational studies would be considered.

The outcomes prioritised for inclusion in the reviews were:

- glycaemic control
  - HbA1c (glycated haemoglobin; minimum follow-up 6 months after completion of the primary intervention)
- adherence to the education intervention
- changes in body mass index (BMI) standard deviation score (SDS)
- achievement and maintenance of weight loss during the programme
- change in level of physical activity (for example hours of exercise per week; minimum follow-up 6 months after completion of the primary intervention)
- health-related quality of life
- satisfaction of children, young people and families with the education intervention.

11.3 Description of included studies

No RCTs were identified for inclusion in the review and despite expanding the search criteria to consider systematic reviews of comparative observational studies, no studies were identified that met the inclusion criteria for this question.

11.4 Evidence profile

No evidence was identified for inclusion for this review question and so there is no evidence profile.

11.5 Evidence statements

No evidence was identified for this review question.

11.6 Health economics profile

A systematic literature search did not identify any published cost effectiveness studies on structured education programmes to improve clinical and patient outcomes in children and young people with type 2 diabetes.

This question was not prioritised for health economic analysis due to the small number of children and young people with type 2 diabetes in the UK.

11.7 Evidence to recommendations

11.7.1 Relative value placed on the outcomes considered

The guideline development group prioritised physical outcomes (related to glycaemic control and other aspects of physical health such as body mass index) and psychosocial outcomes (such as satisfaction of children, young people and families with educational interventions and health-related quality of life) for inclusion in the systematic review, but no evidence was identified for any of the selected measures.

11.7.2 Consideration of clinical benefits and harms

There was no evidence about the effectiveness of structured education for children and young people with type 2 diabetes to inform the guideline development group's considerations about the relative benefits and harms of such interventions. However, the group consensus was that there was potential harm associated with not making any recommendations about education for children and young people with type 2 diabetes. The group also felt that the considerations that had applied for the corresponding question for children and young people with type 1 diabetes were broadly relevant and could reasonably be extrapolated to the type 2 population to justify recommending a continuing programme of education from diagnosis centred on core topics.

The guideline development group selected the core topics based on their consensus view of which aspects of diabetes care would be most important for obtaining health benefits and avoiding harms in children and young people with type 2 diabetes. Topics differed to those that were specified for children and young people with type 1 diabetes to reflect other recommendations in the guideline and differences in the relative importance of particular aspects of diabetes care (for example blood glucose monitoring is not recommended for children and young people with type 2 diabetes and so this was not included as a core topic for type 2 diabetes education).

As with type 1 diabetes, the guideline development group felt that it was important to tailor education programmes related to type 2 diabetes to each child or young person with the condition and their family members or carers (as appropriate), taking account of issues such as personal preferences, emotional wellbeing, age and maturity, cultural considerations, existing knowledge, current and future social circumstances and life goals. The group also felt that encouraging children and young people with type 2 diabetes and their family members or carers (as appropriate) to discuss any concerns and raise any questions they have with the diabetes team was important.

11.7.3 Consideration of health benefits and resource use

There was no evidence to support the consideration of health benefits and resource use but the guideline development group concluded that the recommendations were generally in keeping with current practice and that any uplift in resources was likely to be offset by downstream cost savings derived from health benefits achieved and complications avoided. It is recognised that there are microvascular complications arising from high blood glucose.

These complications (for example kidney failure requiring dialysis and neuropathy leading to amputation) are expensive to treat and have a deleterious effect on health-related quality of life. Children and young people are particularly at risk of these complications given the lifelong nature of type 2 diabetes. Effective treatment can, therefore, represent a very cost-effective use of scarce resources.

11.7.4 Quality of evidence

No evidence was identified for inclusion in the systematic review.

11.7.5 Other considerations

The guideline development group reflected on how their recommendations might apply to subgroups of the population with protected characteristics under equalities legislation and noted that the programme of education should be tailored to the age, cultural background and existing knowledge of the child or young person, and of their family members or carers (as appropriate).

11.7.6 Key conclusions

The guideline development group recommended that healthcare professionals should offer children and young people with type 2 diabetes and their family members or carers (as appropriate) a continuing programme of education from diagnosis. The group specifically recommended that the programme includes the following core topics:

- HbA1c monitoring and targets
- the effects of diet, physical activity, body weight and intercurrent illness on blood glucose control
- the aims of metformin therapy and possible adverse effects
- the complications of type 2 diabetes and how to prevent them.

The group also recommended that healthcare professionals tailor the education programme to each child or young person with type 2 diabetes and their family members or carers (as appropriate), taking account of issues such as: personal preferences; emotional wellbeing; age and maturity; cultural considerations; existing knowledge; current and future social circumstances; and life goals.

The group also mirrored several recommendations related to education for children and young people with type 1 diabetes. These related to:

- explaining advice about regular dental examinations and an eye examination by an optician every 2 years
- encouraging children and young people with type 2 diabetes and their family members or carers (as appropriate) to discuss any concerns and raise any questions they have with the diabetes team
- giving information about local and/or national diabetes support groups and organisations, and the potential benefits of membership
- explaining how to find information about possible benefits from government disability support
- explaining that the Department of Health's Green Book recommends annual immunisation against influenza for children and young people with diabetes
- explaining that the Department of Health's Green Book recommends immunisation against pneumococcal infection for children and young people with diabetes who need insulin or oral hypoglycaemic medicines.

11.8 Recommendations

The current recommendations can be found at https://www.nice.org.uk/guidance/ng18.

12 Management of type 2 diabetes – dietary and weight loss advice and oral drug treatment

This section was updated in 2015.

12.1 Dietary advice

12.1.1 Review question

What is the effectiveness of dietetic advice to optimise glycaemic control in children and young people with type 2 diabetes?

12.1.2 Introduction

This was a new topic covered by the 2015 update scope. The purpose of this review question is to determine whether dietary advice can improve glycaemic control in children and young people with type 2 diabetes. Although the guideline development group phrased their review question in terms of 'dietetic advice', the term 'dietary advice' was used in the final recommendations to mirror other NICE guidelines related to diabetes.

The priority outcomes identified by the group for this question were glycaemic control, as measured by HbA1c (glycated haemoglobin) and adverse events, including change in body mass index (BMI) standard deviation score (SDS), postprandial hyperglycaemia, adherence to dietary advice, health-related quality of life and satisfaction with the intervention. The group agreed that a minimum of 6 months' follow-up was required for HbA1c outcomes in both treatment arms. A minimally important difference (MID) of 0.5 was identified for BMI SDS as relevant interventions should not have been aimed solely at achieving weight loss.

12.1.3 Description of included studies

No randomised controlled trials (RCTs) or systematic reviews were identified for inclusion in this review. After reviewing search results for observational studies, a single comparative retrospective cohort study was identified for inclusion (Willi 2004). A total of 20 participants received the intervention of a very low calorie diet. There were 15 controls, matched on age, race and sex to participants who adhered to the diet for more than 6 weeks. The participants were morbidly obese African-American children and young people with type 2 diabetes.

The study was carried out in the USA. Data were obtained by retrospective review of medical records. The mean age of participants was 14.5 years for all intervention subjects and 14.9 years for intervention subjects and their matched controls. Mean HbA1c for all intervention participants and for those with adherence greater than 6 weeks was 8.8%, and 8.9% for controls. Mean BMI was 43.5 kg/m^2 for all intervention subjects, 44.2 kg/m^2 for participants with adherence greater than 6 weeks and 43.7 kg/m^2 for controls.

The intervention was a very low calorie diet comprising 680 kcal/2845 kJ to 800 kcal/3347 kJ per day, with 80 g to 100 g of protein and less than 30 g each of carbohydrate and fat. Mean duration of the diet was 60 days, ranging from 4 to 130 days.

Of the guideline development group's priority outcomes, HbA1c levels and change in BMI were assessed. No detailed evidence was identified for postprandial hyperglycaemia, adherence to dietary advice, health-related quality of life or satisfaction with treatment. Data for BMI were not reported in the form of SDS.

12.1.4 Evidence profile

The evidence profile for this review question (dietary advice based on glycaemic index) is presented in Table 51.

Table 51: Evidence profile for comparison of a very low calorie diet with usual care in morbidly obese African-American children and young people with type 2 diabetes

Number of studies	Number of children and young people		Effect	
	Intervention	Comparator	Relative (95% confidence interval)	Absolute (95% confidence interval)
Change in BMI by end of diet (approximately 2 months after baseline)				
1 (Willi 2004)	15	15	NA	MD −12.4 (−17.1 to −7.7) [a,b]
Change in BMI by 6 months' follow-up				
1 (Willi 2004)	15	15	NA	MD -12.7 (−18.1 to −7.2) [a,b]
Change in BMI by 12 months' follow-up				
1 (Willi 2004)	15	15	NA	MD -9.5 (−16.2 to −2.8) [a,b]
Change in BMI by 18 months' follow-up				
1 (Willi 2004)	15	15	NA	MD -9.1 (−16.8 to −1.4) [a,b]
Change in BMI by 24 months' follow-up				
1 (Willi 2004)	15	15	NA	MD: −9.1 (−17.8 to −0.3) [a,b]
HbA1c levels at end of diet (approximately 2 months after baseline)				
1 (Willi 2004)	15	15	NA	MD −1.6 (−3.5 to 0.3) [a,b]
HbA1c levels at 6 months after baseline				
1 (Willi 2004)	15	15	NA	MD −0.9 (−3.1 to 1.4) [a,b]
HbA1c levels at 12 months after baseline				
1 (Willi 2004)	15	15	NA	MD −0.5 (−2.7 to 1.7) [a,b]
HbA1c levels at 18 months after baseline				
1 (Willi 2004)	15	15	NA	MD −0.4 (−2.7 to 1.9) [a,b]
HbA1c levels at 24 months after baseline				
1 (Willi 2004)	15	15	NA	MD −1.0 (−3.4 to 1.4) [a,b]

BMI body mass index, CI confidence interval, MD mean difference, NA not applicable, SE standard error
a. Point estimate and SE derived from graphs by NCC-WCH technical team
b. CI calculated using t-distribution due to small sample size

12.1.5 Evidence statements

12.1.5.1 Change in HbA1c levels

One study (total 30 participants) did not demonstrate that a very low calorie diet resulted in a lower HbA1c in morbidly obese African-American children and young people with type 2 diabetes compared with controls at 24 months' follow-up. The quality of evidence for this outcome was very low.

12.1.5.2 Change in body mass index

One study (total 30 participants) found that a very low calorie diet resulted in reduced BMI in morbidly obese African-American children and young people with type 2 diabetes compared with controls by the end of the diet and at up to 24 months' follow-up. The quality of the evidence for this outcome was very low.

12.1.6 Health economics profile

A systematic literature search did not identify any published cost effectiveness studies of dietary advice to optimise glycaemic control in children and young people with type 2 diabetes.

This review question was not prioritised for health economic analysis due to the small number of children and young people with type 2 diabetes in the UK, and the fact that dietary advice is part of current practice and is provided in a form that is unlikely to have major opportunity costs.

12.1.7 Evidence to recommendations

12.1.7.1 Relative value placed on the outcomes considered

The guideline development group agreed that the HbA1c concentration was the highest priority outcome for this question because, in their view, if the use of dietary advice resulted in a reduction in HbA1c by near to or greater than 0.5 percentage points (or 5.5 mmol/mol) then this would represent an important clinical benefit to a child or young person with type 2 diabetes. This decision was underpinned by the group's knowledge of evidence in adults with type 1 diabetes (The Diabetes Control and Complications Trial Research Group 1993) which showed that a 1 percentage point decrease in HbA1c halved the risk of diabetes-related complications. The guideline development group considered that this result could be meaningfully extrapolated to cover the population of children and young people with type 2 diabetes of relevance in this question.

The guideline development group considered that postprandial hyperglycaemia was an important outcome in determining the effectiveness of dietary advice based on glycaemic index. With good glycaemic control, adherence to dietary advice would be more likely.

The group prioritised BMI SDS, adherence to the dietary intervention, health-related quality of life and satisfaction of children, young people and families with treatment as important outcomes.

12.1.7.2 Consideration of clinical benefits and harms

The guideline development group noted that the only study available for inclusion in this review described an unusual intervention in that the participants were advised to take a very low calorie diet of 800 kca/3347 kJ or less. The group noted that the study population consisted of African-American young people in the USA who had severe obesity (BMI greater than 40 kg/m^2). The group was therefore uncertain about the study's applicability to children and young people with type 2 diabetes in the UK. Moreover, the group noted that the study had very serious limitations. The group did not, therefore, base their consideration of benefits and harms on the limited evidence contained in the guideline review (see Quality of evidence below).

The guideline development group considered that offering dietary advice to young people with type 2 diabetes was already considered to be good clinical practice. As discussed elsewhere in this guideline, such advice could potentially contribute to weight loss. Moreover, it is accepted that eating a healthy diet can contribute to maintaining good health and may

specifically reduce the risk of developing cardiovascular disease (a major risk in people with type 2 diabetes). Finally, dietary advice can help to reduce glycaemic excursions and thus should, in principle, contribute to overall glycaemic control. The guideline development group considered that adherence to dietary advice can be difficult and thus required regular discussion. The group recommended, therefore, that it should be given at each contact with a medical professional.

The guideline development group was aware of the potential negative psychological impact of dietary advice. Such advice might be difficult to adhere to and the group was aware of the sense of failure that young people might experience if, for example, they were unsuccessful in achieving intended weight loss. The group considered that this risk would be reduced if other benefits of healthy eating were made clear (such as the standard advice of eating at least 5 portions of fruit and vegetables each day) and the advice was given in a thoughtful and sensitive manner.

12.1.7.3 Consideration of health benefits and resource use

The guideline development group considered that providing dietary advice takes time, particularly as it will need discussion at each contact with the child or young person. However, the group considered that the investment of the healthcare professional's time was essential to achieve success. In any case, as dietary advice is already an accepted part of standard clinical practice in the UK there is unlikely to be a large cost impact arising from a recommendation to provide such advice. NICE guidance exists for obesity management in children and young people and this should be taken into consideration when providing dietary advice for children and young people with type 2 diabetes.

12.1.7.4 Quality of evidence

The group noted that the evidence was limited to 1 included study. The study provided evidence for only 2 of the 6 outcomes prioritised by the guideline development group and the quality of the outcomes reported was graded as very low. The study design did not provide an unbiased methodological approach and the study population of African-American children and young people with severe obesity was not representative of the population in the UK. The intervention was extreme and would not be used in standard clinical practice in the UK. The prescribed diet was ketogenic and required substantial dietary supplementation to provide an adequate intake of nutrients. Such an intense nutritional intervention was unusual and could be harmful without adequate monitoring. Moreover, data for changes in BMI were not reported in the form of SDS scores and were therefore classified as indirect evidence. Furthermore, all data reported in the guideline review were extrapolated from graphs by the NCC-WCH technical team because no comparative numerical data were reported by the study authors. The guideline development group acknowledged that the above considerations meant that the evidence from this study was not relevant and should not be used to guide the formulation of recommendations about dietary advice in this guideline.

12.1.7.5 Other considerations

There were no other considerations.

12.1.7.6 Key conclusions

The evidence identified for inclusion was of very low quality and was, therefore, deemed unsuitable for use as the basis of recommendations for clinical practice. Based on their clinical experience and consensus the guideline development group concluded that dietary advice should be recommended for children and young with type 2 diabetes. Specifically, the group recommended that healthcare professionals should offer children and young people with type 2 diabetes dietetic support to help optimise body weight and blood glucose control, and that at each contact with a child or young person with type 2 diabetes, the diabetes team

should explain to them and their family members or carers (as appropriate) how healthy eating can help to reduce hyperglycaemia and cardiovascular risk and promote weight loss. The guideline development group also recommended that healthcare professionals should provide dietary advice in a sensitive manner, taking into account the difficulties that many people encounter with weight reduction, and emphasising the additional advantages of healthy eating for blood glucose control and avoiding complications.

The group also mirrored several recommendations linked to dietary advice and related issues for children and young people with type 1 diabetes. Those related to:

- encouraging children and young people with type 2 diabetes to eat at least 5 portions of fruit and vegetables each day
- measuring height and weight and plotting on an appropriate growth chart and calculating BMI at each clinic visit
- providing arrangements for weighing children and young people with type 2 diabetes that respect their privacy.

12.1.8 Recommendations

The current recommendations can be found at https://www.nice.org.uk/guidance/ng18.

12.2 Weight loss advice

This section was updated in 2015.

12.2.1 Review question

Does weight loss in children and young people with type 2 diabetes who are overweight or obese improve glycaemic control as measured by haemoglobin A1c (HbA1c)?

12.2.2 Introduction

This was an entirely new topic covered by the 2015 update scope. Although type 2 diabetes is primarily a condition found in adults, the diagnosis is increasingly being made in young people. This increase is linked to the increasing prevalence of obesity in young people. This review question aims to evaluate the effectiveness of weight loss in children and young people with type 2 diabetes who are overweight or obese in terms of improving glycaemic control.

The review does not compare different methods of weight loss but rather it seeks to show whether weight loss has an impact on glycaemic control and related factors. Commonly used weight loss strategies for paediatric populations include lifestyle advice related to diet and exercise. Surgical interventions are not generally recommended for children or young people, although bariatric surgery may be considered in specific circumstances. Bariatric surgery was excluded from the scope for the 2015 guideline update, but the review search strategy did not exclude studies involving bariatric surgery to prevent exclusion of literature that considered multiple weight loss strategies. Ultimately, however, all of the studies related to bariatric surgery and type 2 diabetes that were identified by the literature search were excluded because the studies were undertaken predominantly or wholly in adults.

The outcomes prioritised for inclusion in the review were:

- glycaemic control
  - HbA1c (minimum follow-up 6 months)
- adherence to diabetes management, including self-management

- changes in body mass index (BMI) standard deviation score (SDS)
- remission of diabetes (normal HbA1c and no treatment for diabetes, for example at 1 year after starting the weight loss intervention)
- time to treatment failure (when insulin is required to manage diabetes)
- health-related quality of life
- satisfaction of children, young people and families with the intervention.

12.2.3 Description of included studies

The review identified 1 RCT conducted in the USA for inclusion (TODAY Study Group 2012). This RCT allocated 699 children and young people aged 10 to 17 years to 1 of 3 treatment arms: metformin alone; metformin plus rosiglitazone; or metformin plus a lifestyle intervention programme focused on weight loss. The study aimed to compare the efficacy of the 3 treatment regimens to achieve sustained glycaemic control in children and young people with type 2 diabetes.

To isolate the effect of lifestyle on HbA1c, the guideline review has utilised data from the metformin alone and metformin plus lifestyle intervention arms of the study. Data from the combined pharmaceutical therapies arm (metformin plus rosiglitazone) were not considered for inclusion as rosiglitazone is an antidiabetic drug and is not intended specifically for weight loss. The lifestyle modification programme primarily used self-monitoring, goal setting, reinforcement for goal achievement, stimulus control, social support, problem solving and motivational techniques and comprised 3 phases:

- Lifestyle Change (60 to 90 minutes per session, weekly for months 1 to 6)
- Lifestyle Maintenance (60 minutes per session, bi-weekly for months 7 to 12)
- Continued Contact (45 to 60 minutes per session, monthly for months 13 to 24 then quarterly to the end of the trial).

The family origin of the study population was: 20.3% white non-Hispanic; 32.5% black non-Hispanic; 39.7% Hispanic; 5.9% American Indian; and 1.6% Asian.

Glycaemic control (HbA1c with minimum follow-up of 6 months) was identified as a priority outcome by the guideline development group. However, in this review the number of glycaemic failure cases over 5 years was used as a proxy for glycaemic control. The included study defined glycaemic failure as a persistently elevated glycated haemoglobin level of 8% or higher over a period of 6 months, or persistent metabolic decompensation (defined as the inability to wean the participant from insulin within 3 months of initiation for decompensation or the occurrence of a second episode of decompensation within 3 months of discontinuation of insulin).

Time to treatment failure (in this context this refers to failure to lose weight) was also selected as a priority outcome by the guideline development group and median values for this outcome were reported in this study.

The remaining outcomes prioritised by the guideline development group were not reported in the study. These were: adherence to treatment, changes in body mass index (BMI) standard deviation score (SDS), remission of diabetes, health-related quality of life and satisfaction of children, young people and families with treatment.

Given the absence of evidence regarding changes in BMI SDS, the guideline development group decided to consider a proxy outcome measure related to weight, namely percentage point changes in body weight.

12.2.4 Evidence profile

The evidence profile for this review question (weight loss in children and young people with type 2 diabetes who are overweight or obese) is presented in Table 52.

Table 52: Evidence profile for effectiveness of weight loss in children and young people with type 2 diabetes who are overweight or obese in improving glycaemic control

Number of studies	Number of children and young people		Effect		Quality
	Metformin and lifestyle intervention	Metformin only	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Number of glycaemic failure cases over 5 years[a]					
1 (TODAY Study Group 2012)	109/234 (46.6%)	120/232 (51.7%)	RR 0.90 lower (0.75 to 1.08)	52 fewer per 1000 (from 129 fewer to 41 more)	High
Median time to treatment failure (months)					
1 (TODAY Study Group 2012)	234 (median=11.8 months)	232 (median=10.3 months)	NA[b]	NA[b]	Low
Number of children and young people achieving a reduction of at least 7 percentage points in percent overweight					
1 (TODAY Study Group 2012)	73/234 (31.2%)	56/232 (24.3%)	RR 1.27 higher (0.95 to 1.72)	65 more per 1000 (from 12 fewer to 174 more)	Moderate

CI confidence interval, NA not applicable, RR relative risk, TODAY Treatment options for type 2 diabetes in adolescents and youth
a. The study defined treatment failure as a persistently elevated glycated haemoglobin level of 8% or higher over a period of 6 months or persistent metabolic decompensation (defined as either the inability to wean the participant from insulin within 3 months of its initiation for decompensation or the occurrence of a second episode of decompensation within 3 months of discontinuation of insulin)
b. The 95% CI is entirely within 1 zone related to precision (see 'Methodology for 2015 update, in Section 0)

12.2.5 Evidence statements

12.2.5.1 Number of glycaemic failure cases over 5 years

One study (total 466 participants) did not demonstrate a reduction in the incidence of glycaemic failure from the addition of a weight-loss focused lifestyle intervention to a regimen of metformin monotherapy. The quality of the evidence was high.

12.2.5.2 Median time to glycaemic failure

One study (total 466 participants) reported an increased median time to glycaemic failure of 1.5 months with the addition of a weight-loss focused lifestyle intervention to a regimen of metformin monotherapy. The quality of evidence was low.

12.2.5.3 Reduction in percentage overweight

One study (total 466 participants) reported no increase in the percentage of participants who achieved a reduction in percentage overweight (defined as a reduction in percentage overweight of 7 percentage points) with the addition of a weight-loss focused lifestyle intervention to a regimen of metformin monotherapy. The quality of the evidence was moderate.

12.2.6 Health economics profile

A systematic literature search did not identify any relevant economic evaluations addressing weight loss to improve glycaemic control in children and young people with type 2 diabetes who are overweight or obese.

This question was not prioritised for health economic analysis. The question addresses the link between weight loss and glycaemic control in children and young people with type 2 diabetes, rather than interventions designed to achieve weight loss. As such it is not concerned with decisions between competing alternatives and economic evaluation is neither relevant nor required.

12.2.7 Evidence to recommendations

12.2.7.1 Relative value placed on the outcomes considered

The guideline development group agreed that HbA1c value was the highest priority outcome for this review question because, in their view, if the use of weight loss strategies resulted in a reduction in HbA1c by near to or greater than 0.5 percentage points (or 5.5 mmol/mol) then this would represent an important clinical benefit to a child or young person with type 2 diabetes. This decision was underpinned by the group's knowledge of research in adults with type 1 diabetes (The Diabetes Control and Complications Trial Research Group 1993) which showed that 1 percentage point decrease in HbA1c halved the risk of diabetes-related complications. The guideline development group considered that this result could be meaningfully extrapolated to cover the population of children and young people with type 2 diabetes of relevance in this question.

As described above, the guideline development group accepted the rate of glycaemic failure cases over 5 years as a proxy measure of glycaemic control due to the lack of data related specifically to HbA1c. Remission of diabetes (normal HbA1c and no treatment for diabetes at, for example, 1 year after starting the weight loss intervention) was selected because the group was aware that, although uncommon, it was reportedly a possible and highly desirable outcome of weight loss.

Time to treatment failure was prioritised because there is a perception in clinical practice that any weight loss will generally be achieved only in the short term, but that any reduction in weight has the potential to postpone the need for insulin treatment (although in most cases insulin will be needed eventually because insulin resistance changes and secretion of insulin by the pancreas stops). The group also felt that a longer duration of weight loss may be linked to better long-term outcomes for children and young people with type 2 diabetes.

Changes in body mass index (BMI) standard deviation score (SDS) were prioritised for consideration because of the mechanism by which improvements in glycaemic control were expected to be achieved, and because weight loss is a factor targeted directly by the intervention. BMI SDS is the preferred measure of weight change in young people because it takes account of individual weight differences related to height. However, given the absence of such data in the evidence identified for inclusion in this review, the group felt it was reasonable to consider the proxy measure of percentage point change in body weight.

12.2.7.2 Consideration of clinical benefits and harms

The evidence included in the guideline review did not show that weight loss had benefits related to glycaemic control in obese young people with type 2 diabetes. Although the group who received the metformin and lifestyle intervention lost some weight while the metformin-only group gained weight on average, the difference between the 2 treatment groups (in total 2 percentage points' difference between the groups) was not clinically important. The study

authors stated that neither BMI at baseline nor BMI over time was a determinant of treatment failure.

However, given the very small difference in weight change between the treatment groups, this study did not provide useful information to determine whether substantial weight loss can improve glycaemic control as is widely held to be the case (for example in adults with type 2 diabetes). There was no statistically significant difference in weight loss between the treatment groups to demonstrate that weight loss improves glycaemic control. It is, however, widely recognised that type 2 diabetes is linked to obesity and, moreover, that high BMI is linked to ill health generally and with many of the adverse long-term outcomes associated with type 2 diabetes.

The guideline development group was aware of evidence in adults suggesting that very low calorie diets aimed at weight loss compare favourably to bariatric surgery (Jackness 2013). However, the NICE guideline on obesity recommends that very low calorie diets (800 kcal/day or less) should not be used routinely to manage obesity (defined as BMI over 30 kg/m^2). NICE further recommends that unduly restrictive and nutritionally unbalanced diets should not be used in children and young people (or in adults) because they are ineffective in the long term and can be harmful.

The group also cited a study indicating a link between bariatric surgery and remission of type 2 diabetes in adults (Brethauer 2013). Given that weight loss was the mechanism through which surgery was deemed to achieve the effect of remission, the group felt that it was reasonable to assume that a similar degree of weight loss achieved by other means would be equally beneficial. Moreover, given the fact that bariatric surgery is currently recommended for children and young people only if they meet specified criteria, the guideline development group recognised the importance of considering other interventions aimed at weight loss.

The group emphasised that trying to persuade children and young people to lose weight could be harmful to their self-esteem if the weight loss targets set were not achievable. However, the group felt that these risks could be mitigated if healthcare professionals handled the issues sensitively. The group also felt that such harms were less important that those associated with surgery or long-term adverse health outcomes associated with high BMI and type 2 diabetes generally.

12.2.7.3 Consideration of health benefits and resource use

The guideline development group acknowledged that although giving advice on weight loss is relatively low cost and is already an established part of clinical practice, some weight-loss interventions can be costly. They also noted that the intervention in the included study was particularly intensive and unlike any services currently being commissioned in the NHS. Nevertheless, they felt that there was enough evidence of the benefits of weight loss in improving glycaemic control in children and young people who are overweight and obese that management options recommended in the NICE obesity guideline could be expected to be cost effective in this population.

12.2.7.4 Quality of evidence

Only 1 study met the inclusion criteria for this review question. Although the evidence for 1 outcome was graded as high, the evidence for the other outcome was graded as low. Furthermore, the intervention in the study was not reflective of the type of interventions used in current clinical practice, being very intensive and costly.

12.2.7.5 Other considerations

It is well known from clinical practice that a sedentary lifestyle and being overweight are important risk factors for type 2 diabetes and prognostic markers of poor outcomes in those

with the condition. As these are modifiable, and potentially reversible, risk factors, any interventions that effectively secure weight loss are attractive, especially if it can be clearly established that weight loss improves glycaemic control.

12.2.7.6 Key conclusions

The guideline development group consensus was that, if achieved, weight loss in children and young people with type 2 diabetes who are overweight or obese was likely to be worthwhile, potentially improving glycaemic control and also having other important health benefits. The group felt that care should be taken not to risk damaging the self-esteem of children and young people by setting weight-loss targets that are unrealistic and that support should be offered when necessary. The group's recommendation was, therefore, that at each contact with a child or young person with type 2 diabetes who is overweight or obese, healthcare professionals should advise them and their family members or carers (as appropriate) about the benefits of physical activity and weight loss, and provide support towards achieving this as specified in the NICE guideline on obesity.

The group also made a recommendation for further research to examine the correlation between changes in BMI SDS and absolute HbA1c measurements or changes in HbA1c in children and young people with type 2 diabetes. The group noted that it might be possible to use data collected by the National Paediatric Diabetes Audit to address this research question.

12.2.8 Recommendations

The current recommendations can be found at https://www.nice.org.uk/guidance/ng18.

12.2.9 Research recommendations

16. **What is the correlation between changes in body mass index standard deviation scores and absolute HbA1c measurements or changes in HbA1c in children and young people with type 2 diabetes?**

12.3 Metformin treatment

12.3.1 Review question

What is the effectiveness of metformin in improving glycaemic control in children and young people with type 2 diabetes when compared with usual care or placebo?

12.3.2 Introduction

This was an entirely new topic covered by the 2015 update scope. The objective of this review question is to determine the effectiveness of metformin in the management of type 2 diabetes. The review was limited to RCTs as no systematic reviews of metformin in children and young people with type 2 diabetes were identified.

The outcomes prioritised for inclusion in the review were:

- haemoglobin A1c (HbA1c)
- number of participants needing rescue medication
- number of dropouts
- number of participants with any adverse events, including diabetic ketoacidosis (DKA)
- changes in fasting plasma glucose (FPG)
- changes in body mass index (BMI) standard deviation score (SDS)

- satisfaction with the intervention.

12.3.3 Description of included studies

A single RCT was identified for inclusion for this review question (Jones 2002). This study involved 82 children and young people with type 2 diabetes (age range 10 to 17 years) and compared metformin (dose up to 2000 mg/day) with matching placebo for up to 16 weeks. All participants received training in home capillary blood glucose monitoring (to be performed twice daily at least every other day) at randomisation to treatment and advice about diet and exercise at each study visit. At baseline, the mean BMI was 34.1±11.6 kg/m^2, mean HbA1c was 8.6±1.4% (mean 80 mmol/mol) and mean FPG was 10.1±3.2 mmol/litre.

The guideline development group priority outcomes reported in the study were: mean HbA1c, the number of participants needing rescue medication, the number of dropouts, the number of participants with any adverse events (including DKA) and changes in FPG. Two other priority outcomes – changes in BMI standard deviation scores (SDS) and patient satisfaction with treatment – were not reported.

12.3.4 Evidence profile

The evidence profiles for this review question (metformin monotherapy for type 2 diabetes) are presented in Table 53.

Table 53: Evidence profile for effectiveness of metformin in improving glycaemic control in children and young people with type 2 diabetes when compared with placebo

Number of studies	Number of children and young people		Effect		Quality
	Metformin	Placebo	Relative (95% confidence interval)	Absolute (95% confidence interval)	
HbA1c value (% at endpoint)					
1 (Jones 2002)	36	36	NA	MD between the groups at endpoint 1.1 lower (1.19 lower to 1.01 lower)[a]	High
Number needing rescue medication					
1 (Jones 2002)	4/42 (9.5%)	26/40 (65%)	RR 0.15 (0.06 to 0.4)	552 fewer per 1000 (from 390 fewer to 611 fewer)	High
Number reporting any adverse event (including number with DKA)					
1 (Jones 2002)	29/42 (69%)	24/40 (60%)	RR 1.15 (0.83 to 1.59)	90 more per 1000 (from 102 fewer to 354 more)	High
Number of dropouts					
1 (Jones 2002)	6/42 (14.3%)	4/40 (10%)	RR 1.43 (0.42 to 3.91)	43 more per 1000 (from 58 fewer to 291 more)	High
FPG concentration (change from baseline, mmol/l)					
1 (Jones 2002)	36	36	NA	MD between the groups 3.6 lower (3.83 lower to 3.37 lower)[b]	High

DKA diabetic ketoacidosis, FPG fasting plasma glucose, MD mean difference, NA not applicable, RR relative risk
a. Adjusted mean HbA1c at baseline (%), metformin 7.2±1.2, placebo 8.6±0.2
b. No apparent risk of bias in the included study

12.3.5 Evidence statements

The quality of the evidence for all of the following was high.

One study (total 72 participants) showed a reduction in HbA1c was associated with the use of metformin monotherapy in children and young people with type 2 diabetes.

One study (total 82 participants) showed a smaller proportion of participants needing rescue medication following the use of metformin in children and young people with type 2 diabetes.

One study (total 72 participants) showed a reduction in FPG was associated with the use of metformin in children and young people with type 2 diabetes.

One study (total 82 participants) showed that the numbers of participants for whom adverse events (including DKA) were reported was similar for both treatment groups.

One study (total 82 participants) showed that the number of dropouts was similar for both treatment groups.

There was no evidence for outcomes relating to changes in BMI or patient satisfaction with treatment.

12.3.6 Health economics profile

A systematic literature search did not identify any published cost effectiveness evidence on metformin in improving glycaemic control in children and young people with type 2 diabetes.

This question was not prioritised for health economic analysis due to the small number of children and young people with type 2 diabetes in the UK, and the fact that the intervention is not very costly. For example, the NHS Drugs Tariff (October 2014) reports a cost of £1.32 for a 28-tablet pack of 500 mg metformin, or £0.05 per tablet. The summaries of product characteristics suggest that the usual starting dose is 500 mg or 850 mg metformin hydrochloride once daily in children and young people aged 10 years or older.

12.3.7 Evidence to recommendations

12.3.7.1 Relative value placed on the outcomes considered

The guideline development group agreed that HbA1c value was the highest priority outcome for this question because, in their view, if the use of metformin resulted in a reduction in HbA1c by near to or greater than 0.5 percentage points (or 5.5 mmol/mol) then this would represent an important clinical benefit to a child or young person with type 2 diabetes. This decision was underpinned by the group's knowledge of research in adults with type 1 diabetes (The Diabetes Control and Complications Trial Research Group 1993) which showed that a 1 percentage point decease in HbA1c halved the risk of diabetes-related complications. The guideline development group considered that this result could be meaningfully extrapolated to cover the population of children and young people with type 2 diabetes of relevance in this question.

The guideline development group also prioritised fasting plasma glucose (FPG) as an indicator of glycaemic control because it is a commonly used measure in clinical practice.

The number of participants needing rescue medication was considered useful as a measure of treatment failure as the need for additional intervention implies that taking metformin has not adequately improved glycaemic control. It was, however, noted that the number of participants in the metformin treatment arm needing rescue medication should not be interpreted simply as the drug failing to have a pharmacological impact on blood glucose levels (because the need for rescue medication could arise in relation to incidence of adverse events, non-adherence and patient withdrawal from the allocated treatment). The group also noted that a key consideration for this outcome would be whether the criteria set within the studies to trigger the use of rescue medication (that is, the definition of suboptimal glycaemic control) were considered reasonable and relevant to UK clinical practice.

The group also considered the importance of evaluating the evidence for metformin-related adverse events because there is a widely held view among clinicians that taking metformin is associated with gastrointestinal adverse events such as diarrhoea and vomiting. The group

agreed that such events constituted a dual clinical harm in that, in addition to the physical effects, such symptoms could have a social impact on the child or young person and they could reduce adherence to medicine(s). Patient satisfaction was selected as an outcome of interest due to its link with adherence. Conversely, the group was aware of a proposed additional benefit associated with metformin, namely its ability to achieve a reduction in BMI SDS.

12.3.7.2 Consideration of clinical benefits and harms

The guideline development group concluded that there was strong evidence that metformin was clinically effective in management of type 2 diabetes for the majority of children and young people with this type of diabetes. More specifically, the included evidence demonstrated that treatment with metformin resulted in improved glycaemic control in a clinically important way (the change in HbA1c resulting from treatment with metformin exceeded the group's a priori definition of a minimally important difference [MID], namely 0.5 percentage points or 5.5 mmol/mol). The group also concluded that there was strong evidence that the use of metformin was associated with significantly less frequent recourse to rescue medication. These results were in keeping with the group's experience and confirmed clinical benefits.

The guideline development group noted that the evidence did not support their prior belief that metformin causes gastrointestinal adverse events. The incidence of such events was not significantly greater in the metformin group than in the placebo-treated controls. The guideline development group noted that in the trial the only serious adverse event reported (DKA) occurred in a participant in the placebo group. There was no evidence that the dropout rate was significantly different in the metformin and placebo groups in a way that could have resulted from differential experience of adverse events in the 2 treatment arms. The guideline development group considered, therefore, that the clinical benefits with metformin were not outweighed by a risk of clinical harm due to adverse events.

No evidence was found for the 2 remaining outcomes that had been prioritised for consideration (changes in BMI and patient satisfaction with treatment), nor did the included study give any information about how outcomes might be influenced by the use of various available preparations of metformin. In the absence of evidence the guideline development group weighed up the clinical benefits and harms related to these aspects of the review protocol based on their experience and reached the following conclusions. Although changes in BMI were not reported in this study, the group's clinical experience suggested that metformin does in fact contribute to a small reduction in BMI SDS. Even a small reduction in BMI SDS constitutes a clinical benefit because it contributes to improving glycaemic control and weight loss which, in turn, may induce remission in type 2 diabetes. The group also believed that reducing BMI would have health benefits more generally and could contribute to improved self-esteem in children and young people.

While no evidence was identified comparing different metformin preparations (for example the standard-release formulation of large tablets versus extended-release tablets, powder or oral solution), the guideline development group's experience was that standard-release formulation tablets are difficult for some children and young people to swallow. The other preparations might be better tolerated and might be associated with increased patient satisfaction. With liquid formulations the dosage administered can be altered more easily and adjusted more precisely. This flexibility could be helpful, for example allowing dosage adjustments to be made if the child or young person experiences gastrointestinal symptoms as adverse events. The slow-release preparation is licensed only for use in adults and the other metformin preparations are licensed only for children and young people aged over 10 years. Type 2 diabetes would be very uncommon in children under 10 years of age. These considerations prompted the guideline development group to consider recommending further research on the effectiveness of different metformin preparations (see below).

12.3.7.3 Consideration of health benefits and resource use

The guideline development group considered that the standard-release preparation of metformin is a cost-effective treatment for type 2 diabetes because it is inexpensive (typically costing less than £1.00 per week) and there is compelling evidence for its clinical benefit.

The group agreed that uncertainty remained regarding the cost effectiveness of non-standard preparations. Although these are more expensive, no evidence was identified for inclusion relating to their clinical effectiveness. Given the group's positive clinical experience of using extended-release tablets and liquid metformin (oral solution), the group considered that this was an important area for further research.

12.3.7.4 Quality of evidence

The quality of the evidence was rated as high for all reported outcomes considered in the review. The contributing data were obtained from a single RCT that was judged to be at low risk of bias following the GRADE criteria.

While concerns were raised over differences between the metformin and placebo groups in terms of HbA1c values and FPG concentrations at baseline, these were adjusted for in the analysis reported by the study authors and were not considered to have an inordinate effect on the findings.

Likewise, while the guideline development group would have preferred the outcomes to have been assessed over a longer period than the 8 to 16 weeks of follow-up in the study (to aid understanding of long-term effectiveness of metformin), the group did not feel that the shorter period of follow-up undermined the validity of the findings. RCTs are typically conducted over short time periods because they are difficult and expensive to run. Contributing to the guideline development group's view that short-term follow-up was meaningful, the group considered that, compared with some other aspects of diabetes treatment (for example multiple daily insulin injection regimens), long-term adherence to metformin would be more readily achievable.

The group also noted that while the age range of the study participants (10 to 17 years) did not cover the entire age range relevant to the guideline, it did reflect the age profile of children and young people with type 2 diabetes in the UK and, therefore, those to whom guideline recommendations about the use of metformin were likely to apply. As such the quality of the evidence was not downgraded for indirectness.

The guideline development group noted that the lack of evidence for some prioritised outcomes did not raise sufficient concern about metformin's effectiveness to prevent the group recommending it. The absence of evidence related to alternative preparations (for example extended-release tablets and oral solution) meant that the guideline development group was unable to specifically recommend such preparations. As stated above, extended-release tablets are licensed for use only in adults, while oral solution is licensed for use only in people aged at least 10 years. Given the shared expectation within the group that non-standard preparations would offer the same important clinical benefits as the standard formulation, and the potential to improve patient satisfaction and adherence and to help manage symptoms due to adverse events, the guideline development group decided that this would be an important topic for further research.

12.3.7.5 Other considerations

The gudieline development group noted that although the review protocol for this question did not permit inclusion of studies in which all participants received metformin, they were aware of evidence from such a study that suggested that the effectiveness of metformin decreased over time (TODAY Study Group 2012).

In considering whether to recommend metformin, the group recognised the associated difficulties in sustaining adherence with oral medications, especially for young people.

Changes in social engagement in this age group might, for example, mean that a mild adverse event could lead to non-adherence, therefore jeopardising the sustained long-term benefit of using metformin. Nevertheless, the group considered that this should not dissuade clinicians from recommending the use of metformin for children and young people with type 2 diabetes.

12.3.7.6 Key conclusions

The guideline development group concluded that there was sufficient evidence that metformin monotherapy is both clinically and cost effective in type 2 diabetes in children and young people and therefore recommended its use. Specifically, the group recommended that healthcare professionals should offer standard-release metformin from diagnosis to children and young people with type 2 diabetes.

12.3.8 Recommendations

The current recommendations can be found at https://www.nice.org.uk/guidance/ng18.

12.3.9 Research recommendations

17. What is the long-term comparative clinical and cost effectiveness of different metformin preparations for treating type 2 diabetes in children and young people?

13 Management of type 2 diabetes – targets for and monitoring of glycaemic control

This section was updated in 2015.

13.1 Optimal HbA1c target

13.1.1 Review question

What is the optimal HbA1c target for children and young people with type 2 diabetes?

13.1.2 Introduction

This was a new topic covered by the 2015 update scope. The objective of this review question is to determine the optimal achievable HbA1c target for children and young people with type 2 diabetes. The review was limited to randomised controlled trials (RCTs) in the first instance. The most important outcomes were agreed a priori to be the worsening or development of long-term complications, and also included:

- hypertension
- retinopathy
- nephropathy
- glycaemic control
- severe hypoglycaemic episodes (including nocturnal hypoglycaemia)
- changes in body mass index (BMI) standard deviation score (SDS)
- health-related quality of life
- satisfaction of children, young people and families with the intervention.

13.1.3 Description of included studies

No studies met the inclusion criteria for this review and no evidence table was generated.

13.1.4 Evidence profile

No studies were identified for this review and so there is no evidence profile.

13.1.5 Evidence statements

No evidence was identified for inclusion in this review.

13.1.6 Health economics profile

A systematic literature search did not identify any relevant economic evaluations addressing optimal HbA1c targets for children and young people with type 2 diabetes.

This review was not prioritised for health economic analysis as a target of itself does not incur an opportunity cost, although the target may affect the choice of interventions used.

13.1.7 Evidence to recommendations

13.1.7.1 Relative value placed on the outcomes considered

The guideline development group had hoped to find evidence to determine the optimal HbA1c target for children and young people with type 2 diabetes to minimise the risk of long-term complications without incurring an increase in hypoglycaemic episodes. In particular, the group had hoped to find evidence related to the following long-term complications: hypertension; retinopathy; and nephropathy. The group also hoped to find evidence related to glycaemic control and changes in BMI SDS. They group wished to know whether there was any impact on psychosocial outcomes including health-related quality of life and the satisfaction of hildren, young people and families with treatment.

13.1.7.2 Consideration of clinical benefits and harms

The group was aware that the NICE guideline on type 2 diabetes in adults recommended a target level for HbA1c of 6.5% or less to minimise the risk of long-term complications. The group considered whether this would also be an appropriate target for children and young people with type 2 diabetes. It was noted that if the target was set at an unachievably low level, this would lead to children and young people disengaging with the process of effective HbA1c monitoring. In addition, the group did not wish to set a target that was so low that, were it to be achieved, it would increase the risk of hypoglycaemia. However, it was felt important to set an aspirational target which would have a meaningful effect on the child or young person's long-term health. If the target HbA1c level was set too high, the guideline development group felt that children and young people would be less likely to drive themselves to achieving even lower targets for HbA1c.

Ultimately, the group agreed that 6.5% was an appropriate target for children and young people as it was a safe target that was also aspirational without risking being unachievable. As was the case for the HbA1c target for children and young people with type 1 diabetes, the guideline development group expressed the target HbA1c value in IFCC units (48 mmol/mol).

The group recognised that for some children and young people with type 2 diabetes the specified target for HbA1c may be unattainable. Although efforts should be made towards the ideal HbA1c target, the group's clinical experience suggested that any reduction in HbA1c would be associated with a decreased risk of long-term complications and this would be of clinical benefit. However, the group considered that setting the lowest attainable target of HbA1c should be an a priori decision based on the child or young person's individual circumstances, recognising the important role of support from healthcare professionals towards achieving this aim.

13.1.7.3 Consideration of health benefits and resource use

Achieving a target may have opportunity costs both in terms of the interventions and actions required to improve glycaemic control. The guideline development group recognised that any reduction towards the normal range would improve long-term outcomes for children and young people with type 2 diabetes and thereby reduce the chance of further treatment being required. There was a lack of evidence for a specific HbA1c target in children and young people with type 2 diabetes. The group also felt that the target they had recommended was not so low as to increase the risk of hypoglycaemic episodes. Given this, they agreed that the target for HbA1c of 6.5% was very likely to be cost effective.

13.1.7.4 Quality of evidence

No relevant studies were identified for this review question and so the group relied on other NICE guidance in conjunction with their clinical and patient experience to make recommendations.

13.1.7.5 Other considerations

The group agreed that when setting targets for achieving outcomes with children and young people, it is extremely important to be supportive and encouraging. They noted that for some children and young people it would be extremely difficult to achieve a target HbA1c of 6.5% and so any form of reduction should be praised as the reduction would have some benefit for the future health of the child or young person.

Although the review question did not specifically address the frequency at which HbA1c monitoring should be performed, there was a recommendation in the 2004 guideline about the frequency at which HbA1c monitoring should be performed in children and young people with type 1 diabetes. The group agreed that it would be appropriate to specify the frequency of HbA1c monitoring for type 2 diabetes and hence, based on their clinical and patient experience, they agreed that a 3-monthly schedule for measuring the HbA1c level of the child or young person would be reasonable.

13.1.7.6 Key conclusions

The guideline development group concluded that a strong recommendation to measure HbA1c every 3 months in children and young people with type 2 diabetes, and to aim for an HbA1c level of 48 mmol/mol (6.5%) or lower, was warranted. The group specifically recommended that healthcare professionals should agree an individualised lowest achievable HbA1c target with each child or young person with type 2 diabetes and their family members or carers (as appropriate), taking into account factors such as daily activities, individual life goals, complications and comorbidities.

The group also mirrored several recommendations related to the HbA1c target for children and young people with type 1 diabetes, including those related to:

- calibrating HbA1c results according to IFCC standardisation
- explaining that an HbA1c target level of 48 mmol/mol (6.5%) or lower is ideal to minimise the risk of long-term complications
- explaining that any reduction in HbA1c level reduces the risk of long-term complications
- diabetes services documenting the proportion of children and young people who achieve an HbA1c level of 53 mmol/mol (7%) or lower.

13.1.8 Recommendations

The current recommendations can be found at https://www.nice.org.uk/guidance/ng18.

14 Management of type 2 diabetes in special circumstances – during intercurrent illness or surgery

This section was updated in 2015.

14.1 Introduction

Management of type 2 diabetes during intercurrent illness or surgery was not covered by the scope for the 2015 update, but the guideline development group and NICE recognised that the 2004 recommendations for children and young people with type 1 diabetes should apply equally to those with type 2 diabetes, and so the relevant recommendations are mirrored in this section. The recommendations for the management of type 1 diabetes during intercurrent illness and surgery are presented in Section 8.1 and Section 8.2; however, these topics were not covered by the scope for the 2015 update and so there is no specific evidence to recommendations section.

14.2 Recommendations

The current recommendations can be found at https://www.nice.org.uk/guidance/ng18.

15 Psychological and social issues in children and young people with type 2 diabetes

This section was updated in 2015.

15.1 Psychological interventions

15.1.1 Review questions

What is the effectiveness of psychological interventions to promote engagement with clinical services in children and young people with type 2 diabetes?

What is the effectiveness of psychological interventions to improve outcomes in children and young people with type 2 diabetes?

15.1.2 Introduction

This was a new topic covered by the 2015 update scope. The purpose of these review questions was to determine the effectiveness of psychological interventions aimed at promoting engagement with clinical services and improving outcomes in children and young people with type 2 diabetes. A single search was conducted to cover both review questions, and this included randomised controlled trials (RCTs) and systematic reviews of RCTs. Non-randomised studies were to be reviewed if no RCTs were identified.

Six types of psychological intervention were prioritised for inclusion:

- family therapy (including behavioural family systems therapy [BFST])
- cognitive behavioural therapy (CBT)
- motivational interviewing
- counselling
- mentoring
- peer support (and peer-led interventions).

Interventions and comparators included any combination of the interventions listed above. Comparators could also include any other well-defined psychological intervention.

The guideline development group identified both physical and psychosocial outcomes for these review questions. For the question about engagement with clinical services 1 physical outcome was defined, which was adherence to diabetes treatment. Psychosocial outcomes included: satisfaction of children, young people and families with interventions; changes in risk-taking behaviour, such as smoking; and engagement with clinical services, such as attendance at clinic appointments. For the question about clinical outcomes, physical outcomes included: glycaemic control; HbA1c; adverse events such as diabetes-related hospital admission or self-harm; changes in body mass index (BMI) standard deviation score (SDS); achievement and maintenance of weight loss; and change in physical activity levels. For both HbA1c and physical activity level a minimum follow-up of 6 months post-intervention was specified.

15.1.3 Description of included studies

No studies met the inclusion criteria for either review and so no evidence tables were generated.

15.1.4 Evidence profile

No studies were identified for either review and so there is no evidence profile.

15.1.5 Evidence statements

No evidence was identified for inclusion in either review.

15.1.6 Health economics profile

A systematic literature search did not identify any relevant economic evaluations addressing psychological interventions in children and young people with type 2 diabetes.

This review was not prioritised for health economic analysis as the number of children and young people with type 2 diabetes in the UK is small and because the guideline development group thought there would be little, if any, relevant clinical evidence.

15.1.7 Evidence to recommendations

Due to the absence of any identified evidence for either of the review questions related to psychological interventions (effectiveness of psychological interventions to improve outcomes in children and young people with type 2 diabetes, and effectiveness of psychological interventions to promote engagement with clinical services in children and young people with type 2 diabetes) the evidence to recommendations for these questions have been considered together.

15.1.7.1 Relative value placed on the outcomes considered

The guideline development group agreed that HbA1c value was the highest priority outcome for the review question about the effectiveness of psychological interventions to improve outcomes in children and young people with type 2 diabetes because if interventions resulted in a reduction in HbA1c by near to or greater than 0.5 percentage points (or 5.5 mmol/mol) then this would represent an important clinical benefit to a child or young person with type 2 diabetes. This decision was underpinned by the guideline development group's knowledge of research in adults with type 1 diabetes (The Diabetes Control and Complications Trial Research Group 1993) which showed that a 1 percentage point decease in HbA1c halved the risk of diabetes-related complications, including retinopathy and nephropathy. The guideline development group considered that this result could be meaningfully extrapolated to cover the population of children and young people with type 2 diabetes of relevance in these questions. Due to the inclusion of HbA1c as an outcome, no long-term complications were prioritised because the group felt that HbA1c would capture these long-term outcomes.

Psychosocial symptoms (for example anxiety and depression) were considered to be a high priority for both review questions. The association between anxiety and depression in adults with chronic physical health problems is recognised (see the NICE guideline on depression in adults with a chronic physical health problem: treatment and management). The guideline development group also recognised this as an important association in children and young people and their families based on their clinical and patient experience.

The group prioritised adherence to diabetes treatment because this is often a specified focus of psychological interventions and it is well recognised that better adherence would help to improve glycaemic control.

Changes in health-related quality of life and the satisfaction of children, young people and families with treatment were also considered as important outcomes.

The guideline development group believed that changes in BMI SDS, achievement and maintenance of weight loss and change in physical activity levels were also important

outcomes for consideration in determining the safety of overall diabetes care as children and young people with type 2 diabetes often present with a high BMI.

15.1.7.2 Consideration of clinical benefits and harms

The guideline development group discussed how parents of children and young people with type 2 diabetes are likely to have the condition themselves. There is, therefore, a culture of stigma attached to the parents and their children as type 2 diabetes is viewed as being self-inflicted. This is an important consideration for healthcare professionals when determining the most effective psychological intervention for children and young people with type 2 diabetes. The group suggested that in order to achieve a maximum clinical benefit, the preferred psychological intervention in children and young people with type 2 diabetes and their families should include either multi-systemic therapy, which includes all individuals who may be involved in the care pathway, or family therapy.

The guideline development group acknowledged that pregnancy may be also a concern for young women with type 2 diabetes due to possible future risks for their children.

15.1.7.3 Consideration of health benefits and resource use

The guideline development group noted that there are around 5 large centres in the UK which care for children and young people with type 2 diabetes, but other children and young people with type 2 diabetes are cared for by smaller centres. This means that health resources are not evenly distributed around the country and some centres would need more resources than others. However, the group also discussed the possibility that the small number of children and young people who have type 2 diabetes would be known personally to clinical staff and this may be advantageous in terms of applying psychological interventions. It was acknowledged that there is a concern that the incidence of children and young people with type 2 diabetes may increase in the future, although this has not yet happened despite previous indications. It was, however, noted that this may be because of incomplete recognition of the condition in this age group. As the number of children and young people with type 2 diabetes is small, the cost impact of providing psychological interventions is likely to be small.

The guideline development group noted that the approach to treatment for many children and young people with type 2 diabetes is often the same as for adults with type 2 diabetes. In the experience of the group this often results in incorrect management and subsequent rapid deterioration in health among children and young people with type 2 diabetes and an increased incidence of adverse outcomes. The group felt that this approach would result in a large financial cost of implementing the appropriate treatments later in the course of the disease relative to that incurred if relevant early treatment was administered.

15.1.7.4 Quality of evidence

No evidence was identified for either review question.

15.1.7.5 Other considerations

The guideline development group acknowledged that many children and young people with type 2 diabetes and their families do not speak English as their first language. A national survey was cited which indicated that 40% of children and young people with type 2 diabetes have English as a second language (Barrett 2013). However, the group also noted that this figure is likely to over-represent the ethnic population, especially in London.

Due to the absence of evidence identified for either review question the guideline development group considered the possibility and value of obtaining relevant evidence through future research. It was suggested that follow-up of children and young people with

type 2 diabetes in the transition from paediatric to adult services could provide a useful source of such data. The group highlighted that many children and young people are missed in the earlier years of the disease. This is a concern because type 2 diabetes in this population has a more severe progression than type 2 diabetes in adults, and outcomes for children and young people with type 2 diabetes are poor. Consequently this population is often not suitable to be transferred to primary clinical care at the age of 18 years. The guideline development group therefore considered the possibility of transition to specialist clinics rather than primary care. The National Paediatric Diabetes Audit was also suggested as a source of additional data as this reports both numbers of children and young people and outcomes for type 2 diabetes in terms of HbA1c. However, these data are not reported in relation to psychological interventions.

The guideline development group noted that the lack of similarity in disease progression with adults with type 2 diabetes also meant that it would not be possible to extrapolate research from adults to children and young people. The group therefore considered that other diseases or conditions encountered in the same age group may be useful for extrapolation of the effectiveness of psychological interventions. Obesity, Crohn's disease, cystic fibrosis and rheumatological diseases were cited as examples. However, the guideline development group acknowledged that transition to adult services remains an issue in these conditions. It was therefore suggested that it may be worth examining other similar diseases or conditions which may be applicable to the type 2 diabetes population in children and young people.

15.1.7.6 Key conclusions

The guideline development group concluded that either multi-systemic therapy or family therapy could represent the best approach to psychological interventions in children and young people with type 2 diabetes and their families. Based on the absence of any evidence for either the clinical engagement or clinical outcomes review questions, the group agreed that it was not appropriate to make recommendations on specific psychological interventions, although the group recognised the need for the diabetes team to be aware of the higher risk of emotional and behavioural difficulties in children and young people with type 2 diabetes. The group therefore extrapolated from the recommendations related to psychological interventions for children and young people with type 1 diabetes (see Section 9.8). The guideline development group and NICE also agreed that it was reasonable to extrapolate from recommendations related to advice on smoking and recreational drugs for children and young people with type 1 diabetes (see Section 9.10) as these were agreed to be equally relevant to children and young people with type 2 diabetes, although the topics were not covered by the scope for the 2015 update. These recommendations are presented in Chapter 12.

15.1.8 Recommendations

The current recommendations can be found at https://www.nice.org.uk/guidance/ng18.

15.1.9 Research recommendations

18. What is the clinical and cost effectiveness of psychological interventions for children and young people with type 2 diabetes?

16 Monitoring for associated conditions and complications of type 2 diabetes

This section was updated in 2015.

16.1 Monitoring for hypertension

16.1.1 Review question

What is the optimal monitoring strategy for identifying hypertension in children and young people with type 2 diabetes?

16.1.2 Introduction

This was a new topic covered by the 2015 update scope. The purpose of this review question is to identify the best time at which to start monitoring children and young people for hypertension following diagnosis with type 2 diabetes and how often monitoring should be repeated. Comorbidities such as hypertension are associated with type 2 diabetes due to the pathophysiology of the disease and in children and young people such comorbidities often have a more severe clinical progression. Consequently, it is important to identify children and young people presenting with hypertension sufficiently early to administer effective treatments.

The literature search for this question aimed to identify cohort studies or consecutive case series. Outcomes were prevalence estimates of hypertension at given time intervals after diagnosis, or at different ages.

Important considerations for this review were which parameters (systolic or diastolic blood pressure) to use to identify hypertension, which thresholds are appropriate (for example whether to use the 95th or 98th percentile, and above, for sex, age and height) and how many measurements are required. Subgroup analysis based on age groups was to be undertaken where possible. Outcomes of importance were the prevalence of hypertension at different timepoints after diagnosis and incidence of hypertension over time.

16.1.3 Description of included studies

Eight studies were identified for inclusion in this review. One study was an analysis of baseline data from a randomised controlled trial (RCT; Copeland 2011), 1 was a prospective multi-centre study (Rodriguez 2010), 1 was a prospective chart review (Reinehr 2008), 1 was a prospective follow-up of surveillance data (Shield 2009), 1 was a retrospective chart review (Urakami 2009) and 3 were cross-sectional studies (Eppens 2006; Ettinger 2005; Hotu 2004).

Study locations included the UK and Republic of Ireland (Shield 2009), the USA (Copeland 2011; Ettinger 2005; Rodriguez 2010), the Western Pacific region (Eppens 2006), Germany and Austria (Reinehr 2008), New Zealand (Hotu 2004) and Japan (Urakami 2009). The mean age of the children and young people with diabetes included in the studies ranged from 12.9 to 15.0 years. Two studies reported median ages of 13.2 years in participants with complete follow-up only (Reinehr 2008) and 14.9 years (Eppens 2006).

Numbers of participants ranged from 18 to 704. One study included only 51 of 129 participants in analyses due to incomplete follow-up (Reinehr 2008). One study included different numbers of participants in each analysis based on the availability of data; numbers ranged from 15 to 219 of a total of 410 participants (Rodriguez 2010). One study screened only 80% of participants for hypertension resulting in 265 of a total of 331 participants being

included in the analysis (Eppens 2006). One study analysed data for only 13 of the 18 participants due to measurements not being taken in all individuals (Hotu 2004). One study included a control group of participants without diabetes and, therefore, analyses included in this review comprise only the 26 participants with diabetes (Ettinger 2005). The family origin of participants, where reported, was primarily a mix of white, black, Hispanic and Asian (Copeland 2011; Ettinger 2005; Rodriguez 2010; Shield 2009). One study reported family origin as Maori or Pacific Islander, but did not report the proportions of each (Hotu 2004). Three studies did not explicitly report family origin (Eppens 2006; Reinehr 2008; Urakami 2009), but all participants from 1 study were from the Western Pacific region (Eppens 2006) and all participants from a second study were from Japan (Urakami 2009).

Whether or not participants used anti-hypertensive medication was not taken into account in inclusion or exclusion of participants at baseline in most studies, nor was this clearly reported in some studies. Only 1 study (Ettinger 2005) reported that participants taking antihypertensive medication were eligible for inclusion. Only 1 study reported information on the proportion of participants taking antihypertensive medication (Rodriguez 2010). In this study 13.3% of participants used medication for any reason and 8.1% used them specifically to treat hypertension.

With regard to the definition and measurement of blood pressure, 7 studies defined hypertension using percentiles (Copeland 2011; Eppens 2006; Ettinger 2005; Hotu 2004; Reinehr 2008; Rodriguez 2010; Shield 2009). Six of these studies defined hypertension as greater than the 95th percentile (Copeland 2011; Eppens 2006; Ettinger 2005; Hotu 2004; Reinehr 2008; Rodriguez 2010;). One study defined hypertension as greater than the 98th percentile (Shield 2009). The remaining study used absolute values for systolic and diastolic blood pressure to define hypertension (Urakami 2009).

Five studies (Eppens 2006; Hotu 2002; Reinehr 2008; Shield 2009; Urakami 2009) did not comment on whether an appropriate cuff size was used when blood pressure was measured. Two studies reported measuring blood pressure with appropriate cuff sizes (Copeland 2011; Rodriguez 2010). Repeated measurements of blood pressure for hypertension diagnosis was reported in 2 studies (Ettinger 2005; Rodriguez 2010), 1 of which (Ettinger 2005) did not provide information on whether appropriate cuff sizes were used.

Two studies reported prevalence data at diagnosis in relation to the age of the children and young people included in the study (Reinehr 2008; Urakami 2009). Age was reported either as a median value alongside the interquartile range (Reinehr 2008) or using the overall age range of participants included in the study (Urakami 2009). Subgroup analysis based on age groups was not possible.

Seven studies reported prevalence according to duration of diabetes (Copeland 2011; Eppens 2006; Ettinger 2005; Hotu 2004; Reinehr 2008; Rodriguez 2010; Shield 2009).

16.1.4 Evidence profile

The evidence profiles for this review question (monitoring for hypertension) are presented in Table 54 and Table 55.

Table 54: Evidence profile for prevalence of hypertension by age

Number of studies	Number of children and young people	Prevalence, % (95% confidence interval)	Quality
Median age of 13.2 years at diagnosis; hypertension (blood pressure values >95th percentile)			
1 (Reinehr 2008)	51	44.0% (30.1 to 57.9)[a]	Very low

Number of studies	Number of children and young people	Prevalence, % (95% confidence interval)	Quality
Aged 10 to 15 years at diagnosis; hypertension (systolic blood pressure >130 mmHg and diastolic blood pressure >85 mmHg)			
1 (Urakami 2009)	112	11.6% (5.6 to 17.6)[a]	Very low

a. Calculated by the NCC-WCH technical team.

Table 55: Evidence profile for prevalence of hypertension by duration of diabetes

Number of studies	Number of children and young people	Prevalence, % (95% confidence interval)	Quality
Within 1 year of diagnosis			
Hypertension (systolic or diastolic >95th percentile)			
1 (Rodriguez 2010)	176	18.2% (12.5 to 23.9)[a]	Very low
1 year after diagnosis			
Systolic hypertension (>98th percentile)			
1 (Shield 2009)	59	15.7% (6.2 to 25.2)[a]	Low
Diastolic hypertension (>98th percentile)			
1 (Shield 2009)	59	34.1% (21.8 to 46.4)[a]	Low
Within 2 years of diagnosis			
Hypertension (blood pressure values >90th percentile)			
1 (Copeland 2011)	704	26.3% (23.0 to 29.6)[a]	Low
Hypertension (blood pressure values >95th percentile)			
1 (Copeland 2011)	704	13.6% (11.1 to 16.1)[a]	Low
2 years after diagnosis			
Hypertension (blood pressure values >95th percentile)			
1 (Reinehr 2008)	51	32.0% (18.9 to 45.1)[a]	Very low
Within 3 years of diagnosis			
Hypertension (blood pressure values ≥95th percentile)			
1 (Ettinger 2005)	26	58.0% (38.0 to 78.0)[a]	Very low
Within 4 years of diagnosis			
Hypertension (systolic and diastolic >95th percentile)			
1 (Eppens 2006)	265	8.0% (4.7 to 11.3)[a]	Very low
Hypertension (systolic >95th percentile)			
1 (Hotu 2004)	3	28.0% (5.6 to 50.4)[a]	Very low
Between 1 and 5 years after diagnosis			
Hypertension (systolic or diastolic >95th percentile)			
1 (Rodriguez 2010)	219	27.9% (22.0 to 33.8)[a]	Very low
More than 5 years after diagnosis			
Hypertension (systolic or diastolic >95th percentile)			
1 (Rodriguez 2010)	15	26.7% (2.3 to 51.1)[a]	Very low

a. Calculated by the NCC-WCH technical team

16.1.5 Evidence statements

Prevalence of hypertension according to age

One study (total 51 participants) estimated the prevalence of hypertension, defined as blood pressure values greater than the 95th percentile, in children and young people with type 2 diabetes with a median age of 13.2 years to be 44.0%. The quality of the evidence for this outcome was very low.

One study (total 112 participants) estimated the prevalence of hypertension, defined as a systolic blood pressure of greater than 130 mmHg and a diastolic blood pressure of greater than 85 mmHg, in children and young people aged 10 to 15 years to be 11.6%. The quality of the evidence for this outcome was very low.

Prevalence of hypertension according to duration of diabetes

One study (total 176 participants) estimated the prevalence of hypertension, defined as a systolic or diastolic blood pressure greater than the 95th percentile, within 1 year of diagnosis in children and young people with type 2 diabetes to be 18.2%. The quality of the evidence for this outcome was very low.

One study (total 59 participants) estimated the prevalence of systolic hypertension, defined as values greater than the 98th percentile, at 1 year after diagnosis in children and young people with type 2 diabetes to be 15.7%. The quality of the evidence for this outcome was very low.

One study (total 59 participants) estimated the prevalence of diastolic hypertension, defined as values greater than the 98th percentile, at 1 year after diagnosis in children and young people with type 2 diabetes to be 34.1%. The quality of the evidence for this outcome was very low.

One study (total 704 participants) estimated the prevalence of hypertension, defined as blood pressure values greater than the 90th percentile, within 2 years of diagnosis in children and young people with type 2 to be 26.3%. The quality of the evidence for this outcome was low.

One study (total 704 participants) estimated the prevalence of hypertension, defined as blood pressure values greater than the 95th percentile, within 2 years of diagnosis in children and young people with type 2 diabetes to be 13.6%. The quality of the evidence for this outcome was low.

One study (total 51 participants) estimated the prevalence of hypertension, defined as blood pressure values greater than the 95th percentile, at 2 years after diagnosis in children and young people with type 2 diabetes to be 32.0%. The quality of the evidence for this outcome was very low.

One study (total 26 participants) estimated the prevalence of hypertension, defined as blood pressure values greater than the 95th percentile, within 3 years of diagnosis in children and young people with type 2 diabetes to be 58.0%. The quality of the evidence for this outcome was very low.

One study (total 265 participants) estimated the prevalence of hypertension, defined as a systolic and diastolic blood pressure greater than the 95th percentile, within 4 years of diagnosis in children and young people with type 2 diabetes to be 8.0%. The quality of the evidence for this outcome was very low.

One study (total 3 participants) estimated the prevalence of hypertension, defined as a systolic blood pressure greater than the 95th percentile, within 4 years of diagnosis in children and young people with type 2 diabetes to be 28.0%. The quality of the evidence for this outcome was very low.

One study (total 219 participants) estimated the prevalence of hypertension, defined as a systolic or diastolic blood pressure greater than the 95th percentile, between 1 and 5 years after diagnosis in children and young people with type 2 diabetes to be 27.9%. The quality of the evidence for this outcome was very low.

One study (total 15 participants) estimated the prevalence of hypertension, defined as a systolic or diastolic blood pressure greater than the 95th percentile, more than 5 years after diagnosis in children and young people with type 2 diabetes to be 26.7%. The quality of the evidence for this outcome was very low.

16.1.6 Health economics profile

A systematic literature search did not identify any relevant economic evaluations addressing the optimal monitoring strategy for identifying hypertension in children and young people with type 2 diabetes.

This question was not prioritised for health economic analysis as the number of children and young people with type 2 diabetes in the UK is very small and because the review was not designed to retrieve evidence relating to diagnostic test accuracy and subsequent management which would be necessary to assess cost effectiveness.

16.1.7 Evidence to recommendations

16.1.7.1 Relative value placed on the outcomes considered

The guideline development group felt that there was some clinical uncertainty as to whether hypertension monitoring should be undertaken in children and young people with type 2 diabetes and, if so, whether the monitoring strategy should also take account of duration of diabetes. For this reason, they prioritised prevalence and incidence as outcomes of interest so that they could gain an understanding of both the proportion of children and young people with type 2 diabetes in different age groups who had hypertension and also the rate at which new cases occurred in relation to time from diagnosis.

Evidence was identified only for measuring the prevalence of hypertension, but the guideline development group felt that this provided sufficient information on which to base recommendations.

16.1.7.2 Consideration of clinical benefits and harms

Hypertension is associated with higher risk of morbidity and mortality in the long term. The guideline development group was aware of evidence (UK Prospective Diabetes Study [UKPDS] 1998a; UKPDS 1998b) that suggests that hypertension is even more likely to impact on adverse long-term outcomes than is poor glycaemic control. The group therefore considered that the timely and accurate identification of hypertension presented an important clinical benefit because it can prompt early intervention with antihypertensive medications and other interventions and reduce the risk of these poor long-term outcomes occurring.

The evidence included in the review showed that the prevalence of hypertension was high in the majority of the age groups for which there was evidence, and at the shortest time intervals since diagnosis measured in the studies.

The guideline development group concluded that the only potential harm associated with hypertension monitoring was potential misdiagnosis and ensuing unnecessary treatment. The group felt that this risk was relatively small overall and outweighed by the benefits of accurate identification as early as possible and therefore chose to recommend monitoring from diagnosis. The group did, however, feel that based on their clinical experience, it was appropriate to provide guidance on how to carry out monitoring to reduce the likelihood of

misdiagnosis. In particular they considered it extremely important that the correct size of blood-pressure monitoring cuff was used. This is because many children and young people with type 2 diabetes are obese and so age-labelled cuff sizes used in clinics may be too small, causing hypertension to be diagnosed when it may not be present.

The guideline development group also felt that if a child or young person's blood pressure was found to be above the 95th percentile for their age after a period of rest it should be repeated with ambulatory measurement. The rationale for this is that in some clinics it may not be common practice for children and young people to be given an opportunity to sit and rest for 5 minutes before blood pressure measurement is taken (as was ensured in some of the studies included in the review). Confirmation of the result with ambulatory blood pressure measurement is, therefore, needed to determine accurate measurement.

16.1.7.3 Consideration of health benefits and resource use

The guideline development group felt that achieving timely and accurate monitoring was important for ensuring that the health benefits of the intervention justified the resources used, and as such the group specified using a correctly-sized blood pressure cuff and confirmatory ambulatory monitoring in specific circumstances (see above). The group noted that prevalence of hypertension is high in children and young people with type 2 diabetes and therefore a lot of ambulatory monitoring will be performed, but the group considered that this would be counterbalanced by the small numbers of children and young people with type 2 diabetes in the UK. Overall, the group expected that the downstream cost savings from complications that would be avoided by effective monitoring and treatment would offset the cost of ambulatory monitoring.

16.1.7.4 Quality of evidence

Although the evidence reported in the included studies was of low quality based on GRADE quality assessment, the guideline development group decided that the evidence provided enough information overall to inform decision-making regarding recommendations.

Several of the included studies were conducted in ethnic populations that are not representative of the UK population of children and young people with type 2 diabetes, although 1 study (of higher quality) was conducted in the UK and Republic of Ireland.

The use of hypertensive medication is likely in children and young people with type 2 diabetes, and so prevalence data measured at specific time points after diagnosis may reflect blood pressure measurements in some children and young people already receiving such treatments, rather than the underlying prevalence without antihypertensive treatment. Initiation of hypertensive treatment may also explain the high loss to follow-up in some studies (for example Reinehr 2008) if those participants who start to use antihypertensive treatment are withdrawn from the study.

16.1.7.5 Other considerations

The guideline development group noted that some people worry about having their blood pressure measured and the group felt that this further supported the rationale for providing recommendations that aimed to ensure timely (and accurate) monitoring.

16.1.7.6 Key conclusions

The guideline development group concluded that children and young people with type 2 diabetes should be offered blood pressure monitoring at diagnosis and annually thereafter, and that the benefit associated with this in terms of reducing the risk of long-term complications should be communicated to the children and young people and their family members or carers (as appropriate).

The group therefore recommended that healthcare professionals should offer children and young people with type 2 diabetes screening for hypertension annually starting at diagnosis. They also recommended that healthcare professionals should explain to children and young people with type 2 diabetes and their family members or carers (as appropriate) the importance of annual screening for hypertension and that screening is important because if hypertension is found, early treatment will reduce the risk of complications. The group further recommended that healthcare professionals should use a cuff large enough for the child or young person when measuring blood pressure and that if repeated resting measurements are greater than the 95th percentile for age and sex, healthcare professionals should confirm hypertension using 24-hour ambulatory blood pressure monitoring before starting antihypertensive therapy.

The recommendations related to the optimal monitoring strategy for hypertension in children and young people with type 2 diabetes use the terminology ‘monitoring’ rather than ‘screening’.

16.2 Monitoring for dyslipidaemia

16.2.1 Review question

What is the optimal monitoring strategy for identifying dyslipidaemia in children and young people with type 2 diabetes?

16.2.2 Introduction

This was a new topic covered by the 2015 update scope. The purpose of this review question is to identify the best time at which to start monitoring children and young people for dyslipidaemia following diagnosis with type 2 diabetes and how often monitoring should be repeated. Comorbidities such as dyslipidaemia are associated with type 2 diabetes due to the pathophysiology of the disease and in children and young people such comorbidities often have a more severe clinical progression. Consequently it is important to identify children and young people presenting with dyslipidaemia sufficiently early to administer effective treatments.

The literature search for this question aimed to identify cohort studies or consecutive case series. Outcomes were prevalence estimates of dyslipidaemia at given time intervals after diagnosis, or at different ages. Dyslipidaemia was to be determined based on measurements of any of the following serum lipids:

- total cholesterol
- high density lipoprotein (HDL) cholesterol
- low density lipoprotein (LDL) cholesterol
- triglycerides
- the ratio of HDL to total cholesterol.

Subgroup analysis based on age groups was to be undertaken where possible. Outcomes prioritised for inclusion in the review were prevalence of dyslipidaemia at different time points after diagnosis and incidence of dyslipidaemia over time.

16.2.3 Description of included studies

Seven studies were identified for inclusion in this review. One study was an analysis of baseline data from an RCT (Copeland 2011), 1 was a prospective chart review (Reinehr 2008), 2 were retrospective chart reviews (Le 2013; Urakami 2009) and 3 were cross-sectional studies (Eppens 2006; Ettinger 2005; Hotu 2004).

Study locations included the USA (Copeland 2011; Ettinger 2005; Le 2013), the Western Pacific region (Eppens 2006), Germany and Austria (Reinehr 2008), New Zealand (Hotu 2004) and Japan (Urakami 2009). The mean age of the children and young people with diabetes included in the studies ranged from 12.9 to 15.0 years. Two studies reported median ages of participants with complete follow-up as 13.2 years (Reinehr 2008) and 14.9 years (Eppens 2006). Numbers of participants ranged from 18 to 704. One study included only 51 of 129 participants in analyses due to incomplete follow-up (Reinehr 2008). One study used data for only 13 of the 18 participants due to measurements not being taken in all participants (Hotu 2004). One study included a control group of participants without diabetes and, therefore, analyses included in this review comprise only the 26 participants with diabetes (Ettinger 2005). Three studies reported the ethnicity of participants (Copeland 2011; Ettinger 2005; Le 2013). Participants in 1 of these studies were primarily a mix of white, black and Hispanic (Copeland 2011). The second study included only minority populations of non-Hispanic black or Hispanic Latino participants (Ettinger 2005). Participants in the third study were either non-Hispanic or African-American (Le 2013). One study reported family origin as Maori or Pacific Islander, but did not report the proportions of each (Hotu 2004). Three studies did not explicitly report family origin (Eppens 2006; Reinehr 2008; Urakami 2009), but all participants from 1 study were from the Western Pacific region (Eppens 2006) and all participants from a second study were from Japan (Urakami 2009).

Two studies reported prevalence data at diagnosis in relation to the age of the children and young people included in the study (Reinehr 2008; Urakami 2009). Age was reported either as a median value alongside the interquartile range (Reinehr 2008) or using the overall age range of participants included in the study (Urakami 2009). Six studies reported prevalence according to duration of diabetes (Copeland 2011; Eppens 2006; Ettinger 2005; Hotu 2004; Le 2013; Reinehr 2008). Subgroup analysis based on age groups was not possible.

Different criteria were used to define dyslipidaemia across studies. One study defined dyslipidaemia as having abnormal values for each of total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides (Reinehr 2008). Another study reported the number of children and young people with abnormal values for each of the lipid measures, but these were reported separately (Eppens 2006). One study used the ratio of total cholesterol to HDL to define dyslipidaemia (Hotu 2004). Three studies reported the numbers of participants with abnormal values for some, but not all, of the lipid measurements (Copeland 2011; Le 2013; Urakami 2009). One study did not define dyslipidaemia (Ettinger 2005).

With regard to testing methods, 4 studies (Copeland 2011; Eppens 2006; Ettinger 2003; Urakami 2009) used fasting samples to measure biochemical abnormalities, including total cholesterol, LDL, HDL and triglycerides. Two studies (Hotu 2004; Reinehr 2008) did not report whether or not lipid measurements were taken after fasting. Due to its retrospective study design, 1 study (Le 2013) could not guarantee the fasting status of participants, and so triglyceride measurements were excluded from the analysis.

16.2.4 Evidence profile

The evidence profiles for this review question (monitoring for dyslipidaemia) are presented in Table 56 and Table 57.

Table 56: Evidence profile for prevalence of dyslipidaemia by age

Number of studies	Number of children and young people	Prevalence, % (95% CI)	Quality
Median age of 13.2 years at diagnosis			
Prevalence of dyslipidaemia[c]			
1 (Reinehr 2008)	51	65.0% (51.6 to 78.4)[b]	Very low

Number of studies	Number of children and young people	Prevalence, % (95% CI)	Quality
Aged between 10 and 15 years at diagnosis			
Triglycerides >150 mg/dl (1.7 mmol/l)			
1 (Urakami 2009)	112	33.0% (24.2 to 41.8)[b]	Very low
High density lipoproteins <40 mg/dl (1.0 mmol/l)			
1 (Urakami 2009)	112	21.4% (13.7 to 29.1)[b]	Very low

CI confidence interval, HDL high-density lipoprotein, LDL low-density lipoprotein
a. Dyslipidaemia was defined using the following cut-offs: total cholesterol >5.1mmol/litre (200 mg/dl), LDL >3.3mmol/l (130 mg/dl), HDL <0.9 mmol (35 mg/dl) or triglycerides >1.7 mmol/l (150 mg/dl)
b. Calculated by the NCC-WCH technical team
c. Based on the age range for inclusion in the study as the actual age range of participants was not reported

Table 57: Evidence profile for prevalence of dyslipidaemia by duration of diabetes

Number of studies	Number of children and young people	Prevalence, % (95% CI)	Quality
At 1 year after diagnosis			
Prevalence of LDL >130 mg/dl (3.4 mmol/litre)			
1 (Le 2013)	86	12.5% (5.4 to 19.6)[a]	Very low
Prevalence of HDL <35 mg/dl (0.9 mmol/litre)			
1 (Le 2013)	86	25.0% (15.8 to 34.2)[a]	Very low
Within 2 years of diagnosis			
Low density lipoproteins ≥160 mg/dl (4.1 mmol/litre)			
1 (Copeland 2011)	704	0.4% (0.00 to 0.87)[a]	Low
High density lipoproteins <50 mg/dl (1.3 mmol/litre, females) or <40 mg/dl (1.0 mmol/litre, males)			
1 (Copeland 2011)	704	79.8% (76.8 to 82.8)[a]	Low
Triglycerides ≥200 mg/dl (2.3mmol/litre)			
1 (Copeland 2011)	704	10.2% (8.0 to 12.4)[a]	Low
At 2 years after diagnosis			
Prevalence of dyslipidaemia[c]			
1 (Reinehr 2008)	51	69.0% (56.0 to 82.0)[a]	Very low
Within 3 years of diagnosis			
Dyslipidaemia (not defined)			
1 (Ettinger 2005)	26	69.2% (50.5 to 87.9)[a]	Very low
Within 4 years of diagnosis			
Total cholesterol ≥6mmol/litre			
1 (Eppens 2006)	331	12.0% (8.5 to 15.5)[a]	Very low
Low density lipoproteins >4mmol/litre			
1 (Eppens 2006)	331	12.0% (8.5 to 15.5)[a]	Very low
High density lipoproteins <0.9mmol/litre			
1 (Eppens 2006)	331	10.0% (6.8 to 13.2)[a]	Very low
Triglycerides ≥ 2.2mmol/litre			
1 (Eppens 2006)	331	16.0% (12.1 to 19.9)[a]	Very low

Number of studies	Number of children and young people	Prevalence, % (95% CI)	Quality
Total cholesterol:high density lipoproteins molar ratio >4.5 molar units			
1 (Hotu 2004)	13	85.0% (63.4 to 1.00)[a]	Very low

CI confidence interval, HDL high-density lipoprotein, LDL low-density lipoprotein, RCT randomised controlled trial
a. Calculated by the NCC-WCH technical team
b. Starting point of moderate for quality rating as baseline analysis of an RCT
c. Dyslipidaemia was defined using the following cut-offs: total cholesterol >5.1mmol/l (200 mg/dl), LDL >3.3mmol/l (130 mg/dl), HDL <0.9mmol (35 mg/dl) or triglycerides >1.7 mmol/l (150 mg/dl)

16.2.5 Evidence statements

Prevalence of dyslipidaemia according to age

One study (total 51 participants) estimated the prevalence of dyslipidaemia, defined as total cholesterol more than 5.1 mmol/litre (200 mg/dl), LDL more than 3.3 mmol/litre (130 mg/dl), HDL less than 0.9 mmol (35 mg/dl) or triglycerides more than 1.7 mmol/litre (150 mg/dl), in children and young people with type 2 diabetes with a median age of 13.2 years to be 65.0%. The quality of the evidence for this outcome was very low.

One study (total 112 participants) estimated the prevalence of dyslipidaemia, defined as triglycerides greater than 150 mg/dl (1.7mmol/litre), in children and young people aged 10 to 15 years to be 33.0%. The quality of the evidence for this outcome was very low.

One study (total 112 participants) estimated the prevalence of dyslipidaemia, defined as HDL less than 40 mg/dl (1.0 mmol/litre), in children and young people aged 10 to 15 years to be 21.4%. The quality of the evidence for this outcome was very low.

Prevalence of dyslipidaemia according to duration of diabetes

One study (total 86 participants) estimated the prevalence of dyslipidaemia, defined as LDL greater than 130 mg/dl (3.4 mmol/litre), within 1 year of diagnosis in children and young people with type 2 diabetes to be 12.5%. The quality of the evidence for this outcome was very low.

One study (total 86 participants) estimated the prevalence of dyslipidaemia, defined as HDL less than 35 mg/dl (0.9 mmol/litre), within 1 year of diagnosis in children and young people with type 2 diabetes to be 25.0%. The quality of the evidence for this outcome was very low.

One study (total 704 participants) estimated the prevalence of dyslipidaemia, defined as LDL greater than 160 mg/dl, within 2 years of diagnosis in children and young people with type 2 diabetes to be 0.4%. The quality of the evidence for this outcome was low.

One study (total 704 participants) estimated the prevalence of dyslipidaemia, defined as HDL less than 50 mg/dl in females (1.3 mmol/litre) or less than 40 mg/dl in males (1.0 mmol/litre), within 2 years of diagnosis in children and young people with type 2 diabetes to be 79.8%. The quality of the evidence for this outcome was low.

One study (total 704 participants) estimated the prevalence of dyslipidaemia, defined as triglycerides greater than 200 mg/dl (2.3 mmol/litre), within 2 years of diagnosis in children and young people with type 2 diabetes to be 10.2%. The quality of the evidence for this outcome was low.

One study (total 51 participants) estimated the prevalence of dyslipidaemia, defined as total cholesterol more than 5.1 mmol/litre (200 mg/dl), LDL more than 3.3 mmol/litre (130 mg/dl), HDL less than 0.9 mmol (35 mg/dl) or triglycerides more than 1.7 mmol/litre (150 mg/dl), at 2

years after diagnosis in children and young people with type 2 diabetes to be 69.0%. The quality of the evidence for this outcome was very low.

One study (total 26 participants) estimated the prevalence of dyslipidaemia (undefined) within 3 years of diagnosis in children and young people with type 2 diabetes to be 69.2%. The quality of the evidence for this outcome was very low.

One study (total 331 participants) estimated the prevalence of dyslipidaemia, defined as total cholesterol greater than 6 mmol/litre, within 4 years of diagnosis in children and young people with type 2 diabetes to be 12.0%. The quality of the evidence for this outcome was very low.

One study (total 331 participants) estimated the prevalence of dyslipidaemia, defined as LDL greater than 4 mmol/litre, within 4 years of diagnosis in children and young people with type 2 diabetes to be 12.0%. The quality of the evidence for this outcome was very low.

One study (total 331 participants) estimated the prevalence of dyslipidaemia, defined as HDL less than 0.9 mmol/litre, within 4 years of diagnosis in children and young people with type 2 diabetes to be 10.0%. The quality of the evidence for this outcome was very low.

One study (total 331 participants) estimated the prevalence of dyslipidaemia, defined as triglycerides greater than 2.2 mmol/litre, within 4 years of diagnosis in children and young people with type 2 diabetes to be 16.0%. The quality of the evidence for this outcome was very low.

One study (total 13 participants) estimated the prevalence of dyslipidaemia, defined as a ratio of total cholesterol to HDL of greater than 4.5 molar units, within 4 years of diagnosis in children and young people with type 2 diabetes to be 85.0%. The quality of the evidence for this outcome was very low.

16.2.6 Health economics profile

A systematic literature search did not identify any relevant economic evaluations addressing the optimal monitoring strategy for identifying dyslipidaemia in children and young people with type 2 diabetes.

This question was not prioritised for health economic analysis as the number of children and young people with type 2 diabetes in the UK is very small and because the review was not designed to retrieve evidence relating to diagnostic test accuracy and subsequent management which would be necessary to assess cost effectiveness.

16.2.7 Evidence to recommendations

16.2.7.1 Relative value placed on the outcomes considered

The guideline development group felt that there was some clinical uncertainty as to whether dyslipidaemia monitoring should be undertaken in children and young people with type 2 diabetes, and if so whether the monitoring strategy should also take account of duration of diabetes. For this reason, the group prioritised prevalence and incidence as outcomes of interest so that they could gain an understanding of both the proportion of children and young people with type 2 diabetes in different age groups who had dyslipidaemia and also the rate at which new cases occurred in relation to time from diagnosis.

Evidence was only identified for prevalence of dyslipidaemia, but the guideline development group felt that this provided sufficient information on which to base recommendations in this section.

16.2.7.2 Consideration of clinical benefits and harms

Dyslipidaemia is a risk factor for cardiovascular disease and, therefore, for morbidity and mortality in the long term. In light of this the guideline development group considered that the timely (and accurate) identification of dyslipidaemia presented an important clinical benefit to children and young people with type 2 diabetes because it can prompt early intervention with lipid-lowering agents and reduce the risk of adverse long-term outcomes occurring.

The evidence included in the review showed that the prevalence of dyslipidaemia was high in all of the age groups for which there was evidence, and at the shortest time interval since diagnosis measured in the included studies.

The guideline development group concluded that the only potential harm associated with dyslipidaemia monitoring was misdiagnosis and ensuing unnecessary treatment. The group felt that this risk was relatively small overall and outweighed by the benefits of identification as early as possible and therefore decided to recommend monitoring for dyslipidaemia from diagnosis.

To reduce the likelihood of incorrect measurements being used to determine treatment, the guideline development group felt it was appropriate to recommend taking repeat samples (fasting or non-fasting) before starting treatment. The group felt that it was important to measure total cholesterol, HDL cholesterol, non-HDL cholesterol and triglyceride concentrations as part of screening for dyslipidaemia in children and young people with type 2 diabetes. They did, however, note that the purpose of triglyceride measurement is to enable the calculation of non-HDL (LDL) cholesterol only. Absolute values of triglycerides are not useful in themselves because they are associated with poor glycaemic control and poor diet, both of which are common in children and young people with type 2 diabetes and therefore absolute triglyceride values alone should not direct decisions about specific lipid-lowering treatments.

16.2.7.3 Consideration of health benefits and resource use

The group noted that therapy with lipid-lowering agents is available for children and young people and therefore timely and accurate monitoring was likely to be cost effective as it could lead to treatment and reduce down-stream costs from reduced incidence of complications and adverse long-term outcomes.

Lipid measurement is already common practice and the recommendation that monitoring should take place annually from diagnosis aligns with existing clinic visit schedules so there is unlikely to be any uplift resource use.

16.2.7.4 Quality of evidence

Although the evidence reported in the included studies was of low quality based on GRADE quality assessment, the guideline development group decided that the evidence provided enough information overall to inform decision-making regarding recommendations.

The study that provided no clear definition of dyslipidaemia assessment did not influence the guideline development group’s decision-making, given the uncertainty associated with its results.

Any studies in which dyslipidaemia was defined using triglyceride measurements but fasting status was not reported were downgraded because the group felt that such measurements were likely to be strongly influenced by poor diet and glycaemic control and may, therefore, provide biased results.

16.2.7.5 Other considerations

The guideline development group noted that in the adult population validated risk tables (that take account of lipid levels) exist to determine cardiovascular risk and the need for treatment across different thresholds, but there is no equivalent guide for children and young people.

The guideline development group noted that the definitions of dyslipidaemia used in the studies in the guideline review varied somewhat, but were often similar to:

- total cholesterol more than 5.5 mmol/litre, or
- HDL less than 1.0mmol/litre, or
- ratio of total cholesterol to HDL less than 4.

The group agreed that these cut-offs were in keeping with their understanding of commonly accepted values for consideration of intervention for dyslipidaemia.

The group noted that there may be practical considerations associated with obtaining a fasting sample in children and young people.

16.2.7.6 Key conclusions

The guideline development group concluded that children and young people with type 2 diabetes should be offered dyslipidaemia monitoring at diagnosis and annually thereafter, and that the benefit from this in terms of reducing the risk of long-term complications should be communicated with the children and young people and their family members or carers (as appropriate).

The group therefore recommended that healthcare professionals should offer children and young people with type 2 diabetes screening for dyslipidaemia annually starting at diagnosis. They also recommended that healthcare professionals should explain to children and young people with type 2 diabetes and their family members or carers (as appropriate) the importance of annual screening for dyslipidaemia and that screening is important because if dyslipidaemia is found, early treatment will reduce the risk of complications. The group further recommended that healthcare professionals should measure total cholesterol, HDL cholesterol, non-HDL cholesterol and triglyceride concentrations when screening for dyslipidaemia in children and young people with type 2 diabetes, and that dyslipidaemia should be confirmed using a repeat sample (fasting or non-fasting) before deciding on further management strategies.

The recommendations related to the optimal monitoring strategy for dyslipidaemia in children and young people with type 2 diabetes use the terminology ‘monitoring’ rather than ‘screening’.

16.3 Monitoring for retinopathy

16.3.1 Review question

What is the optimal monitoring strategy for identifying retinopathy in children and young people with type 2 diabetes?

16.3.2 Introduction

This was a new topic covered by the 2015 update scope. The aim of this review was to determine when screening for retinopathy should start in children and young people with type 2 diabetes, and how frequently it should be repeated. The literature search covered cross-sectional studies which reported prevalence of retinopathy, as well as longitudinal studies which reported incidence of new retinopathy over time. Both the age of the children and young people affected and the duration of diabetes were to be considered when assessing

the prevalence and incidence of retinopathy. Only studies that identified retinopathy using retinal photography were included.

16.3.3 Description of included studies

Two studies were identified for inclusion in the review (Levitsky 2013; Shield 2009). Both studies reported prevalence of retinopathy in children and young people with type 2 diabetes. No studies were identified that assessed the incidence of retinopathy.

The first study (Levitsky 2013) reported results from a RCT conducted in the USA (the TODAY study). The trial aimed to investigate the value of metformin and lifestyle interventions in the treatment of type 2 diabetes in children and young people. However, the results included were analysed as cross-sectional data, reporting on the prevalence of retinopathy in all study participants during the final year of the trial. There were 277 participants aged 18 years or younger, and prevalence of retinopathy was reported according to both the age of the participants and the duration of diabetes.

The second study (Shield 2009) presented data from the 1-year follow up of a national incident cohort of young people diagnosed with type 2 diabetes. This study was conducted in the UK and included 73 children and young people with an age range of 10.8 to 17.8 years (mean age 14.5 years).

16.3.4 Evidence profile

The evidence profiles for this review question (monitoring for retinopathy) are presented in Table 58 and Table 59.

Table 58: Evidence profile for prevalence of retinopathy according to age

Number of studies	Number of children and young people	Prevalence, % (95% CI)	Quality
12 to 16 years			
1 (Levitsky 2013)	140	5.7 (2.5 to 11.0)[a]	Moderate[b]
17 to 18 years			
1 (Levitsky 2013)	137	12.4 (7.4 to 19.1)[a]	Moderate[b]
10.8 to 17.8 years			
1 (Shield 2009)	55	0.0 (0.0 to 6.5)[a]	Low[c]

CI confidence interval, RCT randomised controlled trial
a. 95% CI calculated by NCC-WCH technical team from data reported in the article
b. Although the study design was an RCT, data obtained were cross-sectional and observational in nature
c. Serious risk of bias

Table 59: Evidence profile for prevalence of retinopathy according to duration of diabetes

Number of studies	Number of children and young people	Prevalence, % (95% CI)	Quality
12 months			
1 (Shield 2009)	55	0.0 (0.0 to 6.5)[a]	Low[b]
24 to 49 months			
1 (Levitsky 2013)	170	5.3 (2.5 to 9.8)[a]	Low[c,d]
50 to 66 months			
1 (Levitsky 2013)	172	13.4 (8.7 to 19.4)[a]	Low[c,d]

Number of studies	Number of children and young people	Prevalence, % (95% CI)	Quality
67 to 101 months			
1 (Levitsky 2013)	137	22.3 (16.3 to 29.2)[a]	Low[c,d]

CI confidence interval, RCT randomised controlled trial
a. 95% CI calculated by NCC-WCH technical team from data reported in the article
b. Serious risk of bias
c. Although the study design was an RCT, data obtained were cross-sectional and observational in nature
d. Serious indirectness

16.3.5 Evidence statements

Prevalence of retinopathy according to age

One study (total 55 participants) estimated the prevalence of retinopathy in children and young people with type 2 diabetes aged between 10.8 and 12 years at 0%. The evidence for this finding was of low quality.

One study (total 140 participants) estimated the prevalence of retinopathy in children and young people with type 2 diabetes aged between 12 and 16 years to be between 0% and 5.7%. The evidence for this finding was of low to moderate quality.

One study (total 137 participants) estimated the prevalence of retinopathy in children and young people with type 2 diabetes aged between 17 and 18 years to be between 0% and 12.4%. The evidence for this finding was of low to moderate quality.

Prevalence of retinopathy according to duration of diabetes

One study (total 55 participants) estimated the prevalence of retinopathy in children and young people with type 2 diabetes for a duration of 12 months to be 0%. The evidence for this finding was of low quality.

One study (total 170 participants) estimated the prevalence of retinopathy in children and young people with type 2 diabetes for a duration of 24 to 49 months to be 5.3%. The evidence for this finding was of low quality.

One study (total 172 participants) estimated the prevalence of retinopathy in children and young people with type 2 diabetes for a duration of 50 to 66 months to be 13.4%. The evidence for this finding was of low quality.

One study (total 137 participants) estimated the prevalence of retinopathy in children and young people with type 2 diabetes for a duration of 67 to 101 months to be 22.3%. The evidence for this finding was of low quality.

Incidence of retinopathy

No evidence was identified for this outcome.

16.3.6 Health economics profile

A systematic literature search did not identify any relevant economic evaluations addressing the optimal monitoring strategy for identifying retinopathy in children and young people with type 2 diabetes.

This question was not prioritised for health economic analysis as the number of children and young people with type 2 diabetes in the UK is very small and because the review was not designed to retrieve evidence relating to diagnostic test accuracy and subsequent management which would be necessary to assess cost effectiveness.

16.3.7 Evidence to recommendations

16.3.7.1 Relative value placed on the outcomes considered

The guideline development group agreed that the principal aim of retinal screening is to identify retinopathy which requires treatment or poses a risk to sight. This was felt to be of more importance than the identification of background retinopathy, which is sometimes reversible. However, the group also considered that the identification of background retinopathy can be a reminder to both clinicians and children and young people with diabetes of the need to strive for optimal glycaemic control. Therefore the identification of any grade of retinopathy (even that which is not immediately sight threatening) may be of importance. It was noted that the studies included in the guideline reported only presence or absence of retinopathy and did not assess the severity of the condition.

16.3.7.2 Consideration of clinical benefits and harms

The guideline development group agreed that the early identification of retinopathy is of major importance in reducing the risk of sight loss due to diabetes. Therefore, the clinical benefit of screening is considerable. However, it was recognised that identification of retinopathy may cause some distress to children and young people with type 2 diabetes, and to their family members or carers (as appropriate). Even the identification of background retinopathy might be a cause of anxiety, although it does not pose an immediate threat to sight.

Evidence and clinical experience suggests that retinopathy requiring treatment is rare in children and young people with type 2 diabetes. As such the guideline development group felt that there was no need to deviate from the current national screening recommendations that in children and young people with type 2 diabetes screening should start at the age of 12 years. However, the group was concerned about the link between duration of suboptimal blood glucose control and risk of retinopathy which is a particular issue in type 2 diabetes because there may have been a long duration of disease before diagnosis is made. The group noted this concern by making a separate recommendation highlighting that it is at the clinician's discretion to refer any child or young person whom they feel may be at higher risk of retinopathy (for example due to suboptimal glycaemic control or long duration of disease), in addition to the screening offered by the national programme.

16.3.7.3 Consideration of health benefits and resource use

The guideline development group considered that young people aged 12 years or older with type 2 diabetes are already included in the national screening programme and therefore no additional resource use would be required to implement the guideline development group's recommendations.

16.3.7.4 Quality of evidence

The guideline development group was aware that the evidence identified for inclusion in the guideline review ranged from low to moderate quality based on GRADE quality. Due to the paucity of evidence specific to type 2 diabetes in children and young people, no pooling of prevalence estimates was possible and only confidence intervals were available for the data obtained from single studies. This increased the overall quality of some evidence (compared with the guideline review related to monitoring for retinopathy in children and young people with type 1 diabetes). In addition, the evidence identified for this review was more recent and is, therefore, more likely to reflect current clinical practice in the management of diabetes.

16.3.7.5 Other considerations

The guideline development group was aware that a further study (Mayer-Davis 2012) reported a high prevalence of retinopathy in young adults with type 2 diabetes (42%). This study was excluded from the evidence review because the mean age of participants was 21.1±2.8 years. However, the group felt that the study provided further evidence of the high prevalence of retinopathy in young people with type 2 diabetes.

16.3.7.6 Key conclusions

The guideline development group concluded that children and young people with type 2 diabetes should be offered screening for retinopathy from the age of 12 years and annually thereafter, and that the benefit of this in terms of reducing the risk of long-term complications should be communicated to the children and young people and their family members or carers (as appropriate).

The group therefore recommended that healthcare professionals should offer children and young people with type 2 diabetes screening for diabetic retinopathy annually from the age of 12 years. They also recommended that healthcare professionals should explain to children and young people with type 2 diabetes and their family members or carers (as appropriate) the importance of annual screening for diabetic retinopathy and that:

- background retinopathy is often found through screening, and improving blood glucose control will reduce the risk of this progressing to significant diabetic retinopathy
- annual screening is important because if significant diabetic retinopathy is found, early treatment will improve the outcome.

The guideline development group further recommended that healthcare professionals should consider referring children and young people with type 2 diabetes who are younger than 12 years to an ophthalmologist for retinal examination if blood glucose control is suboptimal.

The recommendations related to the optimal monitoring strategy for retinopathy in children and young people with type 2 diabetes use the terminology ‘monitoring’ rather than ‘screening’.

16.4 Monitoring for nephropathy

16.4.1 Review question

What is the optimal monitoring strategy for identifying nephropathy in children and young people with type 2 diabetes?

16.4.2 Introduction

This was a new topic covered by the 2015 update scope. The objective of this review question was to determine when monitoring for nephropathy should start following diagnosis of type 2 diabetes and how frequently it should be repeated. Because a raised albumin excretion rate (termed low-level albuminuria or microalbuminuria) is a risk factor for developing nephropathy, cross-sectional studies that report prevalence of low-level albuminuria or longitudinal studies that estimate incidence of new cases of low-level albuminuria over time were identified and assessed for inclusion. In order to assess at what age or duration of diabetes monitoring should start in children and young people with type 2 diabetes, and how frequently it should be repeated, only studies that reported low-level albuminuria prevalence or incidence stratified by age or duration of diabetes were considered. Low-level albuminuria was measured by either albumin excretion rate (AER) in micrograms/minute or albumin:creatinine ratio (ACR) in micrograms/mg across studies. In accordance with usual nephropathy screening practice in the UK (ACR measured in

mg/mmol), AERs expressed in micrograms/minute and ACRs expressed in micrograms/mg were converted to ACRs expressed in mg/mmol using linear regression equations (Schultz 1999) and interconversion equations (Chavan 2011) used in previous studies, respectively. Studies testing for low-level albuminuria (defined as measured or converted ACR larger than 2.5 mg/mmol in males or 3.5 mg/mmol in females) on at least 2 out of 3 urine collections were included.

Study quality was assessed using the GRADE methodology. Observational studies were the appropriate study design to address this review question and so studies were assigned an initial quality rating of moderate and downgraded based on potential sources of bias.

16.4.3 Description of included studies

Three cross-sectional studies (Farah 2006; Lynch 2013; Yoo 2004) met the inclusion criteria for this review. Two were undertaken in the USA (Farah 2006; Lynch 2013) and 1 in Korea (Yoo 2004).

Sample sizes ranged from 22 to 699. Participants aged between 8 and 28 years were examined across studies (only data from those who were younger than or participants of mean age less than 18 years were analysed in the guideline review).

Both studies from the USA (Farah 2006; Lynch 2013) consisted of young people predominantly from ethnic minority groups. About 88% of participants in 1 study (Farah 2006) and 72% in the other study (Lynch 2013) were Hispanic or African Americans.

Data on the outcome of low-level albuminuria prevalence stratified by age or diabetes duration were identified for inclusion. No data were found for the outcome of prevalence of elevated serum creatinine using serum creatinine concentration.

Low-level albuminuria prevalence stratified by age (less than 11 years) was reported in 1 study (Yoo 2004). Low-level albuminuria prevalence stratified by diabetes duration of less than 2 years was estimated and reported across 3 studies (Farah 2006; Lynch 2013; Yoo 2004). Low-level albuminuria prevalence by diabetes duration ranging from 2 to 5 years was estimated in 1 study (Farah 2006). None of the included studies reported low-level albuminuria incidence by age or diabetes duration.

16.4.4 Evidence profile

The evidence profiles for this review question (monitoring for nephropathy in children and young people with type 2 diabetes) are presented in Table 60 and Table 61.

Table 60: Evidence profile for prevalence of low-level albuminuria[a] by age in children and young people with type 2 diabetes

Number of studies	Number of children and young people	Range of Prevalence, % (Median, %)	Quality
1 (Yoo. 2004)	NC	0 (NA)	Very low

NA not applicable, NC not calculable
a. Low-level albuminuria defined as albumin:creatinine ratio (ACR) more than 3.5 mg/mmol in males and ACR >4.0 mg/mmol in females in at least 2 out of 3 urine collections

Table 61: Evidence profile for prevalence of low-level albuminuria[a] by duration of diabetes in children and young people with type 2 diabetes

Number of studies	Number of children and young people	Range of Prevalence, % (Median, %)	Quality
Duration less than 2 years			
3 (Farah 2006; Lynch 2013; Yoo 2004)	NC	0 to 29.6 (6.3)	Very low
Duration 2 years			
1 (Farah 2006)	NC	29.6 (NA)	Very low
Duration 3 years			
1 (Farah 2006)	NC	32.3 (NA)	Very low
Duration 4 years			
1 (Farah 2006)	NC	32.3 (NA)	Very low
Duration 5 years			
1 (Farah 2006)	NC	32.3 (NA)	Very low

NA not applicable, NC not calculable
a. Low-level albuminuria defined as albumin:creatinine ratio (ACR) >3.5 mg/mmol in males and ACR >4.0 mg/mmol in females in at least 2 out of 3 urine collections

16.4.5 Evidence statements

An asterisk (*) indicates where the total number of participants analysed for each outcome could not be calculated from the published data.

The evidence for all of these findings was of very low quality.

Prevalence of low-level albuminuria by age

Age less than 11 years

One study* estimated the prevalence of low-level albuminuria in children and young people with type 2 diabetes aged less than 11 years to be 0%.

Prevalence of low-level albuminuria by duration of diabetes

Duration less than 2 years

Three studies* estimated the prevalence of low-level albuminuria in children and young people with type 2 diabetes of less than 2 years' duration to be between 0% and 29.6%.

Duration 2 years

One study* estimated the prevalence of low-level albuminuria in children and young people with type 2 diabetes of 2 years' duration to be 29.6%.

Duration 3 years

One study* estimated the prevalence of low-level albuminuria in children and young people with type 2 diabetes of 3 years' duration to be 32.3%.

Duration 4 years

One study* estimated the prevalence of low-level albuminuria in children and young people with type 2 diabetes of 4 years' duration to be 32.3%.

Duration 5 years

One study* estimated the prevalence of low-level albuminuria in children and young people with type 2 diabetes of 5 years' duration to be 32.3%.

Prevalence of elevated serum creatinine using serum creatinine concentration

None of the included studies reported prevalence of elevated serum creatinine using serum creatinine concentration.

16.4.6 Health economics profile

A systematic literature search did not identify any relevant economic evaluations addressing the optimal monitoring strategy for identifying nephropathy in children and young people with type 2 diabetes.

This question was not prioritised for health economic analysis as the number of children and young people with type 2 diabetes in the UK is very small and because the review was not designed to retrieve evidence relating to diagnostic test accuracy and subsequent management which would be necessary to assess cost effectiveness.

16.4.7 Evidence to recommendations

16.4.7.1 Relative value placed on the outcomes considered

The guideline development group felt that there was some clinical uncertainty as to whether nephropathy monitoring should be undertaken in children and young people with type 2 diabetes and, if so, whether the monitoring strategy should take account of duration of diabetes. For this reason they prioritised prevalence and incidence of nephropathy in children and young people with type 2 diabetes as outcomes of interest so that they could gain an understanding of both the number of cases of nephropathy in different age groups and also the rate at which new cases occurred in relation to time from diagnosis.

Evidence was found only for the prevalence of nephropathy but the guideline development group felt that this provided sufficient information on which to base monitoring recommendations for this group of children and young people.

16.4.7.2 Consideration of clinical benefits and harms

The guideline development group considered that the early identification of low-level albuminuria (as a risk factor for nephropathy) presented an important clinical benefit because it can prompt early intervention with angiotensin-converting enzyme (ACE) inhibitors which alter disease progression and reduce the risk of chronic renal disease and ultimately mortality. The group noted that this was particularly important for children and young people with type 2 diabetes because they are at risk of rapid progression to chronic kidney disease, possibly because of associated morbidities such as obesity and hypertension.

The group recognised that, as with all diagnostic tests, false-positive results presented a potential harm in terms of exposing those who received such results to unnecessary treatment and anxiety. Overall, however, the group felt that the benefits of testing for low-level albuminuria outweighed this potential harm and recommended a specific approach to accurate testing of low-level albuminuria, namely using the first urine sample of the day (early morning sample) for the test and confirming positive initial test results using repeat tests.

The group concluded that the majority of evidence supported recommending monitoring for low-level albuminuria from diagnosis because prevalence was high (more than 29%) in

children and young people with type 2 diabetes independent of duration of diabetes. Although the only study for a stratified age group (children with type 2 diabetes under 11 years) showed no prevalence of low-level albuminuria (0%), the group decided that the recommendation of monitoring from diagnosis was not contradicted by this evidence because type 2 diabetes is relatively uncommon in the UK in children under 11 years.

The guideline development group noted that the guideline review was not designed to provide evidence about when treatment should be undertaken based on test results. However, they felt that it was important to provide guidance as to what should be considered a positive result in terms of determining the need for repeat confirmatory testing. The group felt that it was both practical and clinically relevant to base this guidance on the thresholds for treatment outlined in the guideline on type 1 diabetes in adults.

16.4.7.3 Consideration of health benefits and resource use

It was the guideline development group's view that testing children and young people with type 2 diabetes for low-level albuminuria is routine practice but the time at which monitoring starts is not consistent in clinical practice. They acknowledged, therefore, that recommending that monitoring should start at diagnosis would potentially require additional resources in some settings. However, the group felt that any such uplift in resources was likely to be offset by savings from complications avoided.

The guideline development group noted that the ACR thresholds specified in the guideline on type 1 diabetes in adults were different to the ACR thresholds in the included studies for this guideline (the studies used different thresholds for males and females). The guideline development group recognised that the decision to incorporate a single threshold for both sexes into the recommendations might result in a slightly higher number of girls and young women undergoing repeat testing than previously. Again, the group felt that any such uplift in resource use would be marginal and justified by the likely health benefits.

The group noted that false-positive test results have implications for resource use and this provided further support for their decision to recommend a specific approach to testing. They also noted that in some settings it is common practice to carry out 3 tests from the outset, so the new recommendations may result in fewer unnecessary tests being performed.

16.4.7.4 Quality of evidence

Limited evidence of very low quality (based on GRADE criteria) was identified for inclusion in this guideline review. Small sample size and indirectness due to the ethnic profile of the participants (many of whom were Hispanic or African-American in the included studies) were the main criteria for downgrading the quality of evidence.

Furthermore, the group noted that most of the included studies used a higher ACR threshold to determine the presence of low-level albuminuria than that used in UK practice and therefore the results may underestimate the prevalence and incidence of nephropathy in children and young people with type 2 diabetes.

Although the group recognised uncertainty in the evidence identified for inclusion, they decided to make a strong recommendation based on their clinical experience and the potential serious harm of missing early identification of low-level albuminuria and its impact on future complications for children and young people with type 2 diabetes.

16.4.7.5 Other considerations

The guideline development group considered that the first urine sample of the day (early morning urine) should be used for the albumin:creatinine ratio screening test. If the first urine sample of the day is not available, healthcare professionals should use a random sample, but be aware that this is associated with an increased risk of false positive results. The group

noted that young people are often reluctant to provide urine samples and this supported the decision to recommend the use of a random urine sample (which could be collected in clinic) if the first urine sample of the day (early morning urine) is not available.

The guideline development group decided that if the initial albumin:creatinine ratio is above 3 mg/mmol but below 30 mg/mmol (low-level albuminuria), the result should be confirmed by repeating the test on 2 further occasions using first urine samples of the day (early morning urine) before starting further investigation and therapy. The group considered that healthcare professionals should investigate further if the initial albumin:creatinine ratio is 30 mg/mmol or more (proteinuria). The threshold triggering further investigation (30 mg/mmol) is the same as that used in adults with type 1 diabetes and the terminology and definition of low-level albuminuria is the same as that used in the NICE guideline on chronic kidney disease.

Although type 2 diabetes is very uncommon before puberty in the UK, the group believed that those who present with type 2 diabetes in childhood may be at significant risk of low-level albuminuria. This reinforced the group's decision to make a recommendation to start monitoring for low-level albuminuria at diagnosis for all children and young people with type 2 diabetes.

16.4.7.6 Key conclusions

Based on all of the considerations above, the guideline development group concluded that children and young people with type 2 diabetes should be offered testing for low-level albuminuria from diagnosis, and that the benefit of this in terms of reducing the risk of long-term complications should be communicated with the children and young people and their family members or carers (as appropriate).

The group therefore recommended that healthcare professionals should offer children and young people with type 2 diabetes screening for low-level albuminuria (to detect diabetic kidney disease) starting at diagnosis. They also recommended that healthcare professionals should explain to children and young people with type 2 diabetes and their family members or carers (as appropriate) the importance of annual screening for diabetic kidney disease and that:

- using the first urine sample of the day (early morning urine) to screen for low-level albuminuria is important, as this reduces the risk of false positive results
- if low-level albuminuria is detected, improving blood glucose control will reduce the risk of this progressing to clinically significant diabetic kidney disease
- annual screening is important because if diabetic kidney disease is found, early treatment will improve the outcome.

The recommendations related to the optimal monitoring strategy for low-level albuminuria in children and young people with type 2 diabetes use the terminology 'monitoring' rather than 'screening'. In the recommendations the terminology 'low-level albuminuria' is replaced by 'moderately increased albuminuria (ACR 3–30 mg/mmol; 'microalbuminuria').

16.5 Recommendations

The current recommendations can be found at https://www.nice.org.uk/guidance/ng18.

17 Diabetic ketoacidosis

This section was updated in 2015.

17.1 Introduction

The 2004 guideline recommendations related to recognition and management of diabetic ketoacidosis (DKA) focused largely on British Society for Paediatric Endocrinology and Diabetes (BSPED) guidance. For the 2015 update the guideline development group developed specific review questions to allow detailed recommendations to be included in the guideline, rather than needing to refer to the external guidance in its entirety.

The group considered formally applying the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument to the BSPED guidance in accordance with the NICE guidelines manual. The AGREE II instrument is a guideline quality appraisal tool in which 23 items are grouped into 6 domains, each of which reflects a particular aspect of guideline quality: 2 further items provide an overall assessment of quality. However, the guideline development group concluded that the BSPED guideline would not fulfil the requirements of the AGREE criteria to the extent that it could be adopted. The group concluded, therefore, that it was necessary to follow the standard process of using systematic reviews of the evidence for the review questions related to recognition and management of diabetic ketoacidosis (DKA).

Section 17.2 to Section **Error! Reference source not found.** address the specific review questions considered in the 2015 update and these update and replace the evidence reviews and discussion of the BSPED guidance presented in the 2004 guideline. Each of these reviews covered both type 1 and type 2 diabetes.

17.2 Recognition, referral and diagnosis

17.2.1 Symptoms, signs and biochemical indicators of diabetic ketoacidosis

17.2.1.1 Review question

What is the predictive value of symptoms, signs and biochemical abnormalities as indicators of diabetic ketoacidosis in children and young people?

17.2.1.2 Introduction

This question aimed to address the predictive value of particular symptoms, signs and biochemical abnormalities for the diagnosis of DKA in children and young people with either type 1 diabetes or type 2 diabetes. The symptoms identified by the guideline development group as being relevant to this question were polydipsia, polyuria (possibly manifesting as bedwetting), weight loss, dehydration, nausea or vomiting, abdominal pain, respiratory distress and an altered level of consciousness. Biochemical abnormalities to be included in this review were hyperglycaemia, ketosis and acidosis.

In this evidence review (including the associated evidence statements), diagnostic test accuracy measures were classified in accordance with the methods described in Section 0.

Sensitivity and specificity:

- low – 74.9% or below
- moderate – 75% to 89.9%
- high – 90% or above.

Positive likelihood ratio:

- not useful – less than 5
- moderately useful – 5 to less than 10
- very useful – 10 or more.

Negative likelihood ratio:

- not useful – more than 0.5
- moderately useful – more than 0.1 to 0.5
- very useful – 0.1 or less.

17.2.1.3 Description of included studies

Four studies were identified as being relevant to this review question (Fearon 2002; Gilhotra 2007; Prisco 2006; Sheikh-Ali 2008). Two of the studies assessed the diagnostic test accuracy of serum beta-hydroxybutyrate levels in detecting DKA (Sheikh-Ali 2008; Prisco 2006) and the other 2 assessed the diagnostic test accuracy of end-tidal carbon dioxide measurements (Fearon 2002; Gilhotra 2007). No studies were identified which assessed the predictive accuracy of any symptoms or signs for detecting DKA.

The first study was a retrospective, non-consecutive case series conducted in the USA (Sheikh-Ali 2008). Relevant participants were identified using an electronic medical records coding system. Details were obtained for all children and young people hospitalised with uncontrolled diabetes. There were 129 participants, all of whom had type 1 diabetes. The mean age was 10.8±0.4 years (maximum 16 years). The aim of the study was to evaluate the utility of serum beta-hydroxybutyrate in detecting DKA as defined by a serum bicarbonate level of no more than 18 mEq/litre (milliequivalents of solute per litre). The study authors found that on average a serum beta-hydroxybutyrate level of at least 3 mmol/litre equated to a serum bicarbonate level of 18 mEq/litre. They reported data that could be used to calculate diagnostic test accuracy measurements for predicting serum bicarbonate of no more than 18 mEq/litre from measurements of serum beta-hydroxybutyrate of at least 3 mmol/litre.

A prospective case series conducted in Italy also assessed the diagnostic test accuracy of serum beta-hydroxybutyrate levels in detecting DKA (Prisco 2006). The study included 118 children and young people. The study authors assessed the diagnostic test accuracy of ketone levels when defining DKA in 2 different ways, either by a venous pH of less than 7.3 or by a blood glucose level of more than 250 mg/dl (13.9 mmol/litre).

Two prospective cohort studies assessed the use of end-tidal carbon dioxide measurements for the diagnosis of DKA. One study was conducted in the USA (Fearon 2002). Children and young people attending a paediatric emergency department who had known or suspected diabetes were recruited if they presented with hyperglycaemia. End-tidal carbon dioxide levels were measured to assess their predictive value for the diagnosis of DKA. Forty-four children and young people participated in the study, but 2 were excluded from analysis (1 did not give consent and the other was unable to tolerate the monitor without crying). The type of diabetes (type 1 or type 2) was not reported. Participants ranged in age from 2 to 18 years (the mean age was not reported). DKA was defined as a serum bicarbonate measurement of less than 15 mEq/litre with a serum glucose of more than 250 mg/dl and the presence of ketones on urine dipstick. These studies were not combined due to heterogeneity in design.

The final study was conducted in Australia (Gilhotra 2007). This study recruited children and young people with known or suspected type 1 diabetes presenting to a paediatric emergency department. Sixty-three children were enrolled but 5 were excluded (1 because the monitor was not tolerated and 4 because of missing data). The mean age was 10.7 years (range 1 to 18 years). DKA was defined as serum bicarbonate of less than 15 mEq/litre with ketonuria in children and young people with type 1 diabetes.

17.2.1.4 Evidence profile

The evidence profile for this review question (symptoms, signs and biochemical abnormalities as indicators of DKA) is presented in Table 62.

Table 62: Evidence profile for diagnostic test accuracy of serum beta-hydroxybutyrate and end-tidal carbon dioxide as indicators of diabetic ketoacidosis

Number of studies	Number of children and young people	Measure of diagnostic test accuracy (95% CI)				Quality
		Sensitivity	Specificity	Positive likelihood ratio	Negative likelihood ratio	
Serum beta-hydroxybutyrate (cut-off ≥3 mmol/litre) for detecting DKA (defined by serum bicarbonate ≤ 18 mEq/litre)						
1 (Sheikh-Ali 2008)	129	0.92 (0.87 to 0.97)[a]	0.84 (0.70 to 0.91)[a]	5.86 (2.96 to 11.61)[a]	0.08 (0.04 to 0.18)[a]	Very low
Serum beta-hydroxybutyrate (cut-off ≥3 mmol/litre) for detecting DKA (defined by venous pH of <7.3)						
1 (Prisco 2006)	90	0.83 (NC)[b]	0.68 (NC)[b]	2.59 (NC)[b]	0.25 (NC)[b]	Moderate
Serum beta-hydroxybutyrate (cut-off ≥3 mmol/litre) for detecting DKA (defined by blood glucose >13.9 mmol/litre)						
1 (Prisco 2006)	110	0.57 (NC)[b]	0.83 (NC)[b]	3.35 (NC)[b]	0.52 (NC)[b]	Moderate
End-tidal carbon dioxide (cut-point ≤29 mmHg) for detecting DKA						
1 (Fearon 2002)	44	0.83 (0.52 to 0.98)	1.0 (0.88 to 1.0)	NC	0.17 (0.05 to 0.59)[a]	Low
1 (Gilhotra 2007)	63	0.93 (0.70 to 0.99)	0.91 (0.78 to 0.96)	10.03 (3.91 to 25.76)[a]	0.07 (0.01 to 0.49)[a]	Low
End-tidal carbon dioxide (cut-point ≤30 mmHg) for detecting DKA						
1 (Gilhotra 2007)	58	1.0 (0.78 to 1.0)[c]	0.86 (0.72 to 0.95)[c]	7.17 (3.41 to 15.05)[a]	0 (NC)[a,d]	Low
End-tidal carbon dioxide (cut-point <36 mmHg) for detecting DKA						
1 (Fearon 2002)	42	1.0 (0.74 to 1.0)[a]	0.67 (0.47 to 0.83)[a]	3.0 (1.81 to 4.98)[a]	0 (NC)[a,d]	High

CI confidence interval, DKA diabetic ketoacidosis, NC not calculable
a. Calculated by the NCC-WCH technical team from data reported in the article
b. Point estimate reported only; unable to calculate 95% CI from data reported
c. Point estimate reported only, CI calculated by NCC-WCH technical team from data reported in the article
d. Sensitivity=1.0 therefore negative likelihood ratio=0 and CI not calculable

17.2.1.5 Evidence statements

Serum beta-hydroxybutyrate

One study (total 129 participants) showed that serum beta-hydroxybutyrate of 3 mmol/litre or more (defined by serum bicarbonate 18 mEq/litre or less) has a high sensitivity and moderate specificity for the diagnosis of DKA in children and young people. The positive likelihood ratio indicated that the test was moderately useful and the negative likelihood ratio indicated that it was very useful. The evidence for these findings was of very low quality.

One study (total 90 participants) showed that serum beta-hydroxybutyrate of 3 mmol/litre or more (defined by venous pH of less than 7.3) has a moderate sensitivity and low specificity for the diagnosis of DKA in children and young people. The positive and negative likelihood ratios indicated that the test was not useful. The evidence for these findings was of moderate quality.

One study (total 110 participants) showed that serum beta-hydroxybutyrate of 3 mmol/litre or more (defined by blood glucose more than 13.9 mmol/litre) has a low sensitivity and moderate specificity for the diagnosis of DKA in children and young people. The positive and

negative likelihood ratios indicated that the test was not useful. The evidence for these findings was of moderate quality.

End-tidal carbon dioxide

Two studies (total 107 participants) showed that end-tidal carbon dioxide has a moderate sensitivity and high specificity for the diagnosis of DKA in children and young people (using a cut-point of 29 mmHg or less). The positive likelihood ratio indicated that this test was very useful. The negative likelihood ratio suggested that the test was moderately useful. The evidence for these findings was of low quality.

One study (total 58 participants) reported the diagnostic test accuracy of end-tidal carbon dioxide (using a cut-point of 30 mmHg or less) for the diagnosis of DKA in children and young people. The study reported a high sensitivity, moderate specificity, moderately useful positive likelihood ratio and very useful negative likelihood ratio. The evidence for these findings was of low quality.

One study (total 42 participants) reported the diagnostic test accuracy of end-tidal carbon dioxide (using a cut-point of less than 36 mmHg) for the diagnosis of DKA in children and young people. The study reported a high sensitivity, low specificity, not useful positive likelihood ratio and very useful negative likelihood ratio. The evidence for these findings was of high quality.

17.2.1.6 Health economics profile

A systematic literature search did not identify any relevant published economic evidence related to indicators of DKA in children and young people.

This question was not prioritised for health economic analysis as recognition in itself does not incur major opportunity costs and the guideline development group considered that best practice for management of this medical emergency is generally well established.

17.2.1.7 Evidence to recommendations

The guideline development group noted that there is no universally accepted definition of DKA and no compelling evidence for any definition. However, the group consensus was that the following would provide a reasonable definition:

- blood glucose 11 mmol/litre or more, and
- blood pH less than 7.3 or serum bicarbonate of less than 18 mmol/litre, and
- confirmed ketosis (based on blood or urine testing).

Some previously published guidelines (BSPED 2013; Craig 2011; Walsdorf 2014) differ slightly from this approach, suggesting, for example, the use of less than 15 mmol/litre for serum bicarbonate. However, the group considered that the use of a higher serum bicarbonate threshold (less than 18 mmol/litre) would reduce the possibility of missing DKA. The group also noted that in children and young people who are receiving insulin treatment for diabetes and who present with DKA it is possible that the blood glucose may be in the normal range, and so in such individuals only the second and third bulleted criteria need to be fulfilled.

17.2.1.7.1 Relative value placed on the outcomes considered

Children and young people (with or without a prior diagnosis of diabetes) presenting with DKA may have symptoms consistent with diabetes (for example polyuria, polydipsia, weight loss and tiredness) and also symptoms which are recognised as occurring in ketoacidosis (for example nausea, vomiting, abdominal pain, respiratory distress, dehydration and reduced level of consciousness). Many of these clinical manifestations are non-specific and -

might be reported in other clinical contexts. The guideline development group considered that it was important to review available evidence on the predictive value of these various symptoms and signs. In addition, they wished to consider evidence on the predictive value of biochemical abnormalities associated with hyperglycaemia, acidosis and ketosis.

17.2.1.7.2 Consideration of clinical benefits and harms

DKA is a life-threatening complication of diabetes and so the harm associated with missing the diagnosis far outweighs the minimal harm from over-investigation. The tests to be undertaken to identify DKA or to rule it out consist of minimally invasive procedures such as blood testing for hyperglycaemia, pH and ketone levels. The guideline development group's view was that it was particularly important that the tests employed for the diagnosis of DKA should have a high sensitivity (90% or higher).

17.2.1.7.3 Consideration of health benefits and resource use

The cost of delayed or missed diagnosis of DKA is considerable and could result in death. The longer a diagnosis of ketosis is delayed, the sicker the child or young person becomes and the more intensive and protracted treatment is likely to be. For example, early ketosis causes nausea and vomiting and is easily mistaken for food poisoning or gastro-enteritis. This often leads to inadequate insulin being given for fear of causing hypoglycaemia. The individual then becomes much sicker. Near-patient beta-hydroxybutyrate, using ketone strips, is cheaper than a laboratory measurement and a more rapid diagnosis may bring important benefits for this life-threatening condition.

17.2.1.7.4 Quality of evidence

Although there was no available evidence on the predictive value of clinical symptoms or signs individually or in combination, the guideline development group made recommendations based on their clinical knowledge and experience regarding the clinical manifestations that should lead to investigation of DKA.

In the first instance they considered the clinical features that would raise the possibility of DKA in a child or young person not previously known to have diabetes. They agreed that if there was increased thirst, polyuria, recent unexplained weight loss or excessive tiredness (these are recognised clinical manifestations of diabetes mellitus) together with any of a number of other features (nausea or vomiting, abdominal pain, hyperventilation, dehydration or a reduced level of consciousness) then a capillary blood glucose measurement should be obtained. All of these other features are accepted in clinical practice as suggestive of DKA in a person in whom diabetes is suspected or confirmed. If the blood glucose was normal then DKA would be ruled out as an explanation for the symptoms. If the blood glucose was greater than 11 mmol/litre then DKA should be suspected as the likely explanation and the child or young person should immediately be sent to a hospital with acute paediatric facilities.

When children and young people with known diabetes develop DKA they would often have a raised blood glucose but this is not universal. The guideline development group noted that it was well recognised that it is possible for those with a prior diagnosis of diabetes who are receiving insulin therapy to have DKA with a normal glucose level. Some young children with type 1 diabetes and gastroenteritis can develop ketoacidosis with hypo- or normo-glycaemia because of relative insulin deficiency and starvation. This important point was therefore highlighted in a recommendation. The group recommended that DKA should be suspected in any child or young person with diabetes irrespective of the blood glucose level if they had any of the suggestive clinical features (nausea or vomiting, abdominal pain, hyperventilation, dehydration or a reduced level of consciousness). When DKA is suspected in a child or young person with known diabetes the blood ketones (beta-hydroxybutyrate) should be measured using a near-patient method if this is available. Those presenting to their GP, for example, might well have the testing equipment to hand. If the level of beta-hydroxybutyrate is elevated, then they should be sent immediately to a hospital with acute paediatric facilities

because the diagnosis of DKA is likely. If it is not possible in this setting to measure the beta-hydroxybutyrate level then DKA should be suspected and they should be sent immediately to a hospital with acute paediatric facilities.

The guideline development group noted that 2 studies that evaluated diagnostic test accuracy of blood beta-hydroxybutyrate found evidence to support its use in diagnosis, but this was of very low to moderate quality. These studies investigated diagnostic test accuracy of beta-hydroxybutyrate only in terms of its ability to predict DKA based on a single parameter (blood glucose, blood pH or blood ketones), not the combination of these parameters (see below) required to definitively diagnose DKA. Thus the reference test in these studies was not a true 'gold standard' diagnosis of DKA. This limited the applicability of serum beta-hydroxybutyrate as a definitive test for diagnosing DKA. Nevertheless, if the level were elevated the guideline development group considered this made a diagnosis of DKA likely in this setting and if it were normal then DKA would be ruled out (ketosis being an essential component of DKA).

The guideline development group was concerned that whenever DKA was suspected or confirmed, the child or young person and their family members or carers should be fully aware of the serious nature of the concern and that urgent hospital assessment was mandatory – and they made a specific recommendation in this regard. Any delay in attending hospital carried a significant risk. The group recommended that when a child or young person did arrive at the hospital with suspected or confirmed DKA, investigations should be carried out to confirm the suspicion (or rule it out): these would include a capillary blood glucose, capillary blood ketones using a near-patient method (if near-patient testing for capillary blood ketones is not available, use a urine ketone test instead) and lastly a capillary or venous pH and bicarbonate test. These were essential to confirm the diagnosis. The group made a recommendation stating the diagnostic criteria for DKA based on the demonstration of acidosis and ketosis or ketonaemia. They made a recommendation that for the purposes of this guideline and its recommendations on management, DKA should be categorised as severe based on the finding of a blood pH below 7.1.

The group was aware that laboratory measurement of beta-hydroxybutyrate takes time and may delay the diagnosis of DKA. Rapid diagnosis is important in this setting as DKA is potentially life-threatening and the group agreed that near-patient testing on arrival at the hospital would facilitate rapid diagnosis and was advisable.

The only other included studies on diagnostic tests for DKA examined end-tidal nasal carbon dioxide measurement. Although 1 of these studies provided high-quality evidence suggesting that end-tidal nasal carbon dioxide had a high sensitivity and useful negative likelihood ratio, the group was not persuaded that it was of practical value. Moreover, this form of test was not in general use in this setting. There were concerns about the diagnostic test accuracy of measurements with this technique and, importantly, it was often poorly tolerated. The guideline development group did not recommend it.

17.2.1.7.5 Other considerations

The guideline development group was aware of evidence that there may be an increased risk of DKA in certain ethnic groups and children and young people living in deprived areas (Khare 2013). The group made recommendations about the importance of considering contributory factors in those who present with an episode of DKA with a view to reducing the risk of future episodes (see Section **Error! Reference source not found.**).

17.2.1.7.6 Key conclusions

The guideline development group recommended that the biochemical criteria required for the diagnosis of DKA should be as discussed above. The group specifically recommended that healthcare professionals should measure capillary blood glucose at presentation in children

and young people without known diabetes who have increased thirst, polyuria, recent unexplained weight loss or excessive tiredness and any of the following:

- nausea or vomiting
- abdominal pain
- hyperventilation
- dehydration
- reduced level of consciousness.

The group also recommended that if the blood glucose level is above 11 mmol/litre in a child or young person without known diabetes and they have symptoms that suggest DKA, then DKA should be suspected and the child or young person should be sent immediately to a hospital with acute paediatric facilities. A blood glucose of this level would be consistent with a diagnosis of diabetes, and when there are also symptoms suggestive of DKA immediate referral to hospital is essential because DKA is a life-threatening condition requiring urgent management.

The guideline development group emphasised that healthcare professionals should be aware that children and young people taking insulin for diabetes may develop DKA with normal blood glucose levels, and that they should suspect DKA (even if the blood glucose is normal) in children and young people with known diabetes and also in children and young people without known diabetes if any symptoms and signs are present that would trigger capillary blood glucose measurement.

The guideline development group further recommended that when DKA is suspected in a child or young person with known diabetes, blood ketones (beta-hydroxybutyrate) should be measured using a near-patient method if available, and if the level is elevated, the child or young person should be sent immediately to a hospital with acute paediatric facilities. This will identify those with DKA even if the blood glucose is in the normal range, as may happen in children and young people with type 1 diabetes who are using insulin therapy. The group considered whether a specific threshold for blood ketones should be stated in the recommendation about sending the child or young person to a hospital with acute paediatric facilities. The group concluded that a threshold should not be stated because the evidence reviewed for the guideline did not support ketone testing as being a specific test for DKA, and the recommendation should not risk preventing the child or young person being sent to hospital by including an arbitrary threshold that may not quite be met in individual circumstances. The recommendation is not about diagnosing DKA (this will be done in the hospital) and a child or young person with known type 1 diabetes should already have ketone testing equipment and advice about seeking help plus an individualised sick-day management plan so they will be able to detect elevated ketones. Children and young people with type 1 diabetes and their family members or carers (as appropriate) may have the necessary ketone testing strips with them when they present. When DKA is suspected in a child or young person with known diabetes and it is not possible to measure the blood ketones (beta-hydroxybutyrate) using a near-patient method, the child or young person should be sent immediately to a hospital with acute paediatric facilities for further investigation.

A further recommendation emphasised that if DKA is suspected or confirmed in a child or young person, health professionals should explain to them and to their family members or carers (as appropriate) that DKA is a serious matter that needs urgent hospital assessment.

17.2.2 Assessments and investigations at presentation and clinical monitoring and laboratory investigations during treatment

17.2.2.1 Review questions:

What routine assessments and investigations should be used to guide management in children and young people who present with diabetic ketoacidosis (DKA)?

Which of the following should be performed as clinical monitoring during treatment of DKA in children and young people:

- general observations (for example heart and respiratory rate and blood pressure)
- body weight
- hydration status
- fluid balance
- neurological observations
- electrocardiographic (ECG) monitoring?

Which of the following laboratory investigations should be performed to monitor children and young people during treatment for DKA:

- blood glucose
- blood or urine ketones
- serum urea or electrolytes
- acid/base status?

17.2.2.2 Introduction

The review questions regarding routine assessments and investigations at presentation with DKA, and clinical monitoring and laboratory investigations during treatment of DKA, were considered together. The guideline development group prioritised the same outcomes for each of the questions as follows:

- mortality
- degree of dehydration confirmed by post-recovery weight
- detection of hypovolaemia
- detection of laboratory abnormalities (including hypoglycaemia, hypokalaemia, hyponatraemia, persistent acidosis and persistent ketosis)
- detection of complications (including cerebral oedema, venous thrombosis and aspiration)
- healthcare utilisation (for example duration of admission or requirement for ventilation as a proxy for severity of DKA or presence of cerebral oedema).

A combined literature search was conducted to cover all the questions and a single excluded studies list was generated.

The specific objective of the question regarding laboratory investigations to be performed during treatment of DKA was to assess the effectiveness and utility of various laboratory investigations used routinely in clinical practice to measure response to treatment and identify potential complications.

17.2.2.3 Description of included studies

No evidence was identified for inclusion for the question regarding routine assessments to be performed at presentation with DKA, nor for the question regarding clinical monitoring to be performed during treatment of DKA. However, 3 studies were identified which considered laboratory investigations to be performed during treatment of DKA (Noyes 2007; Prisco 2006;

Vanelli 2003). One study was a randomised controlled trial (RCT) (Vanelli 2003) and the other 2 were case series (Noyes 2007; Prisco 2006). All 3 studies focused on blood ketone testing versus urine ketone testing rather than other laboratory investigations.

The RCT (Vanelli 2003) was conducted in Italy and included 33 children and young people (mean age 9.2±3.4 years) who had been admitted to hospital with severe DKA (pH 7.2 or less) or moderate DKA (pH 7.2 to 7.3). The participants were randomly allocated to urine ketone testing or capillary blood beta-hydroxybutyrate testing. The study reported mortality and duration of treatment, but none of the other outcomes prioritised by the guideline development group.

One case series (Prisco 2006) involved 118 consecutive children and young people with newly diagnosed type 1 diabetes of whom 38 (32%) had DKA. This study was also conducted in Italy. The mean age of the participants with DKA was 8.0±2.5 years and their mean venous pH level was 7.20±0.11. Hourly urine and capillary blood samples were used to monitor ketone bodies until metabolic control was achieved. Time to resolution of ketosis was compared for the 2 methods of assessment. The outcome was reported for the entire study group (including participants without DKA), rather than specifically participants with DKA.

The second case series (Noyes 2007) involved 25 children and young people (age range 1 to 14 years) who fulfilled the criteria for DKA. Over the study period the participants presented with a total of 40 episodes of DKA (that is, some participants had multiple episodes of DKA). The median pH at presentation was 7.18 (range 6.98 to 7.38). Blood ketones were checked every 4 hours and all urine passed was assessed by the dipstick method. Time to resolution of ketosis was compared for the 2 methods of measurement.

No evidence was identified with regard to the effectiveness of ketone testing in terms of the following outcomes:

- degree of dehydration or detection of hypovolaemia
- detection of complications (cerebral oedema, venous thrombosis or aspiration)
- healthcare utilisation.

No evidence was identified for inclusion for the following laboratory investigations:

- blood glucose
- serum urea or electrolytes
- acid/base status.

17.2.2.4 Evidence profile

The evidence profile for these review questions (specifically, the question related to laboratory investigations during treatment of DKA) is presented in Table 63.

Table 63: Evidence profile for comparison of blood ketone monitoring versus urine ketone monitoring during treatment of diabetic ketoacidosis

Number of studies	Number of children and young people		Effect		Quality
	Blood ketone monitoring	Urine ketone monitoring	Relative (95% confidence interval)	Absolute (95% confidence interval)	
Mortality					
1 (Vanelli 2003)	0/16 (0%)	0/17 (0%)	NC	NC	High
Time to resolution of ketosis (proxy measure for duration of treatment)					
1 (Vanelli 2003)	16	17	NA	MD 6.5 hours fewer (from 4 to 9.4 fewer)	High

Number of studies	Number of children and young people		Effect		Quality
	Blood ketone monitoring	Urine ketone monitoring	Relative (95% confidence interval)	Absolute (95% confidence interval)	
1 (Prisco 2006)	99	NA	NA	MD 2.3 hours fewer (from 9.42 hours fewer to 4.82 hours more)	Very low
1 (Noyes 2007)	28 episodes of DKA	NA	NA	Median difference 11 hours fewer (range 1 hour fewer to 36 hours fewer)	Low

DKA diabetic ketoacidosis, MD mean difference, NA not applicable, NC not calculable

17.2.2.5 Evidence statements

Mortality

One RCT (total 33 participants) reported no events in either group (blood ketone testing or urine ketone testing) during treatment of DKA. The evidence for this finding was of high quality.

Duration of treatment

One RCT (total 33 participants) reported that children and young people who received blood ketone monitoring during treatment of DKA had a quicker resolution of ketosis compared with those who underwent urine ketone monitoring. The evidence for this finding was of high quality.

One case series (total 28 participants) reported that the time to resolution of ketosis was quicker when blood ketones were monitored than when urine ketones were monitored. The evidence for this finding was of low quality.

One case series (total 99 participants) reported that the time to resolution of ketosis did not differ according to whether blood ketones or urine ketones were monitored. The evidence for this finding was of very low quality.

17.2.2.6 Health economics profile

A systematic literature search did not identify any relevant published economic evidence addressing assessments and investigations at presentation or clinical monitoring and laboratory investigations during treatment of DKA in children and young people.

This question was not prioritised for health economic analysis as the guideline development group considered there were other higher priorities within the guideline.

17.2.2.7 Evidence to recommendations

17.2.2.7.1 Relative value placed on the outcomes considered

The guideline development group considered which clinical factors should be recognised and which investigations should be recommended in children and young people with DKA at the time of presentation and subsequently during treatment. These would be important in determining treatment required at the outset and in guiding subsequent management. For these review questions the group set up the review protocols to focus predominantly on comparative studies as these would best inform clinical practice. Many different strategies for clinical assessment and monitoring could be considered and an appropriate strategy for laboratory and other investigations could both guide treatment and identify complications.

Particular concern related to the development of cerebral oedema and hypokalaemia, both of which are potentially life-threatening complications of DKA.

17.2.2.7.2 Consideration of clinical benefits and harms

The guideline development group agreed that close monitoring is essential for all children and young people presenting with DKA. They made recommendations regarding the observations and clinical assessment that should be performed both to determine the appropriate treatment strategy and subsequently during treatment. These were consistent with current practice and with existing guidance (for example guidance from the British Society for Paediatric Endocrinology and Diabetes [BSPED]). The group was especially concerned that signs of cerebral oedema should not be overlooked and they made a recommendation on the clinical findings that should be recognised as possible early signs of cerebral oedema, as well as signs that should be assumed to indicate cerebral oedema and require urgent specialist advice and treatment (see Section 17.4.2).

With regard to investigations, the guideline development group recommended that at presentation with suspected or known DKA, the following should be measured: capillary blood glucose, urea, electrolytes and levels of bicarbonate, blood gas and beta-hydroxybutyrate. The group noted that DKA should be diagnosed in children and young people with diabetes who have acidosis (indicated by blood pH below 7.3 or plasma bicarbonate below 18 mmol/litre) and either ketonaemia (indicated by blood beta-hydroxybutyrate above 3 mmol/litre) or ketonuria (++ and above on the standard strip marking scale). The group considered that it is not essential that the child or young person should also have hyperglycaemia because DKA can occur with normal blood glucose levels in those using insulin therapy. Moreover, a blood pH below 7.1 was considered indicative of severe DKA.

The group made recommendations regarding the frequency of repeat measurements following commencement of treatment and they recommended that there should be continuous ECG monitoring to provide evidence of developing hypokalaemia. Recognition of resolution of ketosis and acidosis was important. The evidence indicated that blood monitoring of beta-hydroxybutyric acid was preferable to urine monitoring because the latter persisted after resolution of blood ketosis. Monitoring of urea and electrolyte were essential to patient safety and were needed to guide the intravenous fluid regimen.

17.2.2.7.3 Consideration of health benefits and resource use

A single US study (Vanelli 2003) identified in the global search for economic evidence suggested that blood ketone testing reduced the time spent in intensive care by 6.5 hours compared with urine ketone testing, giving a total cost saving of €184 per patient. Another study demonstrated that blood ketone testing resulted in an earlier resolution of DKA (Noyes 2007). Therefore, the guideline development group considered that blood ketone testing was likely to be cost effective as the higher cost of blood ketone testing would be more than offset by a reduction in hospital costs associated with a quicker recovery time. This led the group to recommend that the use of a near-patient blood ketone (beta-hydroxybutyrate) testing method should be considered for rapid diagnosis and monitoring of DKA in children and young people in hospital. A strong recommendation for universal implementation of this method could not be justified on the basis of available evidence.

17.2.2.7.4 Quality of evidence

The studies identified for inclusion in the guideline review all focused on near-patient ketone monitoring. However, the guideline development group recognised that it was essential to make recommendations on the key aspects of clinical monitoring and investigation. These recommendations were therefore based on the group's clinical expertise and were consistent with current clinical practice and in keeping with existing guidelines.

17.2.2.7.5 Other considerations

There were no other considerations.

17.2.2.8 Key conclusions

The guideline development group recommended that when a child or young person with suspected or known DKA arrives at hospital, the following should be measured:

- capillary blood glucose
- capillary blood ketones (beta-hydroxybutyrate) if near-patient testing if available, or urine ketones if it is not
- capillary or venous pH
- bicarbonate.

The group further recommended that DKA should be diagnosed in children and young people with diabetes who have acidosis (indicated by blood pH below 7.3 or plasma bicarbonate below 18 mmol/litre) and either ketonaemia (indicated by blood beta-hydroxybutyrate above 3 mmol/litre) or ketonuria (++ and above on the standard strip marking scale). It is not essential that the child or young person should also have hyperglycaemia because DKA can occur with normal blood glucose levels in those using insulin therapy. The considered that a blood pH below 7.1 was indicative of severe DKA. This is an important indicator because clinical manifestations of severe DKA (such as severe dehydration) may not be recognised reliably against the background of other manifestations of DKA.

Specific recommendations related to clinical monitoring and laboratory investigations during treatment of DKA in children and young people are presented in Section **Error! Reference source not found.** and Section 17.4. These cover:

- informing the responsible senior clinician once a diagnosis of DKA in a child or young person is made
- explaining to the child or young person with DKA and to their family members or carers (as appropriate) about their condition and the care that they may need
- performing and recording clinical observations and laboratory investigations
- providing an appropriate care setting
- liaising with other healthcare professionals as needed (anaesthetists and/or paediatric critical care specialists)
- when to suspect sepsis
- ensuring that healthcare professionals performing monitoring know what to look for and when to seek advice
- performing face-to-face reviews of the child or young person at diagnosis and then at least every 4 hours
- updating the child or young person with DKA and their family members or carers (as appropriate) regularly about their progress.

The guideline development group recommended that children and young people with DKA should be cared for in a facility that can provide the level of care recommended in the guideline. All children and young people with DKA will require expert paediatric medical and nursing care, and most will require intravenous fluids and insulin. Some children and young people will require care in a high-dependency unit or a ward with one-to-one nursing care (those under 2 years who are at increased risk of developing cerebral oedema, and those with severe DKA [blood pH below 7.1] who are likely to be more severely dehydrated and are therefore at increased risk). Children and young people with DKA who are unconscious require urgent anaesthetic review and may need endotracheal intubation to protect their

airway. Likewise, those with a reduced level of consciousness and vomiting may be at risk of aspiration and the group recommended that thought should be given to inserting a nasogastric tube to reduce this risk. In those with hypotensive shock, the guideline development group recommended discussion of inotropes with a paediatric critical care specialist. The group considered, therefore, that such facilities and expertise should be available in any hospital providing care for children and young people with DKA.

Although most children and young people with DKA do not have sepsis, the guideline development group recognised that DKA can be precipitated by sepsis and recommended that sepsis should be suspected if there is fever or hypothermia, hypotension, refractory acidosis or lactic acidosis.

17.2.3 Recommendations

The current recommendations can be found at https://www.nice.org.uk/guidance/ng18.

The recommendations related to initial management during DKA are based on evidence reviewed for the question about clinical monitoring and laboratory investigations during treatment for DKA (see Section 17.2.2).

17.2.4 Recommendations

The current recommendations can be found at https://www.nice.org.uk/guidance/ng18.

17.3 Fluid and insulin therapy

The current recommendations can be found at https://www.nice.org.uk/guidance/ng18.

17.3.1 Intravenous insulin therapy

17.3.1.1 Starting and stopping intravenous insulin therapy

17.3.1.1.1 Review question

When should intravenous insulin therapy be started and stopped in children and young people with diabetic ketoacidosis?

17.3.1.1.2 Introduction

The purpose of this review question is to establish when intravenous insulin therapy should be started and stopped in children and young people with DKA. The review allowed the inclusion of observational studies in addition to RCTs and systematic reviews.

The guideline development group identified several key outcomes for this review:

- mortality
- rate of change of blood glucose
- incidence of hypoglycaemia
- incidence of cerebral oedema
- resolution of acidosis
- hypokalaemia
- resolution of blood ketosis
- healthcare utilisation.

For the part of the question regarding when to start intravenous insulin therapy the intervention was delayed insulin and the comparator immediate insulin. For the part of the question about stopping intravenous insulin outcomes were to be compared according to the blood ketone concentration at which insulin was stopped. Subgroup analyses by type of diabetes and age group were to be undertaken where possible.

The only study identified for inclusion for this review question (Edge 2006) included the Chair of the DKA subgroup as the primary author. To avoid any conflict of interest in the recommendations arising from the review question the NCC-WCH Clinical Director for Children's Health chaired the discussions. Although the Chair of the DKA subgroup participated in discussion of the evidence and formulation of the recommendations, she did not have a casting vote on the agreement of recommendations.

17.3.1.1.3 Description of included studies

A single study was identified for inclusion in this review (Edge 2006). This was a case-control study which addressed the timing at which to start insulin therapy in children and young people with type 1 diabetes and DKA. The study included 43 cases and 169 controls from England, Scotland and Wales. The mean ages of the participants were 8.5 years and 8.9 years for cases and controls, respectively.

Of the guideline development group priority outcomes, only risk of cerebral oedema was reported. Cases were defined as having a diagnosis of DKA-related cerebral oedema. Controls were defined as having a diagnosis of DKA without cerebral oedema. Controls were matched to cases based on age, sex, whether or not diabetes was newly diagnosed and the month of admission. Adjustments were also made for baseline biochemical measures to take account of the severity of acidosis. No subgroup analyses were possible.

No evidence was identified for: mortality, rate of change of blood glucose, hypoglycaemia incidence, resolution of acidosis, hypokalaemia or healthcare utilisation. No evidence was identified which addressed the time at which insulin therapy should be discontinued in children and young people with DKA.

17.3.1.1.4 Evidence profile

The evidence profile for this review question (timing of insulin therapy in children and young people with DKA) is presented in Table 64.

Table 64: Evidence profile for the effect of insulin administered within 1 hour of fluid replacement compared with insulin administered at least 1 hour after fluid administration on the risk of cerebral oedema

Number of studies	Number of patients		Effect		Quality
	Cases (cerebral oedema)	Controls (no cerebral oedema)	Relative (95% CI)	Absolute (95% CI)	
Association between timing of insulin therapy and risk of cerebral oedema					
1 (Edge 2006)	43	169	Adjusted OR: 4.7 (1.5 to 13.9)[a,b]	NA	Moderate
Association between timing of insulin therapy and risk of cerebral oedema, adjusted for baseline biochemical measures to account for severity of acidosis					
1 (Edge 2006)	43	169	Adjusted OR: 12.7 (1.41 to 114.5)[a,b,c]	NA	Moderate

CI confidence interval, OR odds ratio, NA not applicable
a. OR is for participants who received insulin therapy within 1 hour of fluid replacement compared with those who did not
b. Adjusted for matching variables: age, sex and whether diabetes was newly diagnosed as well as baseline acidosis
c. Baseline biochemical measures included in the multivariate model included: plasma glucose, potassium, urea, sodium and paCO2

17.3.1.1.5 Evidence statements

Risk of cerebral oedema

One study (total 212 participants) found an increased risk of cerebral oedema in participants who received insulin therapy within 1 hour of starting rehydration. The same study found an increased risk of cerebral oedema when adjustment was made for baseline biochemical measures of acidosis. The quality of the evidence for both outcomes was moderate.

17.3.1.1.6 Health economics profile

A systematic literature search did not identify any relevant published economic evidence relating to starting and stopping intravenous insulin therapy.

This question was not prioritised for health economic analysis as the timing of starting or stopping intravenous insulin therapy does not have resource implications.

17.3.1.1.7 Evidence to recommendations

Relative value placed on the outcomes considered

The guideline development group was concerned to determine whether early or late commencement of intravenous insulin therapy in DKA might have associated risks or benefits. The group prioritised 7 outcomes as being of potential clinical importance: mortality, rate of change of blood glucose, incidence of hypoglycaemia, resolution of acidosis, incidence of cerebral oedema, incidence of hypokalaemia and healthcare utilisation.

Mortality was important because DKA is an important cause of mortality in people with diabetes. The rate of change of blood glucose concentration was not considered to be a primary objective. Nevertheless, the guideline development group considered it likely that studies would be likely to report this outcome. Hypoglycaemia was an important adverse outcome to be avoided. Resolution of acidosis was also likely to be reported in research studies, although again the group did not consider that this was likely to be a decisive clinical consideration when making recommendations. Cerebral oedema was an important outcome because it was a potential cause of both morbidity and mortality in DKA. It is the cause of death in 80% of children under 12 years who die from diabetes and it is a major cause of permanent disability (Edge 1999). Children and young people are more vulnerable than adults to the development of cerebral oedema. Hypokalaemia was considered an important outcome because it is a cause of mortality in DKA. Finally, healthcare utilisation (for example duration of admission or need for mechanical ventilation) was important. The need for mechanical ventilation was seen as a proxy for incidence of cerebral oedema.

Consideration of clinical benefits and harms

The guideline development group considered that since the included study found an increased risk of cerebral oedema in participants who received intravenous insulin within 1 hour of fluid therapy it is possible that there are physiological reasons why this might occur. For example, it might be that insulin affects some of the membrane transport systems (especially the Na/H transporter) and at the time of rapid changes in osmolality that might be deleterious.

The primary aim of starting insulin therapy in this setting is to resolve ketosis rather than to reduce the blood glucose level. Commencing intravenous fluid therapy prior to insulin is known to be effective in in lowering blood glucose as well as treating dehydration. The guideline development group recognised that there was a lack of published clinical studies regarding the relative risks and benefits associated with early versus deferred insulin administration, but deferring it for at least 1 hour after starting intravenous fluid replacement

was in keeping with current practice and clinical experience suggested that this was a safe strategy.

Consideration of health benefits and resource use

The timing of when to start intravenous insulin administration is not associated with any difference in resource use and so the health benefits and harms are the only relevant considerations in this review question. For example, it is thought that there may be an increased risk of cerebral oedema if intravenous insulin therapy is started too soon after fluid therapy which has to be set against a delay in the resolution of ketosis.

Quality of evidence

The evidence from the only study included in the review regarding the risk of cerebral oedema with early versus deferred commencement of insulin therapy was of moderate quality. The finding that deferring insulin until at least 1 hour after starting rehydration was associated with a reduced risk of cerebral oedema was still significant when adjustment was made for the severity of acidosis in the patient groups.

Other considerations

There were no other considerations.

Key conclusions

Based on their considerations, the guideline development group recommended that in children and young people with DKA intravenous insulin therapy should be withheld for at least 1 hour after beginning intravenous fluid therapy. Specifically, the group recommended starting an intravenous insulin infusion 1 to 2 hours after beginning intravenous fluid therapy in children and young people with DKA.

There was no available evidence regarding the timing of conversion from intravenous insulin to subcutaneous insulin therapy, but based on physiological principles and the importance of insulin therapy to treat ketosis, the guideline development group concluded that this should happen after resolution of ketosis and made a recommendation accordingly. Specifically, the group suggested considering stopping intravenous fluid therapy for DKA in a child or young person if ketosis is resolving provided the child or young person is alert and they can take oral fluids without nausea or vomiting. The group recommended not changing from intravenous insulin to subcutaneous insulin until ketosis is resolving and the child or young person with DKA is alert and they can take oral fluids without nausea or vomiting.

The guideline development group was aware that children and young people with known diabetes might be using insulin therapy before presentation with DKA and the group's recommendations made provision for this in terms of insulin delivery systems that might be in place. Specifically, the group recommended that if a child or young person with DKA is using insulin pump therapy, the pump should be disconnected when starting intravenous insulin therapy and the pump should be restarted at least 60 minutes before stopping intravenous insulin. Similarly, the group recommended that healthcare professionals, in discussion with a diabetes specialist, should think about continuing subcutaneous basal insulin during treatment for DKA in a child or young person who was already using a basal insulin before the onset of DKA. The group recommended starting subcutaneous insulin in a child or young person with DKA at least 30 minutes before stopping intravenous insulin.

17.3.1.2 Dosage of intravenous insulin

17.3.1.2.1 Review question

How should the dosage of insulin be calculated for children and young people with diabetic ketoacidosis (DKA)?

17.3.1.2.2 Introduction

The objective of this review question is to determine the most appropriate dose of insulin to treat DKA in children and young people with either type 1 diabetes or type 2 diabetes. Specifically, the question addresses whether a low dosage of insulin (0.025 U/kg/hour or 0.05 U/kg/hour) may result in fewer adverse outcomes compared with the current 'standard' dosage of 0.1 U/kg/hour.

The guideline development group identified priority outcomes as being:

- mortality
- rate of change of blood glucose
- incidence of hypoglycaemia
- resolution of acidosis
- resolution of blood ketosis
- incidence of cerebral oedema
- hypokalaemia
- healthcare utilisation.

Subgroup analyses were to be undertaken for type 1 and type 2 diabetes and by age group where possible. The review includes observational studies because no RCTs met the inclusion criteria.

17.3.1.2.3 Description of included studies

Three retrospective cohort studies were identified for inclusion in this review (Al Hanshi 2011; Kapellen 2012; Puttha 2010). The studies were carried out in Australia, Germany and the UK, respectively. All 3 studies assessed DKA in children and young people with type 1 diabetes. As no studies addressing DKA associated with type 2 diabetes were identified for inclusion in the review no subgroup analyses by diabetes type were possible.

The number of participants ranged from 64 to 93. The age range of participants was 1.25 to 17.7 years across the 3 studies as a whole. Two of the studies included participants with narrower age ranges of approximately 6 years (Kapellen 2012; Puttha 2010). One study compared the standard dosage of insulin with a lower dose of 0.025 U/kg/hour (Kapellen 2012). The other studies compared the standard dosage of insulin with a lower dose of 0.05 U/kg/hour (Al Hanshi 2011; Puttha 2010).

Data were reported for 4 of the guideline development group's priority outcomes: change in blood glucose from admission, change in blood pH from admission, incidence of hypoglycaemia and incidence of hypokalaemia. One study reported results for children under the age of 5 years in a subgroup analysis (Puttha 2010). Four further outcomes were not reported in sufficient detail to be included in GRADE profiles:

- 1 study reported a case of cerebral oedema using a case-report approach (Kapellen 2012)
- 1 study reported time to normalise acidosis, but no confidence intervals or p-values for between-group differences were reported (Kapellen 2012)
- 1 study reported duration of hospital stay, but it was not clear whether the reported values were means or medians and confidence intervals were not reported (Puttha 2010)

- 1 study reported the time to normalise blood glucose, but no confidence intervals were provided and it was not clear whether the values were means or medians (Kapellen 2012).

No studies reported results for mortality or resolution of ketosis.

17.3.1.2.4 Evidence profile

The evidence profile for this review question (dosage of intravenous insulin) is presented in Table 65.

Table 65: Comparison of insulin dosage of 0.025 U/kg/hour or 0.05 U/kg/hour with a dosage of 0.1 U/kg/hour in children and young people with type 1 diabetes and DKA

Number of studies	Number of children and young people		Effect		Quality
	Low dosage insulin	Standard dosage insulin	Relative (95% CI)	Absolute (95% CI)	
Change in blood glucose from admission (low dosage 0.05 U/kg/hour)					
Children of all ages					
1 (Al Hanshi 2011)	n=33 Median difference: −17 mmol/litre (IQR: -26 to -12)	n=34 Median difference: −21 mmol/litre (IQR: -52 to -15)	NA	p=0.004, adjusted R=0.62[a]	Very low
1 (Puttha 2010)	n=41 MD: 11.3 mmol/litre (8.6 to 13.9)	n=52 MD: 11.8 mmol/litre (8.4 to 15.2)	NA	MD: −0.50 (−4.75 to 3.75)[b]	Very low
Subgroup analysis: children aged less than 5 years					
1 (Puttha 2010)	n=6 MD: 15.9 mmol/litre (2.2 to 29.5)	n=5 MD: 20.1 mmol/litre (10.6 to 29.6)	NA	MD: −4.20 (−20.61 to 12.21)[b]	Very low
Incidence of hypoglycaemia (low dosage 0.025 U/kg/hour)					
1 (Kapellen 2012)	8/23	2/41	RR: 7.13 (1.65 to 30.79)[c]	NA	Very low
Incidence of hypoglycaemia (low dosage 0.05 U/kg/hour)					
1 (Puttha 2010)	0/41	7/80	RR: 0.13 (0.008 to 2.22)[c]	NA	Very low
Incidence of hypokalaemia (low dosage 0.025 U/kg/hour)					
1 (Kapellen 2012)	3/23	15/41	RR: 0.36 (0.12 to 1.10)[c]	NA	Very low
Change in blood pH from admission (low dosage 0.05 U/kg/hour)					
Children of all ages					
1 (Puttha 2010)	n=41 MD: 0.13 (0.09 to 0.18)	n=52 MD: 0.11 (0.07 to 0.15)	NA	MD: 0.02 (−0.04 to 0.08)[b]	Very low
Subgroup analysis: children aged less than 5 years					
1 (Puttha 2010)	n=6 MD: 0.17 (−0.01 to 0.31)	n=5 MD: 0.15 (−0.8 to 0.40)	NA	MD: 0.02 (−0.26 to 0.30)[b]	Very low
Time to pH >7.3 (resolution of acidosis)					
1 (Puttha 2010)	n=41	n=52	NA	MD: -1.3 (−4.4 to 1.8)[b]	Very low

CI confidence interval, IQR interquartile range, MD mean difference, NA not applicable, RR relative risk
a. R represents the correlation between insulin dosage and plasma glucose at 12 hours' follow-up, adjusted for the baseline value and age
b. Confidence intervals calculated by the NCC-WCH technical team using a standard deviation based on the t-distribution due to small sample size
c. Calculated by the NCC-WCH technical team

17.3.1.2.5 Evidence statements

Change in blood glucose from admission

One study (total 67 participants) found a smaller reduction in plasma glucose from admission in a low-dosage insulin group (0.05 U/kg/hour) compared with the standard dosage group (0.1 U/kg/hour). This study also found that insulin dosage was correlated with plasma glucose at 12 hours' follow-up, adjusted for the baseline value and age. Another study (total 93 participants) did not find a difference in change in blood glucose between the low and standard dosage groups (with low dosage of 0.05 U/kg/hour). The quality of the evidence for these outcomes was very low.

Subgroup analysis: children aged less than 5 years

One study (total 11 participants) found no difference in the change in blood glucose between groups (low dosage of 0.05 U/kg/hour). The quality of the evidence for this outcome was very low.

Incidence of hypoglycaemia

One study (total 64 participants) found that the incidence of hypoglycaemia was higher in participants who received a low dosage of insulin (0.025 U/kg/hour) compared with the standard dosage. The quality of the evidence for this outcome was very low.

One study (total 121 participants) found that the incidence of hypoglycaemia was lower in the low insulin group (0.05 U/kg/hour) compared with the standard dosage. The quality of the evidence was very low.

Incidence of hypokalaemia

One study (total 121 participants) found that the incidence of hypokalaemia was lower in participants who received a low dosage of insulin (0.025 U/kg/hour) compared with the standard dosage. The quality of the evidence for this outcome was very low.

Change in blood pH from admission

One study (total 93 participants) found no difference in the change in blood pH from admission between groups (low dosage of 0.05 U/kg/hour). The quality of the evidence for this outcome was very low.

Subgroup analysis: children aged less than 5 years

One study (total 11 participants) found no difference in the change in blood pH between groups (low dosage of 0.05U/kg/hour). The quality of the evidence for this outcome was very low.

Time to resolution of acidosis (pH more than 7.3)

One study (total 93 participants) found no difference in the time to resolution of acidosis (blood pH more than 7.3) between participants who received a low dosage of insulin (0.05 U/kg/hour) compared with those who received the standard dosage. The quality of the evidence for this outcome was very low.

17.3.1.2.6 Health economics profile

A systematic literature search did not identify any relevant published economic evidence related to the dosage of insulin for children and young people with DKA.

This question was not prioritised for health economic analysis as the guideline development group considered there were more important priorities for health economic analysis.

17.3.1.2.7 Evidence to recommendations

Relative value placed on the outcomes considered

The guideline development group wanted to determine whether low-dosage intravenous insulin (for example 0.05 U/kg/hour or 0.25 U/kg/hour) or standard-dosage insulin (0.1 U/kg/hour) during DKA might have associated risks or benefits. They prioritised the following outcomes as being of potential clinical importance: mortality, rate of change of blood glucose, incidence of hypoglycaemia, resolution of acidosis, resolution of ketosis, incidence of cerebral oedema, incidence of hypokalaemia and healthcare utilisation.

Mortality was important because DKA is an important cause of mortality in people with diabetes. The rate of change of blood glucose concentration was not considered to be a primary objective. Nevertheless, the guideline development group considered it likely that studies would report this outcome. Hypoglycaemia is an important adverse outcome, but it should be avoided if adequate intravenous glucose is administered. Resolution of acidosis and ketosis was an important outcome because this is a key objective with insulin therapy during DKA. The primary purpose of insulin in the management of DKA is to switch off ketone production. Cerebral oedema is an important outcome, because it is a potential cause of both morbidity and mortality in DKA. It is the cause of death in 80% of children under 12 years who die from diabetes and it is also a major cause of permanent disability (Edge 1999). Children and young people are more vulnerable than adults to the development of cerebral oedema. Hypokalaemia is an important outcome because it is a cause of mortality in DKA. Finally, healthcare utilisation (for example duration of admission or need for mechanical ventilation) is important. The need for mechanical ventilation is seen as a proxy for incidence of cerebral oedema.

Consideration of clinical benefits and harms

The guideline development group recognised that using a standard insulin dosage of 0.1 units/kg/hour was widespread and appears to be safe and effective. However, some centres do routinely use a lower dose of 0.05 U/kg/hour and again experience was that this was safe and effective. There was limited evidence from comparative studies to determine the optimal insulin dosage and the available evidence could not address the important outcome of mortality. The resolution of acidosis appeared to be equivalent when dosages of 0.05 U/kg/hour and 0.1 U/kg/hour were compared (this outcome was not reported for a dosage of 0.025 units/kg/hour). There was a lack of evidence regarding the relative risks of adverse events such as the incidence of cerebral oedema, hypoglycaemia and hypokalaemia.

Consideration of health benefits and resource use

There was no evidence for any difference between the insulin dosages evaluated. The guideline development group's recommendations allow for the standard insulin dosage of 0.1 units/kg/hour but also permit a lower dose of 0.05 units/kg/hour and will therefore have minimal cost impact, especially in the context of the overall management of the condition. Thus the guideline development group's recommendations will not affect resource use.

Quality of evidence

In all of the included studies the available evidence was of very low quality. The finding in 1 study that hypoglycaemia was more common in participants treated with 0.025 units/kg/hour compared with 0.1 units/kg/hour was contrary to what would be expected. The study authors noted that there was no difference in the incidence of hypoglycaemia during the first 12 hours

of treatment and that the difference between the treatment groups was found only later in the course of treatment (when participants were making the transition from intravenous to subcutaneous insulin). Importantly, the children and young people in the 2 treatment groups in this study were being managed in different centres. This raises the possibility that factors other than the dosage of intravenous insulin were responsible for the observed difference in outcomes in this study. It was noteworthy that the children and young people in the centre using the low-dosage insulin regimen received about twice as much intravenous fluid as those in the standard-dosage centre, presumably reflecting differences in either fluid management policy or severity of dehydration in the participants. Those studies that compared 0.05 units/kg/hour with 0.1 units/kg/hour found no difference in the incidence of hypoglycaemia.

There was no evidence for mortality or incidence of cerebral oedema.

Other considerations

There were no other considerations.

Key conclusions

In accordance with current practice in the UK, and taking account of the lack of good quality comparative studies, the guideline development group recommended that in children and young people requiring intravenous insulin for DKA a dosage of between 0.0 5 U/kg/hour and 0.1 U/kg/hour be used. The group also recommended, given the critical role of insulin in resolving ketosis, that if the blood glucose level was to fall excessively during intravenous insulin therapy while ketosis persisted, insulin treatment should be maintained in a dosage of at least 0.05 U/kg/hour while the glucose level should be managed by increasing the rate of intravenous glucose administration (see Section **Error! Reference source not found.**). The guideline development group, taking account of the lack of quality evidence on this topic, made a research recommendation on the need to conduct an RCT to determine the optimal dosage of intravenous insulin in children and young people with DKA.

17.3.2 Recommendations

The current recommendations can be found at https://www.nice.org.uk/guidance/ng18.

17.3.3 Research recommendations

19. What is the optimal dosage of intravenous insulin for managing diabetic ketoacidosis (DKA) in children and young people?

17.4 Monitoring during therapy

The evidence and recommendations related to monitoring during therapy are considered alongside those for assessments and investigations at presentation (see Section 17.2.2).

17.4.1 Recommendations

The current recommendations can be found at https://www.nice.org.uk/guidance/ng18.

17.4.2 Intravenous osmotic agents

17.4.2.1 Review question

What is the effectiveness of intravenous osmotic agents in the management of cerebral oedema associated with diabetic ketoacidosis?

17.4.2.2 Introduction

The objective of this review question is to assess the effectiveness of intravenous osmotic agents in the treatment of cerebral oedema associated with DKA in children and young people with type 1 or type 2 diabetes.

The main intervention of interest to the guideline development group was the urgent administration of mannitol or hypertonic saline while the child or young person is still on a general paediatric ward. The setting in which intravenous osmotic agents are administered and the duration of treatment were also of interest. The main outcomes of interest were mortality, persistent neurological deficit and healthcare utilisation.

Subgroup analyses were to be undertaken for type 1 and type 2 diabetes, previously recognised diabetes or first presentation and/or by age group where possible. The search strategy covered observational studies as well as RCTs, although no RCTs met the inclusion criteria.

17.4.2.3 Description of included studies

One retrospective cohort study (DeCourcey 2013) was identified for inclusion in this review. The study was carried out in the USA. The study assessed DKA and cerebral oedema in children and young people aged less than 19 years who were treated in tertiary care hospitals. The study was assumed to be related specifically to type 1 diabetes and therefore there are assumed to be no studies relevant to DKA in children and young people with type 2 diabetes. Therefore no subgroup analyses by diabetes type were possible.

The study included 1632 participants with cerebral oedema associated with DKA. The age range of participants was 8.7 to 15.2 years. The study compared outcomes in participants who received mannitol alone, those who received 3% hypertonic saline alone and those who received both mannitol and hypertonic saline as a combined treatment. The study reported the proportion of participants whose treatment involved admission to an intensive care unit (ICU).

Sufficient data were available on 2 of the guideline development group's priority outcomes: mortality and healthcare utilisation (which the study authors expressed as severity of illness). The group's other priority outcome (persistent neurological deficit) was not reported. The study did not report duration of treatment. Mortality subgroup analyses by previously recognised diabetes or first presentation and by age group were not reported separately for any of the treatment groups, although overall mortality by ICD-9 diagnosis codes for diabetes with hyperosmolar state and diabetes with coma, and for different age groups, were reported.

17.4.2.4 Evidence profile

The evidence profile for this review question (intravenous osmotic agents for the management of cerebral oedema) is presented in Table 66.

Table 66: Effectiveness of intravenous osmotic agents in the treatment of cerebral oedema associated with diabetic ketoacidosis in children and young people with type 1 diabetes

Number of studies	Number of children and young people		Effect		Quality
	Mannitol	Hypertonic saline	Relative (95% CI)	Absolute (95% CI)	
Adjusted odds ratio of mortality for hypertonic saline alone versus mannitol alone					
1 (DeCourcey 2013)	NA	NA	2.71 (1.01 to 7.26) [a,b]	NA	Very low
Healthcare utilisation: brain imaging with CT scan (%)					
1 (DeCourcey 2013)	525/1202 (43.7)	109/299 (36.5)	NA	NA	Very low
Healthcare utilisation: mechanical ventilation (%)					
1 (DeCourcey 2013)	184/1202 (15.3)	43/299 (14.4)	NA	NA	Very low
Healthcare utilisation: intensive care unit admission (%)					
1 (DeCourcey 2013)	784/1202 (65.2)	269/299 (90)	NA	NA	Very low

CI confidence interval, NA not applicable
a. Adjusted for discharge year, hospital clustering, gender, mechanical ventilation, brain imaging with CT scan, ICD-9 code (diabetes with hyperosmolar state [250.2] or diabetes with coma [250.3])
b. Treatment group with both hypertonic saline and mannitol was excluded from further analysis as participants treated with both agents would have been switched to the alternative agent once the initial therapy failed and the study database did not allow for the order of therapy intervention to be determined

17.4.2.5 Evidence statements

Mortality

One study (total number of participants is not calculable) found that use of hypertonic saline alone was associated with higher mortality than use of mannitol alone, adjusted for discharge year, hospital clustering, gender, predictors of severity (mechanical ventilation, brain imaging with CT scan and ICD-9 code [250.2 and 250.3]) after non-significant predictors of mortality (age, race and ICU admission) were sequentially removed. Participants treated with both agents were excluded from odds ratio (OR) analysis in the study. The quality of the evidence for this outcome was very low.

Healthcare utilisation

The study (total 1501 participants) was not able to determine whether healthcare utilisation (which the study authors expressed as severity of illness) was a consequence of the treatment as it could not ascertain what clinical criteria were used to warrant treatment. The study found more children and young people treated with hypertonic saline alone were admitted to ICU than those treated with mannitol alone. The same study found a few more children and young people treated with mannitol alone had mechanical ventilation and brain imaging with CT scan than hypertonic saline alone. The quality of the evidence for these outcomes was very low.

17.4.2.6 Health economics profile

A systematic literature search did not identify any relevant published economic evidence relating to the effectiveness of intravenous osmotic agents in the management of cerebral oedema associated with DKA.

This question was not prioritised for health economic analysis as the guideline development group considered that the costs were small relative to the potential benefits and that clinical effectiveness would drive cost effectiveness.

17.4.2.7 Evidence to recommendations

17.4.2.7.1 Relative value placed on the outcomes considered

The guideline development group specified mortality as the highest-priority outcome and this was reported in the included study. Long-term neurological problems were also selected as a priority outcome but these were not reported in the included study. However, the absence of evidence for this outcome did not prevent the group making recommendations.

17.4.2.7.2 Consideration of clinical benefits and harms

The guideline development group noted that cerebral oedema is potentially life threatening and that prompt action to treat cerebral oedema is essential once the condition is detected. The guideline development group was aware that mannitol has been the standard treatment for cerebral oedema but that increasingly hypertonic saline (sodium chloride) is being used in intensive care units (ICUs) for treatment of non-DKA related cerebral oedema and in some settings hypertonic saline is now recommended as first-line treatment.

A possible benefit of hypertonic saline over mannitol is that it can be given repeatedly with persisting benefit whereas mannitol becomes less effective with repeated administration.

The group also noted that mannitol is more readily available on paediatric wards (although this does not hold true for ICUs).

17.4.2.7.3 Consideration of health benefits and resource use

The guideline development group emphasised that effective treatment of cerebral oedema will save lives and noted that it may improve neurological outcomes. The treatment options considered by the group – mannitol and hypertonic saline – were both noted to be low cost, and the group noted that the intention was not to recommend either mannitol or hypertonic saline in preference to the other, but to recommend the use of whichever of the 2 treatments would be readily already available, and therefore it was expected that there would be no uplift in cost associated with the recommendation.

Illustrative costs for mannitol and hypertonic saline are illustrated below, based on the unit costs reported in Table 67. They suggest that for the pack sizes listed the costs would be similar.

Table 67: Unit costs of osmotic agents

Description	Unit quantity	Cost	Source
Soduim chloride 2.7% Intravenous infusion B.P	500 ml	£3.28	http://www.fresenius-kabi.co.uk/files/Fresenius_Kabi_2014_price_list.pd
Mannitol	250 ml[a]	£3.78	BNF April 2015
Mannitol	500 ml	£5.80	BNF April 2015

a. A 250 ml bag of mannitol 20% contains 50 g of mannitol

Following the upper limit of the guideline recommendations a girl aged 12 years weighing 40 kg would require:

- Mannitol 20% – 40 g or 200 ml which could be supplied from 1 bag of 250 ml solution
- Hypertonic saline 2.7% – 200 ml which could be supplied from 1 bag of solution.

17.4.2.7.4 Quality of evidence

The guideline development group noted that the evidence for their priority outcome of healthcare utilisation was slightly indirect in that the study authors reported severity of illness rather than a direct measure of healthcare resource use. The group also noted that a record of administering mannitol or hypertonic saline would provide a reasonable marker for presence of cerebral oedema, although this could not be ascertained with certainty.

The group noted that the evidence was seriously indirect due to the methods used in the study. In particular, the group felt that there was strong risk of bias because hypertonic saline was reported to be used more frequently in ICU settings and it was plausible that the relevant participants would have been more unwell than the other participants. This meant that no conclusions could be drawn in terms of comparing the effectiveness of mannitol and hypertonic saline.

Where both treatments (mannitol and hypertonic saline) were used it was impossible to tell which was used first and again the guideline development group thought it was likely that participants who received both treatments would have been more unwell than the other participants. Therefore nothing could be concluded about the potential benefit of using both treatments sequentially, nor the order in which the treatments were used.

17.4.2.7.5 Other considerations

The dosages for mannitol and hypertonic saline recommended by the guideline development group are broadly in keeping with general statements in the summaries of product characteristics (SPCs) for these products and with ISPAD guidance which reflects current practice in the UK. The guideline development group wished to include the dosages in the recommendations so that the information would be to hand when management of cerebral oedema was necessary, rather than healthcare professionals having to check the dosages separately and thus delay potentially life-saving treatment.

17.4.2.7.6 Key conclusions

The guideline development group concluded that cerebral oedema in children and young people with DKA should be treated promptly using mannitol or hypertonic saline (sodium chloride), whichever is most readily available in the non-ICU setting. Specifically, the group recommended that if cerebral oedema is suspected in a child or young person with DKA, they should be treated immediately with the most readily available of mannitol (20%; 0.5 to 1 g/kg over 10 to 15 minutes) or hypertonic sodium cholride (2.7% or 3%; 2.5 to 5 ml/kg over 10 to 15 minutes). The same treatment should be given to any child or young person with DKA who develops any of the following signs: deterioration in level of consciousness; abnormalities of breathing pattern, for example respiratory pauses; oculomotor palsies; pupillary inequality or dilatation.

The group further recommended that after starting treatment for cerebral oedema with mannitol or hypertonic sodium chloride in a child or young person with DKA, specialist advice on further management, including which care setting would be best, should be sought immediately.

17.4.3 Anticoagulant prophylaxis

17.4.3.1 Review question

What is the effectiveness of routine anticoagulant prophylaxis to prevent venous thrombosis in children and young people with DKA?

17.4.3.2 Introduction

The objective of this review question is to determine whether anticoagulant prophylaxis is effective in preventing venous thrombosis in children and young people with DKA. The guideline development group noted that deep vein thrombosis, visceral thrombosis and cerebral thrombosis would all be relevant in this review question.

17.4.3.3 Description of included studies

For this question the search included both RCTs and comparative observational studies. However, no studies were identified that met the inclusion criteria.

17.4.3.4 Evidence profile

There is no evidence profile for this review question because no studies were identified for inclusion.

17.4.3.5 Evidence statements

No evidence was identified for inclusion for this review question.

17.4.3.6 Health economics profile

A systematic literature search did not identify any relevant published economic evidence relating to routine anticoagulant prophylaxis to prevent venous thrombosis in children and young people with DKA.

This question was not prioritised for health economic analysis as the guideline development group considered there were more important priorities for health economic analysis.

17.4.3.7 Evidence to recommendations

17.4.3.7.1 Relative value placed on the outcomes considered

The guideline development group prioritised the following physical outcomes for consideration in this review question:

- mortality
- incidence of venous thrombosis (of any type, including deep vein thrombosis, visceral thrombosis and cerebral thrombosis)
- incidence of pulmonary embolism
- healthcare utilisation (for example duration of admission, admission to intensive care)
- adverse events, including bleeding and thrombocytopaenia.

The group also prioritised the satisfaction of children, young people and families with the intervention as an outcome for consideration.

The group's priorities reflected the serious nature of potential outcomes associated with venous thrombosis and pulmonary embolism, including the possibility of death, and their selection of priority outcomes reflects this alongside the importance of offering treatments that are acceptable to children and young people with DKA and their families.

17.4.3.7.2 Consideration of clinical benefits and harms

The guideline development group recognised that there is a risk of venous thrombosis in children and young people with DKA (this was based on the group's knowledge of relevant case reports). The extent of this risk has, however, not been accurately quantified.

The group's view was that the use of central venous catheters increases the risk of thrombosis (again this is based on the group's knowledge of case reports).

The group noted that the risk of venous thromboembolism (VTE) in children and young people with DKA compared with other children in an intensive therapy unit (ITU) environment is unknown, and there are potential harms associated with anticoagulant prophylaxis and treatment (the main harm being bleeding).

Overall, the guideline development group noted the lack of evidence for this review question and concluded that there was no general consensus regarding the role of anticoagulant prophylaxis for children and young people with DKA, either in terms of benefits or harms.

17.4.3.7.3 Consideration of health benefits and resource use

The guideline development group did not enter into detailed consideration of the cost effectiveness of alternative management strategies based on anticoagulant prophylaxis because they did not wish to recommend this form of treatment due to a lack of evidence related to its clinical effectiveness.

17.4.3.7.4 Quality of evidence

No evidence was identified for inclusion for this review question, but the guideline development group did not view this area as a priority for future research.

17.4.3.7.5 Other considerations

There were no other considerations.

17.4.3.7.6 Key conclusions

The guideline development group concluded that anticoagulant prophylaxis was not to be recommended for children and young people with DKA and they agreed not to make any recommendations on this topic. The group did, however, recommend that healthcare professionals should be aware of the increased risk of venous thromboembolism in children and young people with DKA, especially those with central venous catheters.

17.4.4 Recommendations

The current recommendations can be found at https://www.nice.org.uk/guidance/ng18

17.4.5 Recommendations

The current recommendations can be found at https://www.nice.org.uk/guidance/ng18.

18 Service provision

18.1 Multidisciplinary teams

Type 1 diabetes can have a potentially devastating acute and long-term effect on a child or young person and their family. The management of type 1 diabetes, education, empowerment and support of the child or young person and their family in the first few weeks can have a long-term effect on their acceptance of the condition, and their skills and enthusiasm in its management.[21] [evidence level IV]

The National Service Framework for Children states that:[22]

'Children and young people [with type 1 diabetes] should receive care that is integrated and coordinated around their particular needs, and the needs of their family. They, and their parents, should be treated with respect, and should be given support and information to enable them to understand and cope with the [diagnosis of diabetes] and the treatment needed. They should be encouraged to be active partners in decisions about their health and care, and, where possible, be able to exercise choice.'

The National Service Framework for Diabetes Delivery Strategy states that:[23]

'A care plan is at the heart of a partnership approach to care and a central part of effective care management. The process of agreeing a care plan offers people active involvement in deciding, agreeing and owning how their diabetes will be managed. Whilst the overall goal is a genuine partnership, the person with diabetes must feel that they are comfortable with what is proposed and that they do not have to bear more responsibility than they wish.'

18.1.1 What is the optimum location (home versus hospital) for the management of children and young people with newly diagnosed type 1 diabetes?

In the past there has been some controversy as to whether or not children and young people with type 1 diabetes should be managed in hospital or at home soon after diagnosis.

A systematic review identified 2 RCTs,[24,25] 3 retrospective cohort studies[26–28] and a prospective cohort study.[29,30] [evidence level Ia] The systematic review found that owing to the low quality or limited applicability of the studies identified the results were inconclusive. However, the data suggested that home or outpatient management of type 1 diabetes in children at diagnosis did not lead to any disadvantages in terms of metabolic control, acute diabetes complications and hospitalisations, psychosocial variables and behaviour, or total costs.[30] [evidence level Ia]

The 2 RCTs included in the systematic review compared home care packages to standard hospital inpatient care for the management of children and young people over the age of 2 years with newly diagnosed type 1 diabetes.[24,25] [evidence level Ib] The trials were conducted in Finland and Canada, and the children and young people were followed for 2 to 5 years. The outcomes reported were HbA1c, diabetes-related adverse events, diabetes knowledge, adherence to treatment, family impact, stress, satisfaction, child behaviour, social cost, insulin dosage, family social variables and rate of re-admission. In the Finnish study, the 2 treatment groups received the same content and quantity of patient education, although few specific details were provided in the report. In the Canadian study, both treatment groups had 24-hour telephone access to a diabetologist or a diabetes nurse; the diabetes care team also included a psychologist and a social worker. Children and young people who lived more than 1 hour's travelling time from the hospital were excluded from the study.

The Finnish study found no significant difference in HbA1clevels between the 2 treatment groups (n=60).[25] [evidence level Ib] The Canadian study reported improved glycaemic control in the home care group.[24] [evidence level Ib] However, in this study the treatment groups

differed in terms of continuity of care, and the home care group spent more hours with a diabetes nurse. These factors could explain the improved glycaemic control in the home care group.

Both studies examined diabetes-related hospital admissions in the post-initial management period. Neither study found a significant difference between home and hospital care groups. The Finnish study measured insulin dosage, and showed a statistically significant decrease in insulin use among children and young people treated as outpatients.[31] [evidence level Ib] The Canadian study found no statistically significant differences between home and hospital care groups in terms of psychosocial outcomes, knowledge of diabetes, adherence to insulin therapy, family impact, satisfaction, child behavioural problems or social costs. This study did find significantly higher perceived stress levels among young people in the home care group after 1 month, although the difference was not significant at 12 months or 24 months. Perceived stress levels among parents did not differ significantly between home and hospital care groups at any time (n=63).[24] [evidence level Ib]

We did not identify any RCTs that investigated the location of initial management in the UK. A retrospective cohort study based in Leicester reported significantly fewer diabetes-related hospital re-admissions among children and young people who received home-based care.[25] [evidence level IIb] However, glycated haemoglobin concentrations did not differ significantly between home and hospital care groups. In this observational study, the difference between the rates of hospital re-admission in the home and hospital care groups may have been due to differences between the 2 groups that were not related to the location of initial management.

A descriptive observational study from Birmingham showed that 14% of children and young people with diabetes could be fully managed at home from the time of diagnosis. The mean length of inpatient hospital-based care for children and young people with newly diagnosed type 1 diabetes was 2 days.[32] [evidence level III]

Another descriptive observational study from the USA reported that 35% of children and young people with newly diagnosed type 1 diabetes were treated as outpatients.[33] [evidence level III]

Three non-experimental descriptive studies reported outcomes for children and young people receiving initial management at home or in hospital.[26,29,34] [evidence level III] However, these studies were likely to have been affected by bias because children and young people who receive hospital-based initial management usually have severe symptoms which may be associated with long-term outcomes. The first study showed that the incidence of severe hypoglycaemia, diabetic ketoacidosis, diabetes-related complications and HbA1 did not differ significantly between children and young people receiving home- and hospital-based care.[26] [evidence level III] The second study reported that hospitalisation episodes and ketoacidotic episodes were more common in children and young people treated initially as inpatients than in children and young people managed initially as outpatients (hospitalisation episodes: RR 3.7, 95% CI 1.5 to 9.0; ketoacidotic episodes: RR 3.1, 95% CI 1.5 to 6.3). However, there was no significant difference in the incidence of severe hypoglycaemia between the 2 treatment groups.[34] [evidence level III] The third study found no significant differences in re-admission and emergency room visits, knowledge, responsibility of care, coping skills or quality of life between children and young people who received home- and hospital-based education. However, there were small differences in adherence to blood glucose regulation, emergency precautions and family functioning.[29] [evidence level III]

Two further studies investigated the effects of reducing the length of hospital-based care. An RCT compared early discharge, care in a hospital-based family apartment, and conventional hospital-based care.[35] [evidence level Ib] There was no significant difference in glycaemic control or readmission rates between the 3 groups. A non-randomised controlled trial that compared short (average 9 days) and long (approximately 23 days) initial hospital stays found no significant differences in metabolic control, percentage of children and young

people that tested positive for C-peptide (an indicator of endogenous insulin production) after 2 years, insulin dosage[31,36] or psychosocial function[31,36] between the 2 treatment groups. [evidence level IIa]

We found an economic study based on a Canadian RCT.[37] This study was based on data from 1 hospital and home care programme. The home care programme consisted of 2 nurse visits a year and a 24-hour telephone support service. Home care patients were offered psychosocial support and counselling and were offered an additional clinic visit with a diabetologist. Overall, the cost of home care was found to be higher. The increased cost of home care was attributable to increased specialist diabetes nursing care and increased psychosocial counselling, although the cost to parents was lower.

18.1.2 Diabetes care teams

The clinical management of children and young people with type 1 diabetes is normally organised by a team of healthcare professionals.

A 1998 survey of consultant paediatricians who provide care for children and young people with diabetes aged under 16 years in the UK found variation across the country on who provided care for children and young people with diabetes (n=244 paediatricians, n=17,192 children and young people).[18] [evidence level III] Of these consultant paediatricians, 78% expressed a specialist interest in diabetes, and 91% saw children in a designated diabetes clinic. There was a specialist nurse in 93% of the clinics, 66% of whom were trained to care for children and 47% of whom had a caseload of more than 100 children. A paediatric dietitian was present in 65% of the clinics, and in 25% of clinics some form of specialist psychology or counselling was available.

The young people's consultation day organised for this guideline in collaboration with the NCB found that:[38] [evidence level IV]

- Young people with type 1 diabetes felt that healthcare professionals should be skilled in gaining the confidence of young people by educating them about diabetes in accessible language, treating them as individuals and with respect, and ensuring that they are given the opportunity to contribute to decisions about their diabetes care.
- Young people with type 1 diabetes and their parents felt they should have 24-hour access to a named specialist nurse with whom they could speak confidentially and who they could contact between clinic appointments.
- Some young women with type 1 diabetes stated a preference for a female doctor with whom they felt they would be more comfortable.
- Young people with type 1 diabetes and their parents felt that it was important to see the same members of the diabetes care team wherever possible.
- Young people with type 1 diabetes liked age-banded clinics.
- Young people with type 1 diabetes were happy to miss school in order to attend clinic appointments, but their parents would prefer clinic appointments to be available outside of school hours.
- Parents of young people with type 1 diabetes suggested that clinic appointments should be flexible enough to take into account school terms, timetables and examination schedules.
- Parents of young people with type 1 diabetes felt that there should be easy access to psychology services and suggested that paediatric diabetes care teams should include a psychologist.

18.1.3 Recommendations

The current recommendations can be found at https://www.nice.org.uk/guidance/ng18.

18.2 Communication between organisations

18.2.1 Education and care institutions

It is important that children and young people with diabetes receive appropriate care at schools, crèches and nurseries. To be able to give appropriate care, staff members need an appropriate level of diabetes education, and this should be relevant to activities that take place on the premises as well as those associated with participation in school trips and camps.

A study of 85 Manchester teachers who had some contact with children and young people with diabetes found that only 39% had adequate knowledge of diabetes. In primary school teachers, the main source of information was parents of children and young people with type 1 diabetes. Secondary school teachers received information on diabetes from a wider variety of sources, including radio, television, other school staff, teaching literature, newspapers and magazines.[666] [evidence level III] A study in Liverpool with 97 teachers of children and young people with diabetes completed an 18-item yes/no format questionnaire of factual information, but without statistical validation of results.[667] [evidence level III] A third study used a multiple-choice questionnaire to assess school personnel's knowledge of diabetes, although the tool was not validated statistically and several items had more than 1 correct answer. Studies suggested that teachers lacked knowledge about many aspects of diabetes and possessed inadequate information (n=475 teachers who responded to a questionnaire).[668] [evidence level III] A study in 308 staff members in a school in Sweden also highlighted a high proportion of school staff who had limited knowledge of diabetes.669 [evidence level III]

An RCT examined an education module for teachers in the USA. The study found that the group of teachers who were randomised to receive the education module had a higher diabetes knowledge score after education than the control group (21.47 ±3.62 versus 17.50 ±6.14, p=0.032, n=159 teaching staff)[670] [evidence level Ia] A non-controlled intervention study that evaluated an educational programme found that diabetes knowledge increased after education (75 ±11.0 versus 94 ±4.1, p<0.004, n=156 school personnel).[671] [evidence level IIb]

A booklet available from Diabetes UK provides schools with information needed to give support to children and young people with diabetes and general information.[672] [evidence level IV] Particular concerns are the treatment of hypoglycaemia and the administration of insulin (see Section 7). Close communication between the local diabetes care team and the school health service and teachers and other staff is essential.

A collaboration between the Department of Health and the Department for Education produced a document about supporting pupils with medical needs in school. The document considered the following 3 areas.[673] [evidence level IV]

- There is no legal duty requiring school staff to administer drugs to children and young people, and so this remains a voluntary role. However, school staff who are in charge of pupils have a duty in common law to act in the same manner as a responsible parent in order to ensure that children and young people remain safe and healthy while on school premises. In certain circumstances teachers might be expected to administer drugs or take appropriate action in an emergency.
- Each school is advised to draw up general policies and procedures in order to support pupils with medical needs.
- The use of individual healthcare plans is suggested in order to ensure that school staff are sufficiently informed about a pupil's medical needs, including the administration and storage of drugs. It was recommended that such plans should be jointly agreed between the pupil's parents, medical carers and teachers and they should provide explicit advice

about appropriate measures to be followed in an emergency. Drugs must be readily available in an emergency and must not be locked away.

A discussion article has also recommended the following.[674] [evidence level IV]

- The school health service must take a lead in supporting pupils with medical needs, with the school nurse acting as the focal point. In particular, school heath profiles could be used as an index of local need, which might be incorporated into pupils' service plans. Health professionals should arrange training events, which could be supported by written material for teachers on childhood illness.
- Local educational authorities should, as a matter of urgency, ensure that each school has general policies in place with respect to the administration of medicines to children and young people.
- Teachers must continue to respond as positively as they can when they encounter a pupil with medical needs. They should try to increase their knowledge of childhood chronic illness and they should be supported in this respect by local educational authorities and trade unions.
- Parents and carers must acknowledge that they hold the prime responsibility for their children's welfare and that accountability for the administration of medicines must be negotiated with rather than demanded of school staff.

We found no evidence of studies relating to the provision of support or advice to crèches, nurseries or other educational or care institutions.

A leaflet available from Diabetes UK provides information for adult carers (babysitters, other parents, etc.) to be used when a child with diabetes comes to stay.[675] [evidence level IV]

18.2.2 Government support

Children and young people with type 1 diabetes and their families should be offered information about Disability Living Allowance, including details of how to submit a claim.

Diabetes UK has published a leaflet that provides information on the Disability Discrimination Act 1995 (protection against discrimination in education).[676] [evidence level IV]

18.2.3 Support groups

A large number of organisations exist to represent the views of children and young people with type 1 diabetes across the UK. National and local groups support children and young people and their families and recently there has been an increase in electronic communication through dedicated websites.

The young people's consultation day organised for this guideline in collaboration with the NCB found that young people with type 1 diabetes valued meeting other young people with type 1 diabetes and might benefit from formalised arrangements for meeting each other.[38] [evidence level IV]

These findings were similar to those reported in other studies, including the Diabetes UK YD Group, Firbush Summer Camp.[677] [evidence level IV]

18.2.4 Recommendations

The current recommendations can be found at https://www.nice.org.uk/guidance/ng18.

18.2.5 Research recommendation

This section was updated in 2015.

20. [2004] Further research is needed to evaluate the effects of low blood glucose levels on learning, attendance at school and educational attainment.

18.3 Transition from paediatric to adult care

Young people with type 1 diabetes have specific health needs relating to the physical and socio-cultural changes of adolescence. At the same time they move from a children's health service into the adult healthcare system.[678] [evidence level IV] This period may frequently lead to a deterioration in glycaemic control.[562] [evidence level III] Non-adherence to insulin regimen is a major factor in the deterioration of glycaemic control.[501] [evidence level IIb]

Where possible it may be appropriate to consider a special transition service. A 1998 survey of consultant paediatricians who provide care for children and young people with diabetes aged under 16 years in the UK found that 53% transferred young people into young adult diabetes clinics as opposed to general adult clinics (n=17,192 children and young people).[18] [evidence level III]

We found no studies that examined the clinical or cost effectiveness of transition clinics. However, several studies compared children's and adult clinics.

A survey investigating the transfer of young people from children's to adult clinics in the Oxford region showed that age of transfer ranged from 13.3 years to 22.4 years (mean age 17.9 years, n=229). The rate at which clinic attendance occurred at least every 6 months dropped from 98% at 2 years before transfer to 61% at 2 years after transfer ($p<0.0005$). A letter of transfer was identified in the clinical records for 86% of the young people, and the attendance rate at the first appointment in the new clinic was 79%.[679] [evidence level III]

Another study examined young people's knowledge of adult clinics before transfer, preparation for transfer, and how young people felt about the move (n=43). Young people who were attending an adolescent or transition clinic seemed to have little knowledge about the clinic they would be going to in the future. However these people may have received the information closer to the time of transfer. Of the young people attending adult clinics, 35% had discussed the change beforehand, 16% reported having had a choice about the move, 84% felt they were ready to move, and 40% felt they were well prepared by staff for the move. However, 79% were not pleased to move.680 [evidence level III]

A Canadian survey examined the experience of young people with type 1 diabetes during the period of transfer from paediatric to adult care (n=212). The mean age at transfer was 18.5 years, and this was lower than the age of transfer suggested by the patients (18.8 years); 21% of patients felt they should have been transferred earlier, whereas 65% felt they should have been transferred later. After transfer, 13% had no regular contact with adult care services, 3% had contact with a family physician, and the remainder had contact with an endocrinologist or a diabetes clinic. Thirty-three per cent of patients felt they had a problem with the transition from paediatric to adult care. Twenty-seven per cent experienced a delay of more than 6 months between their last visit to the paediatric clinic and their first visit to the adult clinic (in 17% of patients this delay was greater than 1 year).[681] [evidence level III]

A Finnish study examined glycaemic control in young people 1 year before and 1 year after they were transferred from a paediatric clinic to an adult clinic. The mean age at transfer was 17.5 years (n=61). The mean HbA1 level improved from 1 year before transfer to 1 year after transfer (11.2 ±2.2% versus 9.9 ±1.7%, n=49, $p<0.001$), and from the first visit to the adult clinic to 1 year later (11.2 ±2.3% versus 9.9 ±1.7%, n=49, $p<0.001$).[682] [evidence level III]

An Australian survey of young people with type 1 diabetes found that patients wished to be treated in a range of care places (72.3% public hospital, 42.9% private specialist, and 14.3% general practitioner only, n=105). They also had differing views on the age of transfer (5.7% felt that transfer should occur before the age of 17 years, 48.6% felt that transfer should

occur between the ages of 17 years and 20 years, and 44.8% felt that transfer should occur at any age up to 25 years).[683] [evidence level III]

A UK survey of young people in Exeter showed that the average age of transfer was 15.9 years (range 12 to 20 years, n=69), and 27.3% offered some reason for transfer of care. The patients thought that it would be more helpful to visit the young adults' clinic before transfer than for a nurse or physician from the young adults' clinic to visit the paediatric clinic. The young people thought that the staff in the paediatric clinic assigned more importance to school progress and family relations than did staff in the young adults' clinic (school progress: 2.9 versus 2.4, $p<0.05$; family relations: 3.3 versus 2.7, $p<0.05$), but less importance to exercise, avoidance of complications and blood glucose levels (exercise: 3.7 versus 4.2, $p<0.05$; avoidance of complications: 4.5 versus 4.9, $p<0.05$; blood glucose levels: 4.5 versus 4.9, $p<0.05$). The paediatric and young adults' clinic staff did not differ in their assignment of importance to diet, insulin management or privacy.[684] [evidence level III]

The young people's consultation day organised for this guideline in collaboration with the NCB found that some parents suggested that age of transfer of young people with type 1 diabetes from paediatric to adult services should be standardised and that clinics should be jointly run by paediatric and adult services to provide continuity of care, whereas other parents thought that young people with type 1 diabetes should be involved in the decision about when transfer should occur. Young people with type 1 diabetes liked age-banded clinics.[38] [evidence level IV]

The National Service Framework for Diabetes states that transfer of young people with diabetes from paediatric services to adult services often occurs at a sensitive time in relation to the young person's diabetes and personal life.[23] [evidence level IV] The culture change that occurs at transition is found to be unacceptable by many young people, and young people's attendance rates at adult clinics are often low. Sensitive and skilled care at transition can assist in achieving good diabetes management, with a consequent avoidance of complications. A multidisciplinary approach is particularly effective for young people at transition.

Young people with type 1 diabetes who are preparing for transition to adult services should be informed that some aspects of diabetes management will change at transition.

18.4 Recommendations

The current recommendations can be found at https://www.nice.org.uk/guidance/ng18.

18.5 Research recommendation

21. [2004] Further research is needed to investigate young people's experiences of transition from paediatric to adult services for people with type 1 diabetes.

19 Health economics

19.1 Introduction

This section was updated in 2015.

This section provides details of the review of published health economic literature conducted for the 2015 update and the health economic modelling undertaken for selected review questions in the 2015 update.

19.2 Review of the literature

A global search was undertaken for health economic evidence covering the entire scope of the 2015 update (see Appendix B:). Two studies were included in the literature review (Ellis 2008; Christie 2014), the first of which was relevant to the review question about psychological interventions for children and young people with type 1 diabetes, while the second was relevant to the review question about structured education for children and young people with type 1 diabetes. Both studies are described in detail below.

19.2.1 Psychological interventions for children and young people with type 1 diabetes

A US study (Ellis 2008) undertook a cost analysis of multisystemic therapy (MST) to evaluate whether intensive home-based psychotherapy could reduce diabetic ketoacidosis (DKA) related admissions to hospital in young people with poorly controlled blood glucose compared with standard care. The analysis was based on the results of a randomised controlled trial (RCT) recording DKA admissions at the conclusion of the trial (Ellis 2007). The perspective of the study was that of a third party payer and that of the hospital; costs included an intervention cost of USD 6,934, obtained using an 'ingredients' approach, and the cost of DKA admissions estimated from hospital costs and revenues from the hospital financial database. The cost year was not stated explicitly but was based on financial data collected during the study.

The authors reported that MST led to savings of USD 23,886 from the hospital perspective and USD 72,226 from a third-party perspective. The costs were not reported with any measure of uncertainty although p-values were presented for differences in admission rates at 6 different time points across the 24 months of the study. However, the costs the authors reported were only for young people with any DKA admissions. They reported that 24 young people in the control arm of the study had 85 admissions and that 21 MST-treated young people had 45 admissions. They therefore calculated a treatment cost for the 21 MST-treated young people of USD 145,614. However, a total of 64 participants were randomised to MST against 63 participants assigned to the control group. Therefore, the total treatment costs should have been based on a numerator of 64 patients which would have given MST-treatment costs of USD 443,776, meaning that treatment costs would no longer be offset from the savings in reduced DKA admissions, with MST-treatment costing more than USD 200,000 more from either perspective.

19.2.2 Structured education for children and young people with type 1 diabetes

A UK study (Christie 2014) considered the cost effectiveness of a structured psychoeducational programme compared with current NHS practice for children and young people with type 1 diabetes as part of the Child and Adolescent Structured Competencies Approach to Diabetes Education (CASCADE) study, a cluster RCT. The economic evaluation took the form of a cost utility analysis with blood glucose control data from the RCT used to populate an economic model. Clinical evidence from this study was presented in the

evidence review for structured education for children and young people with type 1 diabetes (see Section 5.4).

The model considered the long-term costs and effects of the intervention by comparing HbA1c) levels in the intervention and control groups. Markov chain Monte Carlo (MCMC) submodels were used to simulate the progression of a range of diabetes complications. The models, which were the same for the intervention and control groups, consisted of a number of mutually exclusive health states and at the end of each time period, or cycle, a patient could move to 1 or more different states, the transition probabilities being determined by an individual's HbA1c level.

The analysis was undertaken from the perspective of the NHS with future costs discounted at 3%. In order to cost the CASCADE intervention the mean resource use to provide the intervention was multiplied by the unit cost of those resources. Quality adjusted life years (QALYs) were estimated by assigning health state utilities to the various health states and multiplying by the time spent in the respective states. The model addressed parameter uncertainty by performing probabilistic sensitivity analysis (PSA) using Monte Carlo simulation and 1-way sensitivity analysis to pinpoint variables which had the largest impact on model outcomes.

The study authors reported that the cost of the structured education intervention was £683 per child or young person, but that the intervention was dominated by current NHS practice which produced as many QALYs but at lower cost. Driving this result was the trial outcomes which showed that the intervention did not produce lower HbA1c at 12 months or 24 months when compared with current NHS practice.

19.3 Cost effectiveness of multiple daily injections compared with mixed insulin injections in children and young people with type 1 diabetes

The 2004 guideline recommended multiple daily injection (MDI) regimens for young people to help optimise their glycaemic control. Children and young people who did not achieve satisfactory glycaemic control with MDI were recommended, if appropriate, to receive alternative insulin therapy such as once, twice or 3-times daily mixed insulin regimens or continuous subcutaneous insulin infusion (CSII) using an insulin pump. Young people with type 1 diabetes and difficulties adhering to MDI regimens were recommended to receive twice-daily injection regimens.

The 2004 guideline recommended further research to compare the effectiveness of MDI regimens with mixed insulin injection therapies in children and young people with type 1 diabetes. While long-term studies (for example the UK Prospective Diabetes Study [UKPDS] and the Diabetes Control and Complications Trial [DCCT]) have indicated that MDI regimens can improve clinical outcomes by achieving blood glucose levels close to normal, the associated daily costs of diabetes care are higher than with a conventional mixed insulin approach.

Section 19.3.1 focuses on the immediate medical and follow-up costs for MDI and mixed insulin regimens during the first year after the initial diagnosis.

Since the results of improved glycaemic control are most likely to occur during a patient's remaining lifetime, cost and quality of life considerations have to include the development of relevant long-term complications as well as the treatment costs. Section 19.3.2 describes the overarching model that was used to assess the cost effectiveness of MDI versus mixed insulin injections.

19.3.1 Treatment costing

A costing tool was developed in Microsoft Excel™ to evaluate the treatment, management and follow-up costs of MDI and mixed insulin injections in the first year following the initial diagnosis of type 1 diabetes. The costs derived were used as input parameters in the more comprehensive cost effectiveness model which is described in Section 19.3.2.

19.3.1.1 Modelling direct medical costs

The comparison of costs for MDI and mixed insulin regimens aims to highlight differences in costs resulting from different insulin injection regimens. Costs related to the individual insulin dose that were assumed to be common to all treatment alternatives were, therefore, not included in the cost analysis. Costs for consumables required for self-monitoring of blood glucose levels and administration of insulin injections were included, as well as costs associated with the personnel involved in the initial diagnosis and review of treatment.

19.3.1.1.1 Staffing costs

The hourly rates for the healthcare professionals involved in instigating insulin treatment and supporting this process are presented in Table 68. The hourly rates are then multiplied by the total time input to provide an estimate of the total staff cost.

Table 68: Staffing hourly costs

Healthcare professional	Hourly cost	Source
PDSN[a]	£49	Curtis 2013
Dietitian[b]	£35	Curtis 2013
Diabetologist[c]	£139	Curtis 2013
Clinical psychologist[d]	£134	Curtis 2013

PDSN paediatrics diabetes specialist nurse
a. Based on a community specialist nurse on Agenda for Change Band 6.
b. Based on a hospital dietitian on Agenda for Change Band 5.
c. Based on a medical consultant
d. Based on a clinical psychologist

The costing of staff time was based on the following assumptions.

- Clinical staff and time inputs required at the time of diagnosis are the same for all insulin regimens.
- Time inputs from clinical staff are the same for twice and 3-times daily injection regimens.
- Dietetic and telephone advice for MDI is required more frequently than for twice or 3-times daily injections regimens.
- Dietetic advice for MDI (during home or school visits) requires more time inputs from a dietitian or paediatric diabetes specialist nurse (PDSN) to cover additional carbohydrate counting instruction.
- Time inputs from a multidisciplinary team (PDSN, dietitian, diabetologist and psychologist) during quarterly follow-up consultations are the same for all injection regimens and are, therefore, excluded from the cost analysis.

Table 69 presents an overview of all clinical staff involved at diagnosis and their respective time commitments. Table 70 gives a similar overview for the follow-up after initial diagnosis. The main difference between twice or 3-times daily injections and MDI regimens relates to more time-intensive dietary advice required for carbohydrate counting instruction for MDI both at home and at school. The final additional advice for MDI (delivered by telephone, email or text) is assumed to be delivered every other day for 1 additional month, by which time the individual dose is assumed to be stabilised and patients will not require any further formal advice.

Table 69: Time inputs of clinical staff for multiple daily injections and 2- or 3-times daily injections at diagnosis

Professional	Time (minutes) 2 or 3 times daily[a]	Time (minutes) Multiple daily injections[a]
Diabetologist	10	10
PDSN	120	120
Dietitian	120	120

PDSN Paediatric diabetes specialist nurse
The guideline development group was the source of these estimates for 'typical' practice whilst acknowledging there may be variation across different centres

Table 70: Time inputs of clinical staff for MDI and 2/3 times daily injections during early follow-up

Action	Professional	Time (minutes) 2 to 3 times daily[a]	Time (minutes) Multiple daily injections[a]
Instruction (home)	PDSN	120	-
Instruction (clinic)	Diabetologist	-	60
Home visits for 3 days (at 1 hour)	PDSN	-	180
Dietetic advice	Dietitian	60	180
School visits	Dietitian	120	240
School visits	PDSN	-	180
Additional advice[c, d]	PDSN	240	290
Clinic visit before delivery of routine clinical care	PDSN	120	60

PDSN Paediatric diabetes specialist nurse
a. The guideline development group was the source of these estimates for 'typical' practice whilst acknowledging there may be variation across different centres
b. Additional advice would typically take the form of a telephone call, email or text and would take 10 minutes Additional advice for 2-3 times daily injections was assumed to occur twice daily for the first 5 days and then once daily for an additional 2 weeks
c. Additional advice for MDI was assumed to occur once daily for the first 2 weeks, and once every other day for an additional month

19.3.1.1.2 Consumables

The unit costs of consumables used in insulin administration and self-monitoring of blood glucose (SMBG) are shown in Table 71.

Table 71: Unit costs of consumables

Item	Cost/unit	Manufacturer/brand[a]	Source
Insulin Aspart pre-filled pens	£6.12	NovoRapid®	BNF (October 2014)[b]
Insulin Detemir pre-filled pens	£8.40	Levemir®	BNF (October 2014)[c]
Biphasic Insulin Aspart pre-filled pens	£5.98	NovoMix®	BNF (October 2014)[d]
Needles	£0.09	NovoFine®	NHS Drugs Tariff (October 2014)[e]
Blood glucose strips	£0.14	SD CodeFree®	NHS Drugs Tariff (October 2014)[f]
Lancets	£0.03	iCare Advanced®	NHS Drugs Tariff (October 2014)[g]

BNF British National Formulary
a. There are many different providers of the consumables listed in this table and the inclusion of a particular product is for illustrative purposes. It is not intended as an endorsement of that product against any of its competitors.

b. Five 3 ml FlexPen® prefilled disposable injection devices (range 1 to 60 units, allowing 1-unit dosage adjustment) costs £30.60
c. FlexPen® prefilled disposable injection device (range 1 to 60 units, allowing 1-unit dosage adjustment) costs £42.00
d. Five 3 ml FlexPen® prefilled disposable injection devices (range 1 to 60 units, allowing 1-unit dosage adjustment) costs £29.89
e. £9.24 for a pack of 100 (8 mm/30 gauge)
f. £6.99 for a pack of 50
g. £2.85 for a pack of 100 (0.38 mm/30 gauge)

Costs for consumables are assumed to be different for twice and 3-times daily injections and MDI regimens. Included are costs for consumables required for self-monitoring of blood glucose (SMBG) levels (strips for blood glucose testing and lancets) and administration of insulin injections (prefilled disposable pens and needles). Since meters for blood glucose testing are available free of charge, they are not included in the cost summary (see Table 72).

Table 72: Consumables used in insulin administration and self-monitoring of blood glucose per year

Item	2 times daily	3 times daily	Multiple daily injections
Insulin Aspart pre-filled pens	-	-	41
Insulin Detemir pre-filled pens	-	-	33
Biphasic Insulin Aspart pre-filled pens	66	73	-
Needles	730	1095	1825
Blood glucose strips	1825	1825	1825
Lancets	1825	1825	1825

The total cost of consumables is derived by multiplying the unit costs in Table 71 by the respective quantities in Table 72. A needle is required for each injection and it assumed that MDI consists of 5 daily injections (4 short-acting and 1 long-acting). Similarly, a blood glucose strip and new lancet are required for each self-monitoring blood glucose test and the values in Table 71 are based on 5 such tests per day, as per the recommendations in the guideline (see Section 6.11).

Details of how annual pen usage was estimated are given below. The guideline development group considered that, given the age range covered by the guideline, the total daily insulin dose would vary between 10 and 100 units. For cost purposes a total daily insulin dose of 50 units was assumed as this was thought to be a reasonable approximation of the modal daily dose. It was assumed that 2 units of insulin would be wasted per injection as airshots.

Estimating the annual number of prefilled disposable pens for twice daily (mixed) injections

It is assumed that each injection uses 27 units including 2 units as airshots. Each pen has 300 units in total.

Number of injections per pen[g]: 300÷27≈11 injections

Pen life: 11÷2=5.5 days

Pens per year: 365÷5.5≈66 pens

[g] With 3 wasted units when the pen is close to empty (11×27=297 units)

Estimating the annual number of prefilled disposable pens for 3-times daily (mixed) injections

It is assumed that each injection uses 19 units including 2 units as airshots. Each pen has 300 units in total.

Number of injections per pen[h]: 300÷19≈15 injections

Pen life: 15÷3=5 days

Pens per year: 365÷5=73 pens

Estimating the annual number of pre-filled disposable pens for multiple daily injections

It is assumed that a child or young person with type 1 diabetes would be on a daily dose of 25 units of short-acting insulin which would be taken as 4 injections. Therefore it was assumed that each injection would use 8 units including 2 units as airshots. Each pen has 300 units in total.

Number of injections per short-acting pen[i]: 300÷8≈37 injections

Short-acting pen life: 37÷4=9 days

Short-acting pens per year: 365÷9≈41 pens

It is also assumed that the child or young person would be on a daily dose of 25 units of long-acting insulin which would be taken as a single injection. Therefore it was assumed that each injection would use 27 units including 2 units as airshots. Each pen has 300 units in total.

Number of injections per long-acting pen[j]: 300÷27≈11 injections

Long-acting pen life: 11÷1=11 days

Long-acting pens per year: 365÷11≈33 pens

19.3.1.1.3 Overall treatment costs

The overall costs of 2- or 3-times daily injections and MDI regimens are summarised in Table 73 and Figure 1.

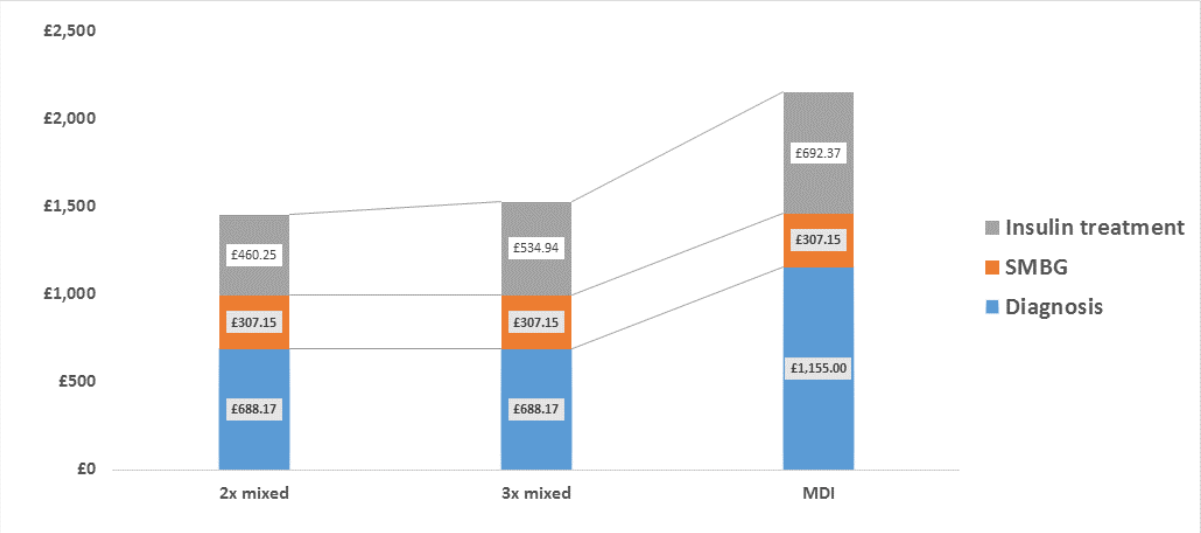
Table 73: First year treatment costs 2- or 3-times daily injections and multiple daily injection regimens

Category	2-times daily	3-times daily	Multiple daily injections
Staffing	£688	£688	£1,155
Consumables - insulin	£460	£535	£692
Consumables - SMBG	£307	£307	£307
Total	£1,456	£1,530	£2,155

SMBG self monitoring blood glucose

[h] With 15 wasted units when the pen is close to empty (15×19=285 units)
[i] With 4 wasted units when the pen is close to empty (37×8=296 units)
[j] With 3 wasted units when the pen is close to empty (11×27=297 units)

Figure 1: : Graph showing treatment costs of 2- or 3-times daily injections and multiple daily injections



Source: Costing tool developed for the 2015 update

In the cost effectiveness model described in Section 19.3.2, a treatment cost is required for the first year of treatment and for subsequent years. For the first year treatment costs the model uses the total costs for MDI and 3-times daily mixed insulin as shown in Table 73. For subsequent years the treatment cost is assumed to be given by the consumables costs (insulin and SMBG) shown in Table 73, which is £999 for MDI and £842 for mixed insulin.

In the review protocol (see Appendix E:) mixed insulin was defined as fewer than 4 injections per day. For costing purposes a 3-times daily injection was assumed as this more closely resembles current practice and it reflects the comparator used in the study that was used to estimate the effectiveness of MDI in the cost effectiveness model (Adhikari 2009).

19.3.2 Using the IMS Core Diabetes Model to assess the cost effectiveness of multiple daily injections versus mixed insulin injections

19.3.2.1 Reasons for using the IMS Core Diabetes Model

Type 1 diabetes is an incurable condition with potential implications for health-related quality of life and longevity. Data from trials and observational studies are insufficient to quantify these long-lasting effects. However, the health economic approach adopted in the IMS Core Diabetes Model allows the effects to be modelled by taking data from a wide variety of sources and synthesising them to estimate the lifelong consequences and costs of comparator interventions.

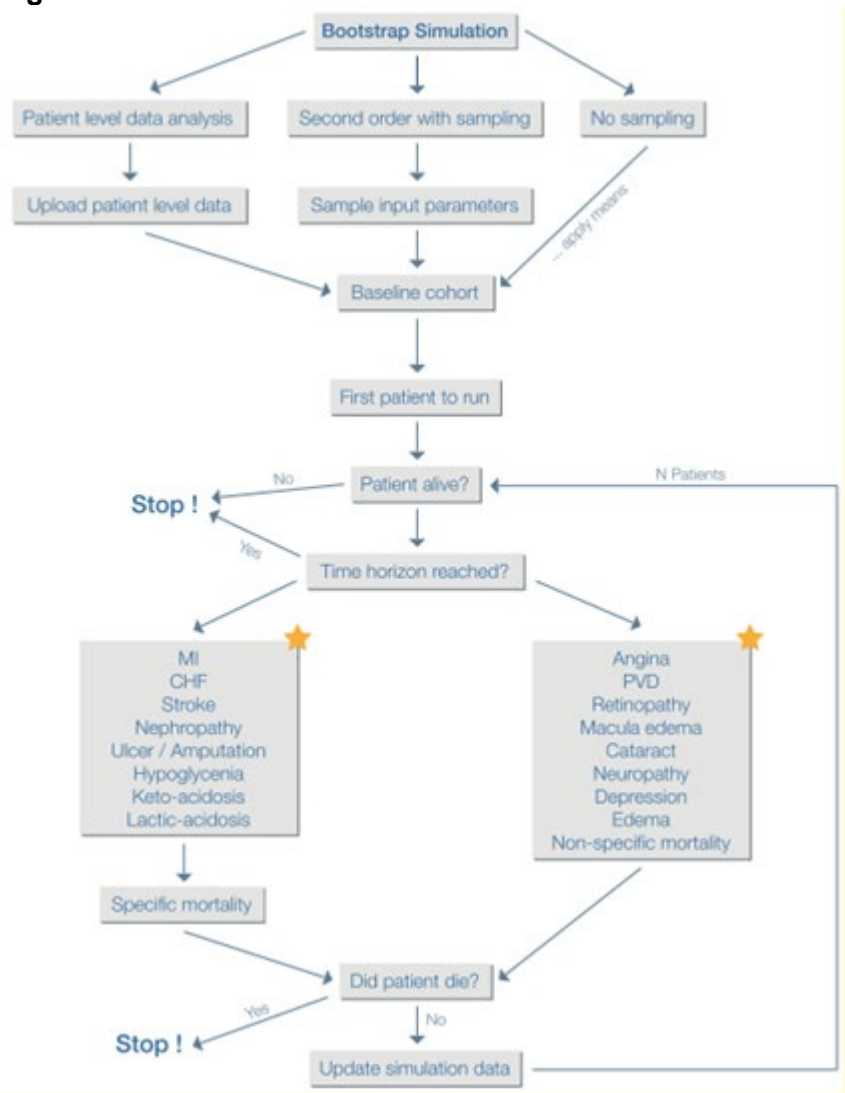
Type 1 diabetes is a condition with many complications and associated comorbidities. Within the timeframe of a clinical guideline it was not possible to model the complex lifetime relationships and therefore the decision was taken across all NICE diabetes guidelines being updated in 2015 to use a bespoke model which was already in use and had been validated. A validation study of the IMS Core Diabetes Model has been recently published (McEwan 2014). Furthermore, the IMS Core Diabetes Model has been used previously in NICE Technology Appraisals (NICE 2008) and therefore its use can be considered to promote a

consistent methodological approach to the evaluation of the cost effectiveness of interventions used for type 1 diabetes.

19.3.2.2 IMS Core Diabetes Model approach

The IMS Core Diabetes Model has been described in more detail elsewhere (Palmer 2004). The basic structure of the model is shown in Figure 2.

Figure 2: Schematic of model structure



Source: IMS health (reproduced with permission)

The model is accessed through the Internet and can be used to assess a wide variety of interventions in hypothetical cohorts of patients with either type 1 or type 2 diabetes. The model has a modular format with input parameters across a wide range of patient, clinical and economic characteristics. The input parameters used in this analysis are shown in Section 19.3.2.3.

The IMS Core Diabetes Model consists of 17 interdependent submodels, as shown in Figure 2, as part of a Markov modelling approach. In Markov models patients can be in one of a number of defined but mutually exclusive 'health states'. Over time, or 'cycles', patients may transition to different health states. The developers of the IMS Core Diabetes Model have argued, especially in the context of diabetes, that this may not be realistic as patients can have any number of complications at the same time. To overcome this, the 17 submodels

run in parallel allowing patients to develop multiple complications simultaneously across the duration of the simulation.

The model uses Monte Carlo simulation with results for 1000 patients simulated over 1000 iterations. At the start of an iteration, which in this model is at the point of diagnosis, a patient is assigned a number of characteristics such as HbA1c and systolic blood pressure. The patient's health state is them simulated over a maximum period of 90 years[k]. At various points in the model the patient encounters 'chance nodes' where their progress – death, for example – is determined by a random number generator. Therefore, each patient in each iteration has a 'random walk' through the model. In each iteration summary data exist for the hypothetical cohort of 1000 patients and when the simulation has been run this summary exists across 1000 simulations from which summary results are then generated, such as mean QALYs and costs.

Non-parametric bootstrapping methods are used to sample from input parameter distributions where these have been specified with a non-zero standard deviation (SD). Cost effectiveness is presented as a ratio[l] and therefore standard methods, such as univariate confidence intervals (CIs), cannot be used to quantify uncertainty around the point estimate. Bootstrapping is a statistical technique for estimating uncertainty of an estimator by repeat sampling from the original sample with replacement. This provides repeated estimates of cost and effect pairs from the MDI and 3-times daily injection interventions. The mean values of these estimates can then be used to calculate incremental cost effectiveness ratios (ICERs) underpinned by the underlying distribution of cost effectiveness. A more detailed description of the approach to probabilistic sensitivity analysis in the IMS Diabetes Core Model is described in more detail elsewhere (IMS CORE Diabetes Model Research Team and IMS Health Economics and Outcomes Research 2014, available from www.core-diabetes.com/).

Within the IMS Core Diabetes Model a number of approaches can be used to estimate QALYs, all of them derived as functions of the diabetes complications experienced in each year of the model along with any acute events that occur. The method presented here is the 'Core default (minimum approach)'. In this method, if a patient has multiple events within 1 year the lower of the multiple health state utility values is used.

19.3.2.3 Model inputs

The various inputs into the base-case model are described below in Section 19.3.2.3.1 to Section 19.3.2.3.6.

19.3.2.3.1 Model population

The model was run for a population of young people aged 12 years. The incidence of type 1 diabetes follows a bimodal distribution (Felner 2005) with an initial peak in between 4 to 6 years and a bigger peak between 10 to 14 years. Therefore, the guideline development group considered that an age of 12 years at diagnosis was a reasonable age on which to base the model. The group did not consider that sampling from an age distribution would be particularly helpful as age at diagnosis would be unlikely to be an important driver of cost effectiveness given that type 1 diabetes is an incurable, lifelong condition and therefore all young people with type 1 diabetes are likely to derive similar long-term benefits from an intervention that is effective over their remaining lifespan.

The full baseline characteristics of the model population are given in Table 74.

[k] Many patients will die within the timeframe of the model
[l] Costs ÷ effects

Table 74: Model baseline characteristics

Characteristic	Value	Standard deviation	Source
Patient demographics			
Age (years)	12.0	0 years	Guideline development group
Diabetes duration (years)	0.0	0 years	Model is 'from diagnosis'
Proportion male	0.512	-	ONS 2011
Proportion white[a]	0.812	-	ONS 2011
Proportion black[a]	0.045	-	ONS 2011
Proportion Asian/other[a]	0.143	-	ONS 2011
Baseline risk factors			
HbA1c	11.4%	1.9%	Adhikari 2009
SBP	110 mmHg	-	Guideline development group
T-CHOL	162 mg/dl	30.9 mg/dl	Edge 2008
HDL	58 mg/dl	14.7 mg/dl	Edge 2008
LDL	81 mg/dl	23.2 mg/dl	Edge 2008
TRIG	115 mg/dl	92 mg/dl	Edge 2008
BMI	19 kg/m^2	-	RCPCH
eGFR	120 ml/min/1.73 m^2	-	Guideline development group
HAEM	14 g/dl	-	Guideline development group
WBC	6.8 106/ml	-	CORE default
Heart rate	85 bpm	-	Guideline development group
Proportion smoker	0.06	-	Guideline development group
Cigarettes/day	0	-	Guideline development group
Alcohol consumption	0 ml/week	-	Guideline development group
CVD complications			
Proportion myocardial infarction	0	-	Guideline development group
Proportion angina	0	-	Guideline development group
Proportion PVD	0	-	Guideline development group
Proportion stroke	0	-	Guideline development group
Proportion heart failure	0	-	Guideline development group
Proportion atrial fibrillation	0	-	Guideline development group
Proportion LVH	0	-	Guideline development group
Renal complications			
Proportion MA	0	-	Guideline development group
Proportion GRP	0	-	Guideline development group
Proportion ESRD	0	-	Guideline development group
Retinopathy complications			
Proportion BDR	0	-	Guideline development group
Proportion PDR	0	-	Guideline development group
Proportion SVL	0	-	Guideline development group
Macular oedema			
Proportion ME	0	-	Guideline development group

BDR background diabetic retinopathy, CVD cardiovascular disease, eGFR estimated glomerular filtration rate, ESRD end stage renal disease, GRP gross proteinuria, HAEM haemoglobin, HbA1c glycated haemoglobin, HDL high-density lipoprotein, LDL low-density lipoprotein, LVH left ventricular hypertrophy, MA microalbuminuria, ME macular oedema, PDR proliferative diabetic retinopathy, PVD peripheral vascular disease, SBP systolic blood pressure, SVL severe visual loss, T-CHOL total cholesterol, TRIG triglycerides, WBC white blood cell
a. These data about children and young people aged 10 to 14 years in England and Wales are taken from the UK 2011 census

Within the IMS Core Diabetes Model these input parameters are defined in the 'Cohort module'. These parameters can be considered as falling into 1 of 2 types:

- continuous – for example HbA1c at baseline
- proportions – for example gender (in this case the characteristic of each patient in the simulation is generated randomly according to the proportion specified; so a patient in the model has a 51.2% chance of being male based on the reported proportion of males in the 10 to 14 age group in England and Wales).

19.3.2.3.2 Costs

The costs, other than costs associated with treatment (MDI or 3-times daily insulin injections in this case), are presented in Table 75. Costs were discounted at 3.5% per year as per the NICE Reference Case. A 20% variation in costs, the model default, was used for sampling in PSA.

Table 75: Model costs

Item	Cost	Source
Management		
Statins	£38.22	Atorvastatin 80 mg 28 days. MIMS January 2013
Aspirin	£13.70	Following ischemic event; 75 mg 28 days. MIMS November 2013
ACE inhibitors	£18.54	Average cost of 5 generics; MIMS August 2013
Screening for MA	£3.02	Weighted: 80% once per year; 20% 3 times per year; unit cost £2.16 Lamb 2009
Screening for GRP	£2.91	2 per year; unit cost £1.42 Lamb 2009 Inflated to 2013 costs
Stopping ACE due to side effects	£19.96	28 days of Angiotensin receptor antagonist (losartan 50 mg or candesartan 8 mg). NHS Commercial Medicines Unit, 2011
Eye screening	£35	Based on annual national cost of £70m for 2 million diabetics screen once per year (based on personal communication with UK National Screening Committee, Dec 2013)
Foot screening programme	£42	Podiatrist outpatient visit, NHS reference cost 2012/13
Non-standard ulcer treatment (e.g. Regranex)	£0	IMS default value (Regranex has been discontinued in the UK)
Anti-depression treatment	£489	Type 1 diabetes update guideline development group
Screening for depression[a]	£0	
CVD complications		
Myocardial infarction: 1st year	£3,731	NICE Lipids guideline, CG181
Myocardial infarction; subsequent years	£788	NICE Lipids guideline, CG181

Item	Cost	Source
Angina: 1st year[b]	£6,406	NICE Lipids guideline, CG181
Angina: subsequent years[b]	£288	NICE Lipids guideline, CG181
CHF: 1st year	£3,596	NICE Lipids guideline, CG181
CHF: subsequent years	£2,597	NICE Lipids guideline, CG181
Stroke: 1st year	£4,170	NICE Lipids guideline, CG181
Stroke: subsequent years	£155	NICE Lipids guideline, CG181
Stroke death within 30 days	£1,174	NICE Lipids guideline, CG181
PVD: 1st year	£952	NICE Lipids guideline, CG181
PVD: subsequent years	£529	NICE Lipids guideline, CG181
Renal complications		
Haemodialysis: 1st year[c]	£30,480	NICE Peritoneal Dialysis clinical guideline, CG125
Haemodialysis: subsequent years[c]	£30,480	NICE Peritoneal Dialysis clinical guideline, CG125
PD: 1st year[c]	£24,520	NICE Peritoneal Dialysis clinical guideline, CG125
PD: subsequent years [c]	£24,520	NICE Peritoneal Dialysis clinical guideline, CG125
Renal transplant: 1st year[c]	£20,373	NICE Peritoneal Dialysis clinical guideline, CG125
Renal transplant: subsequent years[c]	£7,609	NICE Peritoneal Dialysis clinical guideline, CG125
Acute events		
Major hypoglycaemia	£333	Hammer 2009 Inflated to 2013 costs
Minor hypoglycaemia[d]	£0	
Ketoacidosis event	£0	This parameter was not used in the model as no data were available on ketoacidosis event rates associated with the interventions compared in the economic analyses.
Lactic acid event	£0	Assumed no cost of management required (expert opinion)
Oedema onset (adv.ev.)	£0	Assumed no cost of management required (expert opinion)
Oedema follow up (adv.ev)	£0	Assumed no cost of management required (expert opinion)
Eye disease		
Laser treatment	£697	NHS Reference Costs 2012/13
Cataract operation	£1024	NHS Reference Costs 2012/13
Following cataract operation	£80	NHS Reference Costs 2012/13
Blindness: year of onset	£5585	NHS Reference Costs 2012/13
Blindness: subsequent years	£5396	NHS Reference Costs 2012/13
Neuropathy/foot ulcer/amputation		
Neuropathy: 1st year	£362	MIMS April 2014 (online version), Duloxetine 60 mg daily (first-line treatment in CG96) – IMS default value
Neuropathy: subsequent years	£362	MIMS April 2014 (online version), Duloxetine 60 mg daily (first-line treatment in CG96) – IMS default value
Amputation (event based)	£11,290	NICE Lower limb peripheral arterial disease (PAD) clinical guideline (CG147)
Amputation prosthesis (event based)	£15,250	NICE Lower limb peripheral arterial disease (PAD) clinical guideline (CG147)

Item	Cost	Source
Gangrene treatment[e]	£5,483	Ghatnekar 2002
After healed ulcer[e]	£266	Ghatnekar 2002
Infected ulcer	£7,328	https://www.diabetes.org.uk/Documents/nhs-diabetes/footcare/footcare-for-people-with-diabetes.pdf
Standard uninfected ulcer	£4,070	https://www.diabetes.org.uk/Documents/nhs-diabetes/footcare/footcare-for-people-with-diabetes.pdf
Healed ulcer history of amputation	£25,296	NICE 2012 (CG 147)

ACE angiotensin-converting-enzyme, CHF chronic heart failure, CVD cardiovascular disease, GRP gross proteinuria, MA macular oedema, MIMS Monthly Index of Medical Specialties, PVD peripheral vascular disease
a. Part of standard management
b. For the cost of angina it was assumed that one-third of angina episodes would be unstable and two-thirds would be stable
c. Costs updated using the Hospital and Community Health Services (HCHS) index 2012/13(d)
d. Assumed that child and young person deals with this at home without incurring any costs to NHS
e. Inflated to 2014 value

The costs of treatment are presented in Table 76. Section 19.3.1 described how these costs were derived.

Table 76: Model treatment cost in first year following diagnosis and in subsequent years

Treatment	Cost	Source
MDI: 1st year	£2,154	Calculated (see Section 19.3.2.3.2)
MDI: subsequent years	£999	Calculated (see Section 19.3.2.3.2)
Mixed: 1st year	£1,530	Calculated (see Section 19.3.2.3.2)
Mixed: subsequent years	£842	Calculated (see Section 19.3.2.3.2)

MDI multiple daily injections
a. *Mixed is for 3-times daily injections*

19.3.2.3.3 Health state utilities

Within the IMS Core Diabetes Model are a number of health states, each of which has a health state utility attached. The health state utility is used to derive a QALY for each simulated patient where each health state utility is multiplied by the number of years lived in that state. Table 77 shows the health state utilities associated with model states and events. Event utilities are negative because they indicate that a lower health state utility will be experienced compared with the scenario where no such adverse event had occurred.

The CORE default method (minimum approach) was used. In this approach, if a patient has a history of multiple events, the model uses the lowest health state utility from the relevant comorbidities. This assumes that the other conditions will have a negligible further impact on quality of life over and above the most severe condition.

Table 77: Model health state utilities

State/event	Value	SD	Source
Type 1 no complications	0.814	0	Clarke 2002
Myocardial infarction event	−0.055	0.01	Beaudet 2014
Post myocardial infarction	0.759	0.01	Beaudet 2014
Angina	0.695	0.01	Beaudet 2014
CHF	0.677	0.01	Beaudet 2014
Stroke event	−0.164	0.01	Beaudet 2014

State/event	Value	SD	Source
Post stroke	0.65	0.01	Beaudet 2014
PVD	0.724	0.01	Beaudet 2014
MA	0.814	0.01	Assume equal to baseline
GRP	0.737	0.01	Beaudet 2014
Haemodialysis	0.621	0.03	Beaudet 2014
PD	0.581	0.03	Beaudet 2014
Renal transplant	0.762	0.12	Beaudet 2014
BDR	0.745	0.02	Beaudet 2014
BDR wrongly treated	0.745	0.02	Assume equal to BDR
PDR laser treated	0.715	0.02	Beaudet 2014
PDR no laser	0.715	0.02	Assume equal to PDR
ME	0.745	0.02	Beaudet 2014
SVL	0.711	0.01	Beaudet 2014
Cataract	0.769	0.02	Beaudet 2014
Neuropathy	0.701	0.01	Beaudet 2014
Healed ulcer	0.814	0.01	Assume equal to baseline
Active ulcer	0.615	0.01	Beaudet 2014
Amputation event	−0.28	0.01	Beaudet 2014
Post amputation	0.534	0.01	Beaudet 2014
Major hypoglycaemia events	−0.012	0	Beaudet 2014
Minor hypoglycaemia events	0	0	Beaudet 2014
Ketoacidosis event	0	0	No data
Lactic acid event	0	0	No data
Fear of hypoglycaemia event	0	0	No data
Oedema event (adv.ev.)	−0.04	0.006	Matza 2007
Post oedema (adv.ev.)	0.814	0.01	Beaudet 2014
Depression not treated	0.6059	0	Goldney 2004
Depression treated	0.814	0	No data

BDR background diabetic retinopathy, CHF chronic heart failure, GRP gross proteinuria MA microalbuminuria, ME macular oedema (edema), PD peritoneal dialysis, PDR Proliferative diabetic retinopathy, PVD peripheral vascular disease, SD standard deviation, SVL severe visual loss
a. Where 'No data' is indicated the model uses the health state utility for type 1 diabetes with no complications

19.3.2.3.4 Ongoing management

Table 78 shows input parameters that relate to various facets of the ongoing management of type 1 diabetes.

Table 78: Management inputs

Category	Proportion/value	Source
Concomitant mediation		
Primary prevention – aspirin	0.456	Minshall 2008
Secondary prevention – aspirin	0.755	The Action to Control Cardiovascular Risk in Diabetes Study Group 2008
Primary prevention – statins	0.450	Minshall 2008
Secondary prevention – statins	0.878	The Action to Control Cardiovascular Risk in Diabetes Study Group 2008

Category	Proportion/value	Source
Primary prevention – ACE inhibitors	0.500	Minshall 2008
Secondary prevention – ACE inhibitors	0.708	The Action to Control Cardiovascular Risk in Diabetes Study Group 2008
Screening and patient management		
Foot ulcer prevention programme	0.992	National Diabetes Audit
Screened for eye disease	1.000	Ismail-Bergi 2010
Screened for renal disease	1.000	Ismail-Bergi 2010
Receiving intensive insulin after myocardial infarction	0.877	Mcmullin 2004
Treated with extra ulcer treatment	0.570	Lyon 2008
Screened for depression – no complications	0.830	Jones 2007
Screened for depression – complications	0.830	Jones 2007
Other		
Reduction in incidence of follow-up with preventative programme	0.310	O'Meara 2004
Improvement in ulcer healing rate with extra ulcer treatment	1.390	Kantor 2001
Reduction in amputation rate with footcare	0.340	O'Meara 2004
Sensitivity eye screening	0.920	Lopez-Bastida 2007
Specificity eye screening	0.960	Lopez-Bastida 2007
Sensitivity GRP screening	0.830	Cortes 2006
Specificity MA screening	0.830	Cortes 2006
Specificity MA screening	0.960	Cortes 2006

ACE angiotensin-converting-enzyme, GRP gross proteinuria, MA microalbuminuria
a. These values are based on adult population but cannot be varied by age in the model

19.3.2.3.5 Clinical inputs

These inputs in the IMS Core Diabetes Model come under what is termed the 'clinical' module and they are intended to capture the natural history of the disease, to reflect the relationships between risks and events and impact of interventions on risk.

Inputs entered as a proportion indicate the proportion of the simulated cohort who will experience a particular condition. So, for example, the value for 'Proportion initial CHD event MI female' would give the proportion of women who experienced a myocardial infarction as their first cardiovascular event. In addition, various risk adjustments can be varied as part of the clinical module.

Various clinical input parameters in the model are shown in Table 79 to Table 91.

Table 79: HbA1c adjustments

Event	Risk reduction	Source
10% lower HbA1c BDR intensive	39%	DCCT 1996
10% lower HbA1c BDR conventional	34%	DCCT 1996
10% lower HbA1c PDR intensive	43%	DCCT 1996
10% lower HbA1c PDR conventional	37%	DCCT 1996
10% lower HbA1c SVL intensive	0%	No data
10% lower HbA1c SVL conventional	0%	No data
10% lower HbA1c ME intensive	13%	Klein 2009
10% lower HbA1c ME conventional	13%	Klein 2009

Event	Risk reduction	Source
10% lower HbA1c MA intensive	28%	DCCT 1996
10% lower HbA1c MA conventional	24%	DCCT 1996
10% lower HbA1c GRP intensive	37%	DCCT 1996
10% lower HbA1c GRP intensive	47%	DCCT 1996
10% lower HbA1c ESRD intensive	21%	Rosolowsky 2011
10% lower HbA1c ESRD conventional	21%	Rosolowsky 2011
10% lower HbA1c neuropathy intensive	32%	DCCT 1996
10% lower HbA1c neuropathy conventional	29%	DCCT 1996
1%-point lower HbA1c MI	20%	Nathan 2005
1%-point lower HbA1c cataract	0%	Grauslund 2011
1%-point lower HbA1c HF	23%	Lind 2011
1%-point lower HbA1c stroke	20%	Nathan 2005
1%-point lower HbA1c angina	20%	Nathan 2005
1%-point lower HbA1c – haemodialysis mortality	12%	Morioka 2001
1%-point lower HbA1c – PD mortality	12%	Morioka 2001
1%-point lower HbA1c – renal transplant mortality	0	Wiesbauer 2010
1%-point lower HbA1c – 1st ulcer	17%	Monami 2009

BDR background diabetic retinopathy, ESRD end stage renal disease, GRP gross proteinuria, HbA1c glycated haemoglobin, HF heart failure, MA microalbuminuria, ME macular oedema (edema), MI myocardial infarction, PD peritoneal dialysis, PDR proliferative diabetic retinopathy, SVL severe visual loss

Table 80: Systolic blood pressure adjustments

Event	Risk reduction	Source
10 mmHg lower SBP all micro T1	13%	Adler 2000
10 mmHg lower SBP SVL T1	0%	No data

SBP systolic blood pressure, SVL severe visual loss

Table 81: Myocardial infarction

Event/variable	Value	Source
Proportion intensive CHD event MI female	0.361	D'Agostino 2000
Proportion intensive CHD event MI male	0.522	D'Agostino 2000
Proportion subsequent CHD event MI female	0.474	D'Agostino 2000
Proportion subsequent CHD event MI male	0.451	D'Agostino 2000
Increased risk MI if MA	1	IMS Core default
Increased risk MI if GRP	1	IMS Core default
Increased risk MI if ESRD	1	IMS Core default
Multiplier for risk recurrent MI if DIGAMI intensive control	1	No data
Multiplier for risk post MI mortality if DIGAMI intensive control	1	No data
Multiplier aspirin primary MI	0.82	Antithrombotic Trialists' (ATT) Collaboration 2009
Multiplier aspirin secondary MI	0.80	Antithrombotic Trialists' (ATT) Collaboration 2009
Multiplier statins primary MI	0.70	Brugts 2009
Multiplier statins secondary MI	0.81	Shepherd 2002

Event/variable	Value	Source
Risk reduction with ACE 1st MI	0.78	Heart Outcomes Prevention Evaluation (HOPE) Study Investigators 2000
Risk reduction with ACE recurrent MI	0.78	Heart Outcomes Prevention Evaluation (HOPE) Study Investigators 2000

ACE angiotensin-converting-enzyme inhibitor, CHD cardiovascular heart disease, DIGAMI Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction, ESRD end stage renal disease, GRP gross proteinuria, MA microalbuminuria, MI myocardial infarction

Table 82: Myocardial infarction mortality

Event/variable	Value	Source
Probability sudden death 1st MI male	0.393	Sonke 1996
Probability sudden death 1st MI female	0.364	Sonke 1996
Probability death recurrent MI male	0.393	Sonke 1996
Probability death recurrent MI female	0.364	Sonke 1996
Multiplier 12 month mortality MI conventional treatment	1.45	Malmberg 1995
Multiplier aspirin mortality 1st year MI	0.88	Antiplatelet Trialists' Collaboration 1994
Multiplier aspirin subsequent years MI	0.88	Antiplatelet Trialists' Collaboration 1994
Multiplier statin mortality 1st year MI	0.75	Stenestrand 2001
Multiplier statin subsequent years MI	1	No data
Multiplier aspirin sudden death MI	1	No data
Multiplier statin sudden death MI	1	Briel 2006
Multiplier ACE inhibitor sudden death MI	1	No data
Risk reduction with ACE MI long term mortality	0.64	Gustafsson 1999
Risk reduction with ACE MI 12 month mortality	0.64	Gustafsson 1999

ACE angiotensin-converting-enzyme inhibitor, MI myocardial infarction

Table 83: Stroke

Variable	Value	Source
Multiplier stroke MA	1	IMS Core default
Multiplier stroke GRP	1	IMS Core default
Multiplier stroke ESRD	1	IMS Core default
Multiplier aspirin primary stroke	0.86	Antithrombotic Trialists' Collaboration 2009
Multiplier aspirin secondary stroke	0.78	Antithrombotic Trialists' Collaboration 2009
Multiplier statin primary stroke	0.81	Brugts 2009
Multiplier statin secondary stroke	0.84	The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators 2006
Risk reduction with ACE 1st stroke	0.67	Heart Outcomes Prevention Evaluation (HOPE) Study Investigators 2000
Risk reduction with ACE rec stroke	0.72	PROGRESS Collaborative Group 2001

ACE angiotensin-converting-enzyme inhibitor, ESRD end stage renal disease, GRP gross proteinuria, MA microalbuminuria

Table 84: Stroke mortality

Event/variable	Value	Source
Probability 30-day death 1st stroke male	0.124	Eriksson 2001
Probability 30-day death 1st stroke female	0.124	Eriksson 2001
Probability 30-day death recurrent stroke male	0.422	Eriksson 2001
Probability 30-day death recurrent stroke female	0.422	Eriksson 2001
Multiplier aspirin mortality 1st stroke	0.84	Antiplatelet Trialists' Collaboration 1994
Multiplier aspirin mortality subsequent stroke	0.84	Antiplatelet Trialists' Collaboration 1994
Multiplier statin mortality 1st stroke	1	Manktelow 2009
Multiplier statin mortality subsequent stroke	1	Manktelow 2009
Multiplier aspirin sudden death stroke	0.95	Sandercock 2008
Multiplier statin sudden death stroke	1	Briel 2006
Multiplier ACE inhibitor sudden death stroke	0.49	Chitravas 2007
Risk reduction with ACE stroke long term mortality	1	Asberg 2010
Risk reduction with ACE stroke 12 month mortality	1	Asberg 2010

ACE angiotensin-converting-enzyme inhibitor

Table 85: Heart failure

Event/variable	Value	Source
Increased risk if MA	1	IMS Core default
Increased risk if GRP	1	IMS Core default
Increased risk if ESRD	1	IMS Core default
Risk reduction if aspirin	1	No data
Risk reduction if statin	1	No data
Risk reduction if ACE inhibitor	0.8	Heart Outcomes Prevention Evaluation (HOPE) Study Investigators 2000
Risk reduction death if ACE inhibitor	0.8	Ascencao 2008
Multiplier death male	1	Ho 1993
Multiplier death female	1.7	Ho 1993

ACE angiotensin-converting-enzyme inhibitor, ESRD end stage renal disease, GRP gross proteinuria, MA microalbuminuria

Table 86: Angiotensin converting enzyme inhibitor adjustments for microvascular complications

Event	Risk reduction	Source
BDR	0.75	Chaturvedi 1998
PDR	0.19	Chaturvedi 1998
ME	1	No data
SVL	1	No data
No ≥MA	0.79	Penno 1998
MA ≥GRP	0.41	Penno 1998
GRP ≥ESRD	0.63	Lewis 1993

Event	Risk reduction	Source
Neuropathy	1	No data

BDR background diabetic retinopathy, ESRD end stage renal disease, GRP gross proteinuria, MA microalbuminuria, ME macular oedema (edema), PDR proliferative diabetic retinopathy, SVL severe visual loss

Table 87: Angiotensin converting enzyme inhibitor side effects

Event	Probability	Source
Side effects stopping ACE inhibitors subsequent years	0	IMS Core default
Side effects stopping ACE inhibitors 1st year	0	IMS Core default

ACE angiotensin-converting-enzyme inhibitor

Table 88: Probability of adverse events

Event	Probability	Source
Death – major hypo	0	IMS Core default
Death – ketoacidosis	0.027	Maclsaac 2002
Death – lactic acidosis	0.43	Campbell 1985
Increased risk of major hypo with ACE inhibitor	1	IMS Core default

ACE angiotensin-converting-enzyme inhibitor

Table 89:Foot ulcer and amputation

Event	Probability	
Gangrene to amputation with gangrene	0.1818	Persson 2000
Gangrene to healed amputation	0.3082	Persson 2000
Death following onset of gangrene	0.0098	Persson 2000
Death with history of amputation	0.004	Persson 2000
Death following healed ulcer	0.004	Persson 2000
Developing recurrent uninfected ulcer	0.0393	Persson 2000
Amputation following infected ulcer	0.0037	Persson 2000
Infected ulcer ≥amputation healed	0.0445	Persson 2000
Infected ulcer ≥death	0.0098	Persson 2000
Infected ulcer ≥gangrene	0.0075	Persson 2000
Infected ulcer ≥uninfected ulcer	0.1397	Persson 2000
Recurrent amputation	0.0084	Borkosky 2012
Uninfected ulcer ≥death	0.004	Persson 2000
Uninfected ulcer ≥gangrene	0.0473	Persson 2000
Uninfected ulcer ≥healed ulcer	0.0787	Persson 2000
Developing ulcer with neither neuropathy or PVD	0.00025	Ragnarson 2001
Developing ulcer with either neuropathy or PVD	0.006092	Ragnarson 2001
Developing ulcer with both neuropathy and PVD	0.006092	Ragnarson 2001

PVD peripheral vascular disease

Table 90: Depression

Variable	Value	Source
Multiplier for all cause death if depression	1.33	Egede 2005
Multiplier for CHF if depression	1	No data
Multiplier MI if depression	1	No data
Multiplier for depression if neuropathy	3.1	Yoshida 2009
Multiplier for depression if stroke	6.3	Whyte 2004
Multiplier for depression if amputation	1	No data

CHF chronic heart failure, MI myocardial infarction

Table 91: Other

Event	Probability	Source
BDR ≥SVL	0.0148	IMS Core default
Reversal of neuropathy	0	No data

BDR background diabetic retinopathy, SVL severe visual loss

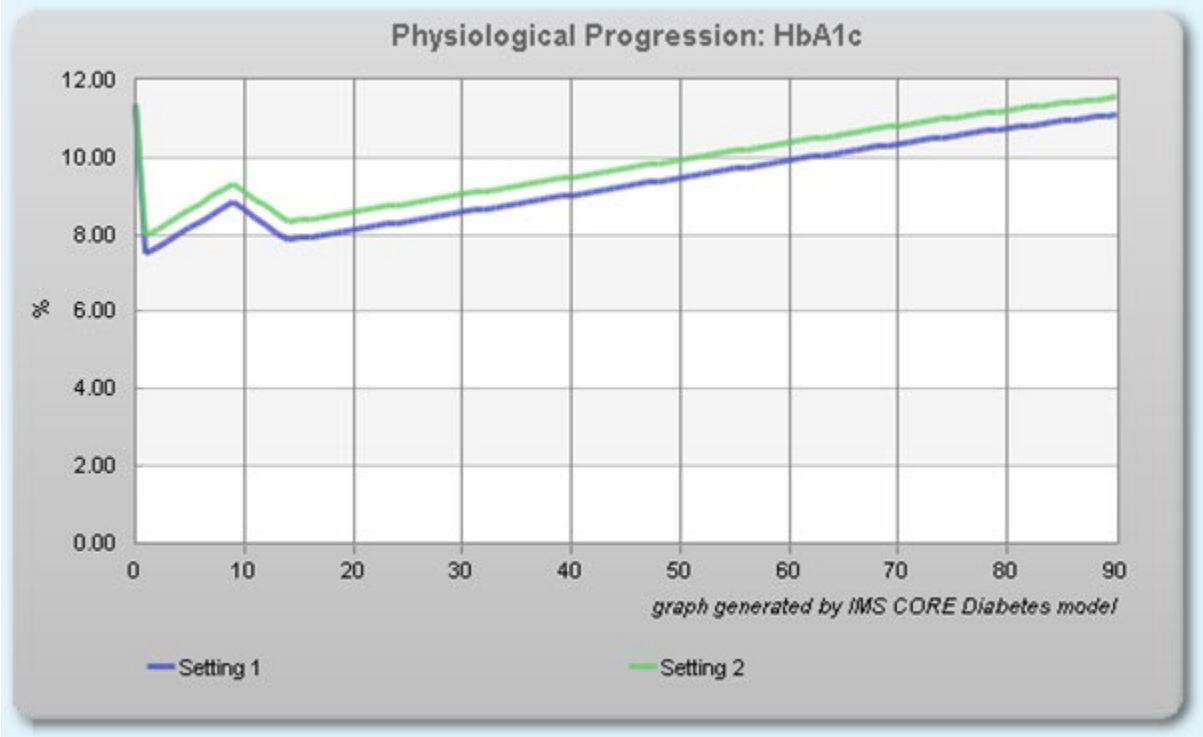
In addition there are a number of input parameters governing transition probabilities for renal disease, eye disease, cardiovascular disease (CVD) and depression. There are probability inputs for non-specific mortality and physiological parameter progression tables. Existing values within the IMS Core Diabetes Model were used for all of these inputs with the exception of HbA1c progression which was modified in line with guideline development group opinion to better reflect the progression of this parameter in childhood. The progression specified is shown in Table 92 and in Figure 3.

Table 92: HbA1c progression for type 1 diabetes

Index	Value
0	0.17
9	−0.2
14	0.045

a. Index denotes the year and progression changes by the value indicated until a time point is identified when a different annual rate of regression is specified

Figure 3: HbA1c progression for multiple daily injections (setting 1) and 3-times daily (mixed) injections (setting 2)



Setting 1: multiple daily injections
Setting 2: 3-times daily (mixed) injections

19.3.2.3.6 Treatment

The change in HbA1c as a result of treatment was based on a study that was included in the clinical review of the evidence undertaken for this guideline (Adhikari 2009). In this study, the 3-times daily injections group received mixed intermediate-acting insulin (neutral protamine Hagedorn, NPH) and rapid-acting insulin (lispro or aspart) at breakfast, rapid-acting insulin (lispro or aspart) at dinner and intermediate-acting insulin (NPH) at bedtime. Those on multiple daily injections received rapid-acting insulin (lispro or aspart) at mealtimes and a long-acting insulin (glargine) at bedtime. The guideline development group noted that different insulins were used in the different arms of the study, but the group's view was that although glargine may offer marginal benefit with respect to nocturnal hypoglycaemia, there is little evidence of sustained benefit in terms of improved HbA1c. The group also noted that glargine cannot be mixed with fast-acting insulin, meaning that it could not be used in a twice or 3-times daily (mixed) regimen. It is therefore impossible to truly compare like with like. Different insulins are a feature of the different injection regimens and the guideline development group therefore considered the study valid to inform the health economic model.

The change in HbA1c reported in this study between the MDI intervention and 3-times daily injections (mixed) from baseline at 12 months was used as the treatment efficacy. The inputs for treatment efficacy are outlined in Table 93 and are also shown graphically in Figure 3.

Table 93: Change in baseline HbA1c

Intervention	Mean change	Standard deviation	Source
MDI	−3.9% points	1.6% points	Adhikari 2009
Mixed	−3.4% points	1.6% points	Adhikari 2009

MDI multiple daily injections
a. 'Mixed' refers here to an intervention where insulin injections are given 3 times daily

Within the IMS Core Diabetes Model these inputs occur within a 'Treatment Module'. Within that module it was specified that the MDI intervention should have 'intensive' insulin therapy and that 3-times daily injections should have 'conventional' insulin therapy. Also specified in the treatment module was that 'Framingham progression' should be used for systolic blood pressure, total cholesterol, low density lipoprotein, high density lipoprotein and triglycerides. Adverse events were also specified for each treatment as outlined in Table 94. The guideline development group noted that it was not possible to adjust these adverse events by age and instead set them based on their experience of type 1 diabetes in children and young people, but recognised that these rates would not necessarily reflect actual event rates as the children and young people passed into adulthood. However, differences were not outlined between the different treatments and therefore the guideline development group did not consider that this would have an important impact on results.

Table 94: Adverse events

Event	Risk	Source
Minor hypo event	5000 per 100 patient years	Guideline development group
Major hypo event	7.5 per 100 patient year	Guideline development group
Ketoacidosis event rate	9 per 100 patient years	Guideline development group

Finally, risk adjustment for statins and angiotensin converting enzyme (ACE) inhibitors was selected within the 'Treatment Module'.

19.3.2.4 Results

A PSA suggested that MDI was likely to be cost effective relative to 3-times daily (mixed) injections. Table 95 summarises key discounted results and an incremental comparison of the 2 interventions is given in Table 96. Figure 4 shows the results of all 1000 simulations displayed on the cost effectiveness plane and Figure 5 shows the cost effectiveness acceptability curve.

Table 95: Summary results

Output	Multiple daily injections[a]	3-times daily (mixed)[a]
Life expectancy (years)[b]	19.5 (19.3 to 19.6)	18.7 (18.6 to 18.9)
QALYs	14.7 (14.6 to 14.9)	14.0 (13.9 to 14.1)
Costs	£54,374 (£53,445 to £55,303)	£56,130 (£55,188 to £57,072)

QALY quality adjusted life years
a. 95% confidence intervals are given in parentheses
b. Life expectancy is measured from age 12 years

Table 96: Incremental analysis of multiple daily injections relative to 3-times daily (mixed) injections

Output	Mean (95% CI)
Life expectancy (years)	0.72 (0.70 to 0.74)
QALY	0.72 (0.70 to 0.73)
Costs	−£1,756 (−£1,952 to −£1,560)
Incremental cost-effectiveness ratio	MDI dominates

CI confidence interval, MDI multiple daily injections, QALY quality adjusted life year

Figure 4: Cost effectiveness plane showing incremental costs and quality of life years of multiple daily injections relative to 3-times daily (mixed) injections

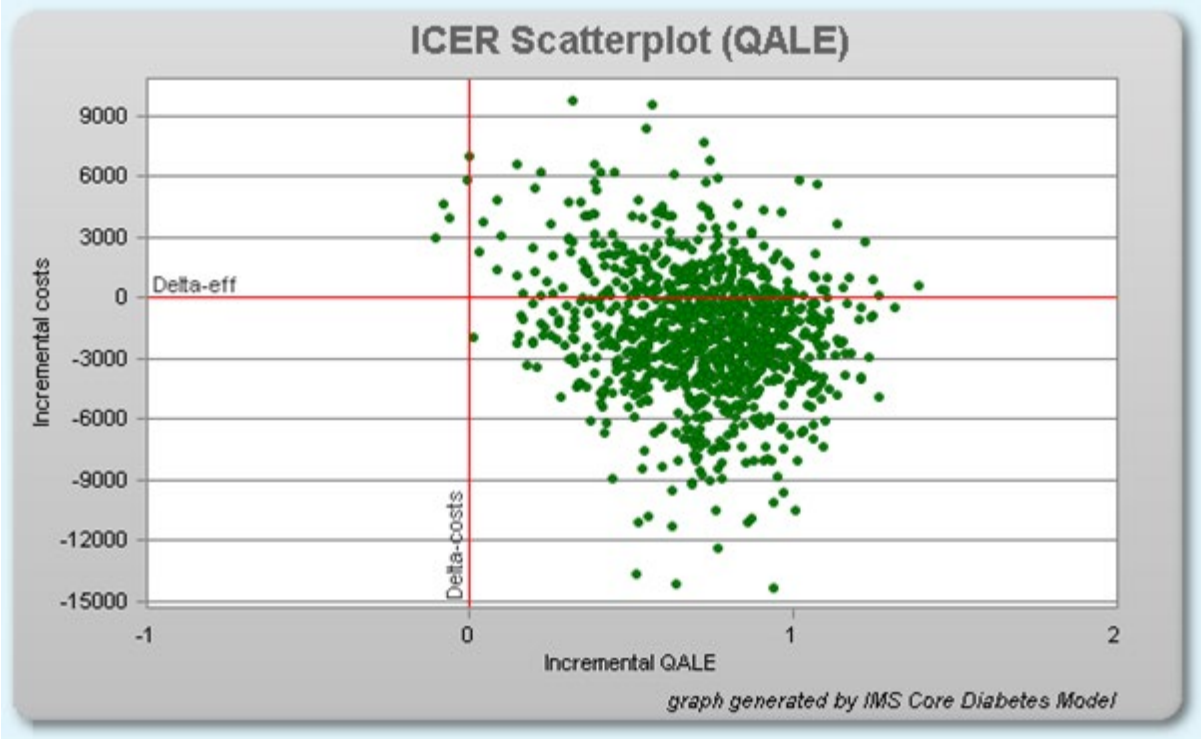


Figure 5: Cost effectiveness acceptability curve

Figure 5 shows the probability of MDI being cost effective as the willingness to pay for a QALY varies. According to this PSA, MDI has almost a 90% chance of being cheapest and, as Figure 4 shows, nearly all of the simulations produced an incremental QALY gain for MDI. The probability of MDI being cost effective at a willingness to pay of £20,000 per QALY is 98.6%, suggesting a very high likelihood that MDI is cost effective compared with 3-times daily injections at a cost effectiveness threshold often used by NICE.

A range of other outputs from the model are presented in Figure 6 to Figure 13. Setting 1 denotes MDI and setting 2 denotes 3-times daily (mixed) injections.

Figure 6: Breakdown of total costs

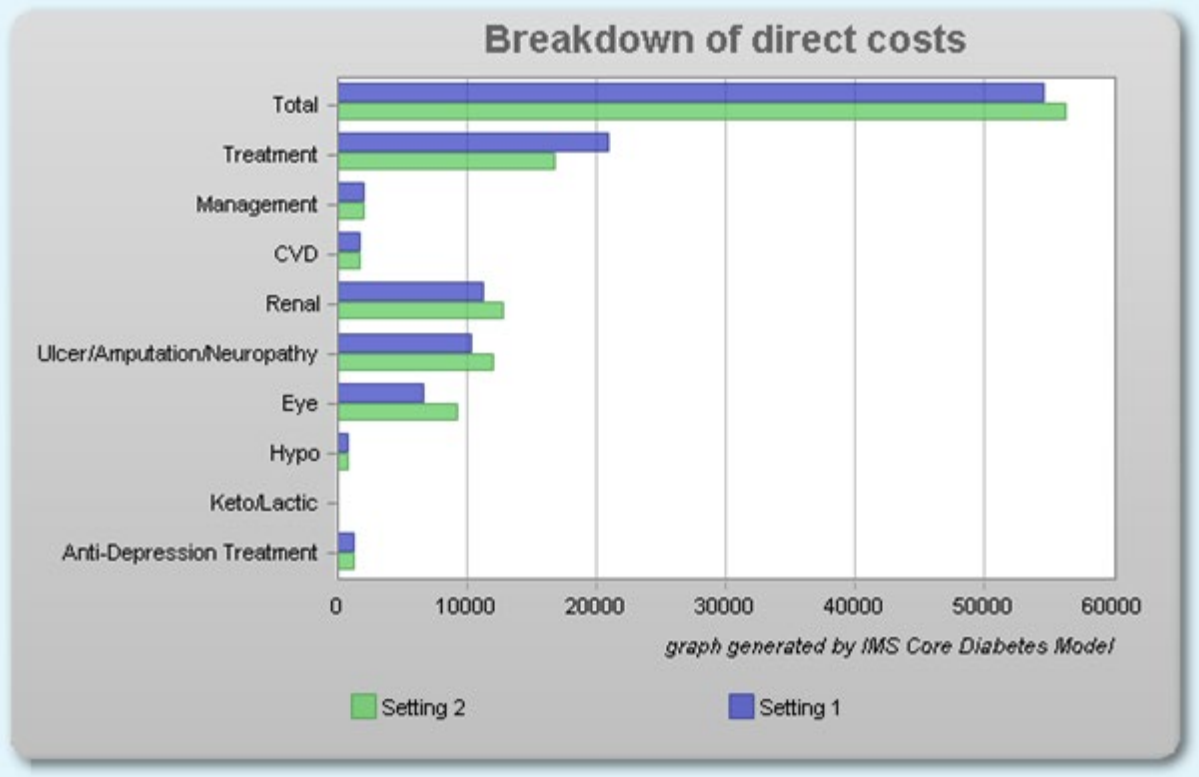


Figure 7: Breakdown of direct costs over time

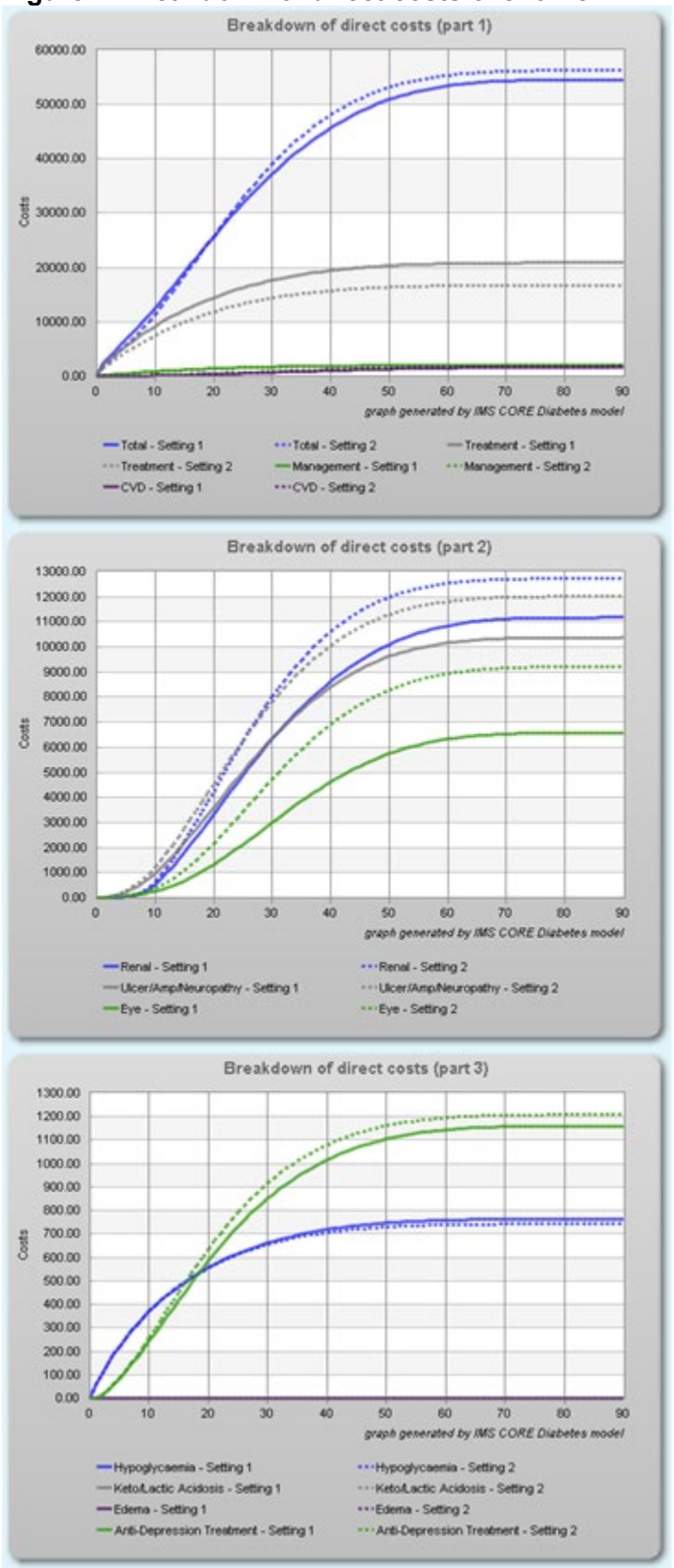


Figure 8: Cumulative incidence of eye disease over time

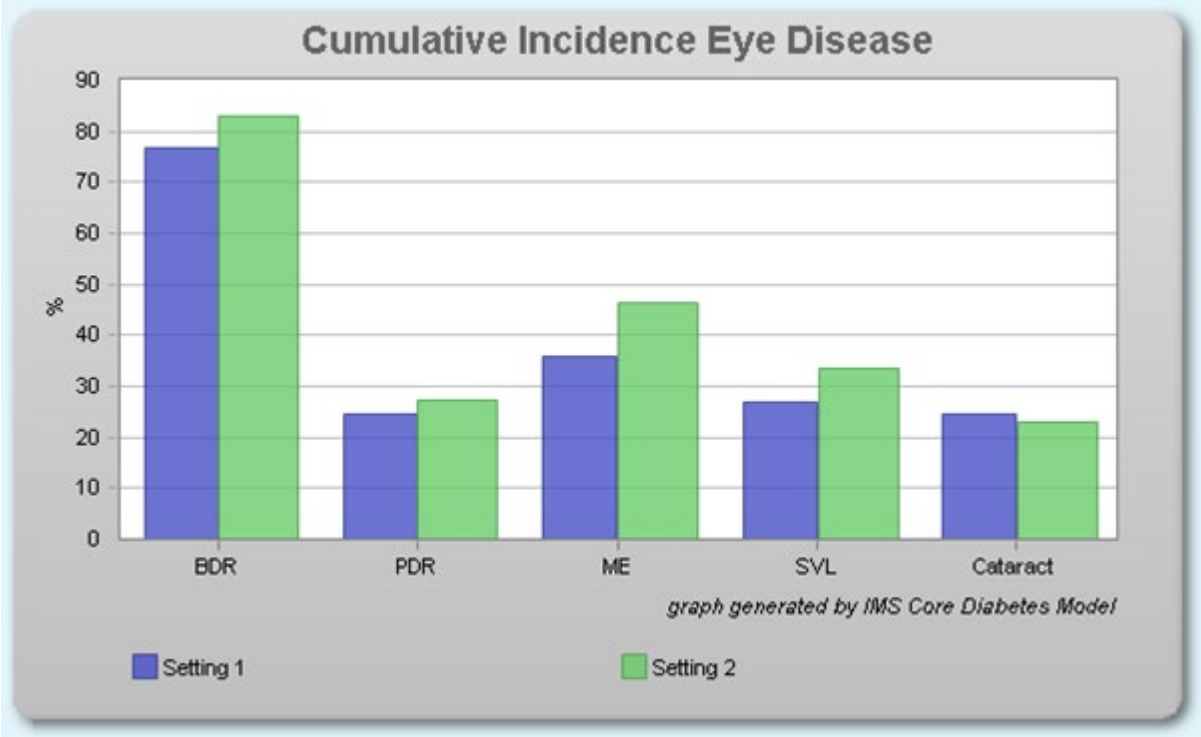


Figure 9: Cumulative incidence of renal disease over time

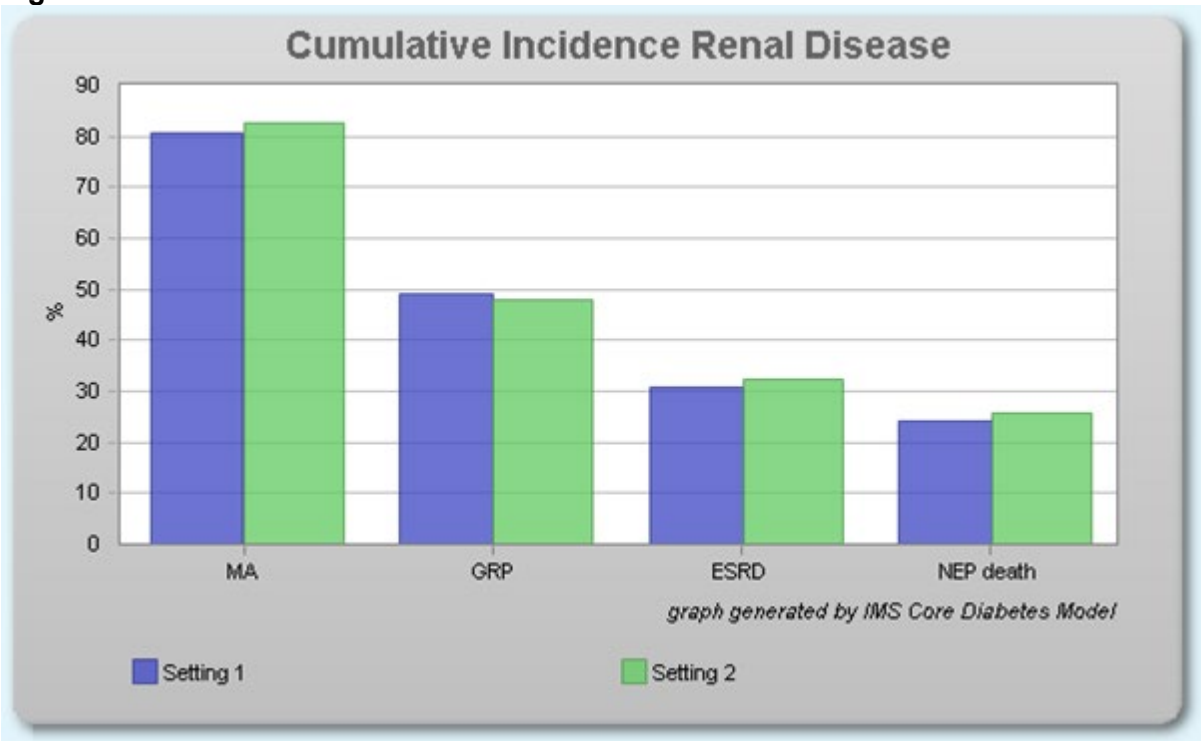


Figure 10: Cumulative incidence of ulcer over time

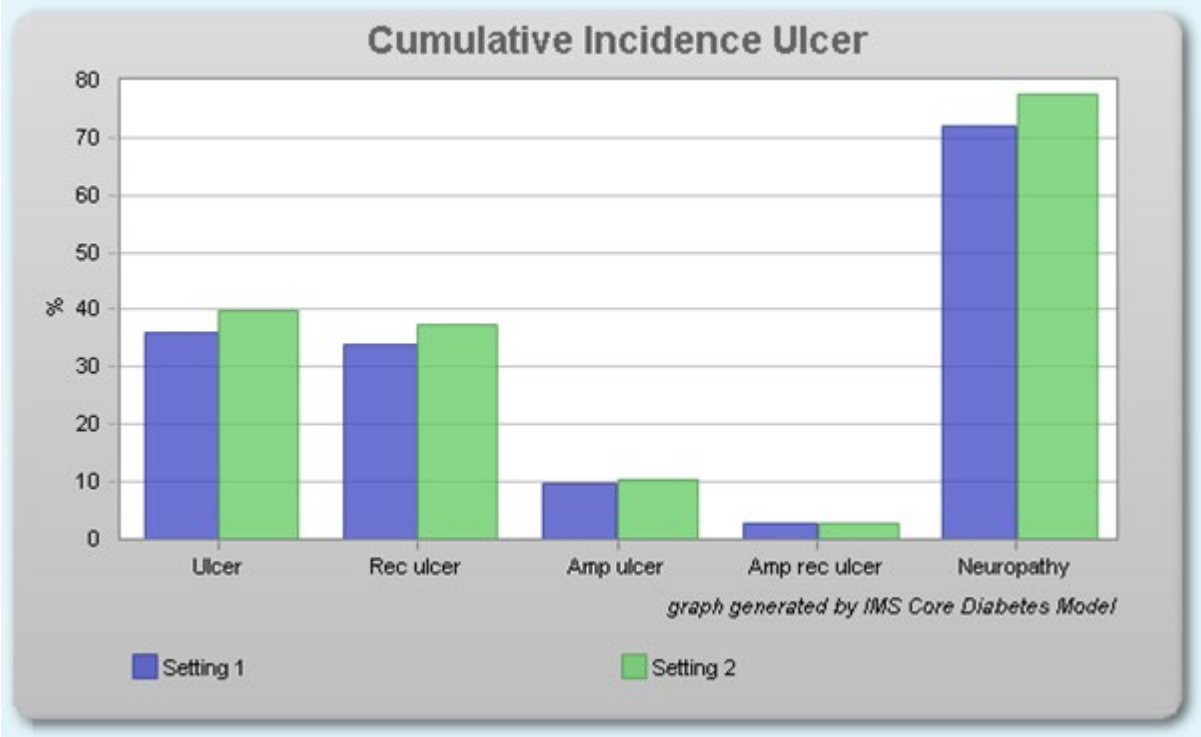


Figure 11: Cumulative incidence of cardiovascular disease over time

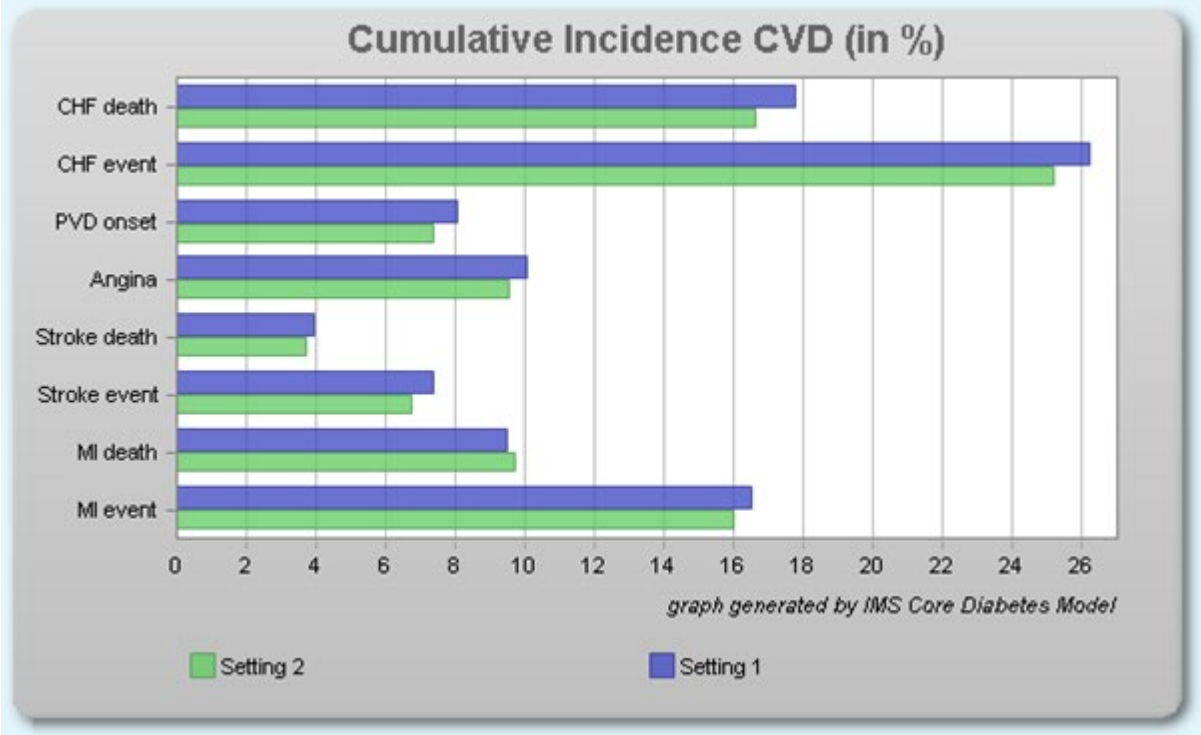
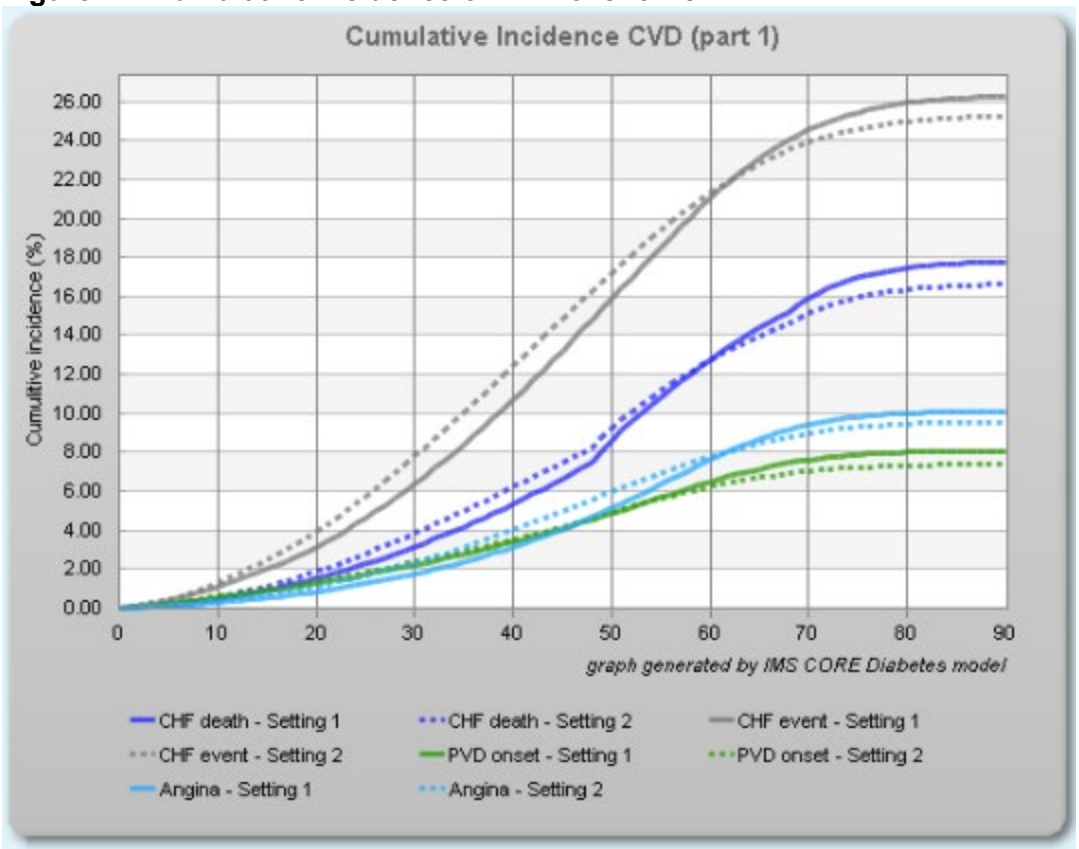


Figure 12: Cumulative incidence of CVD over time



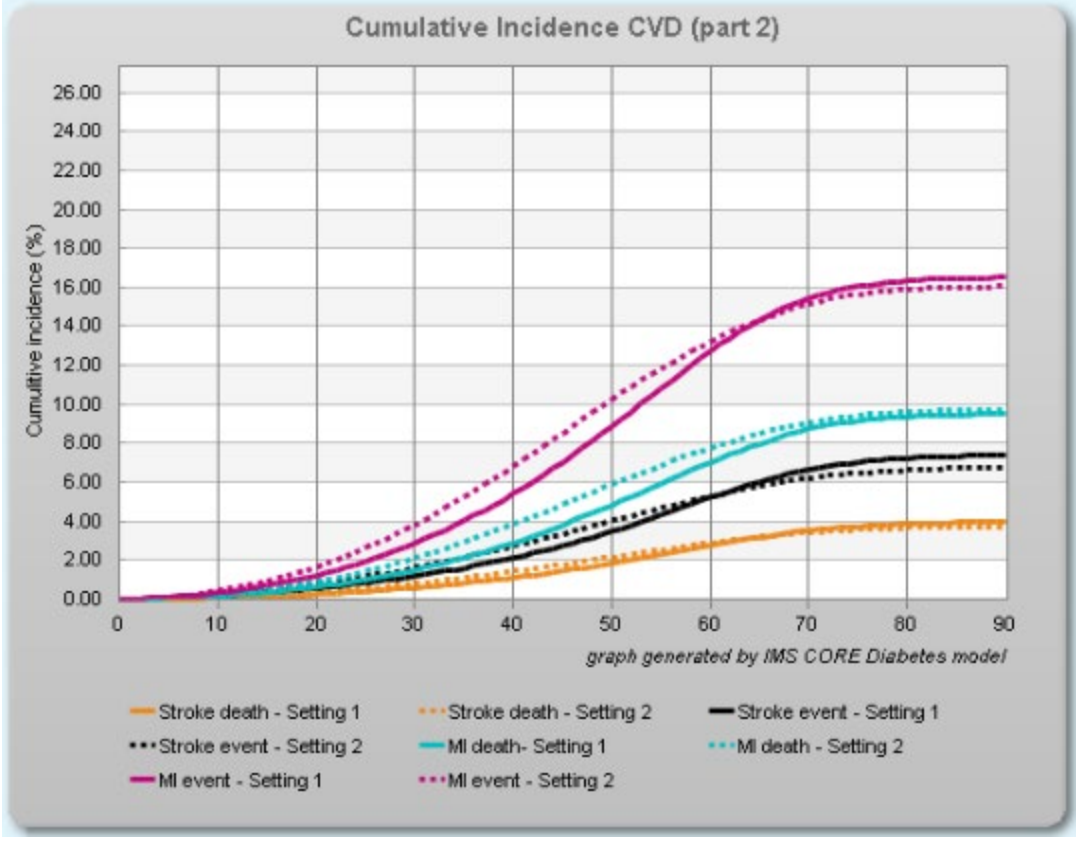
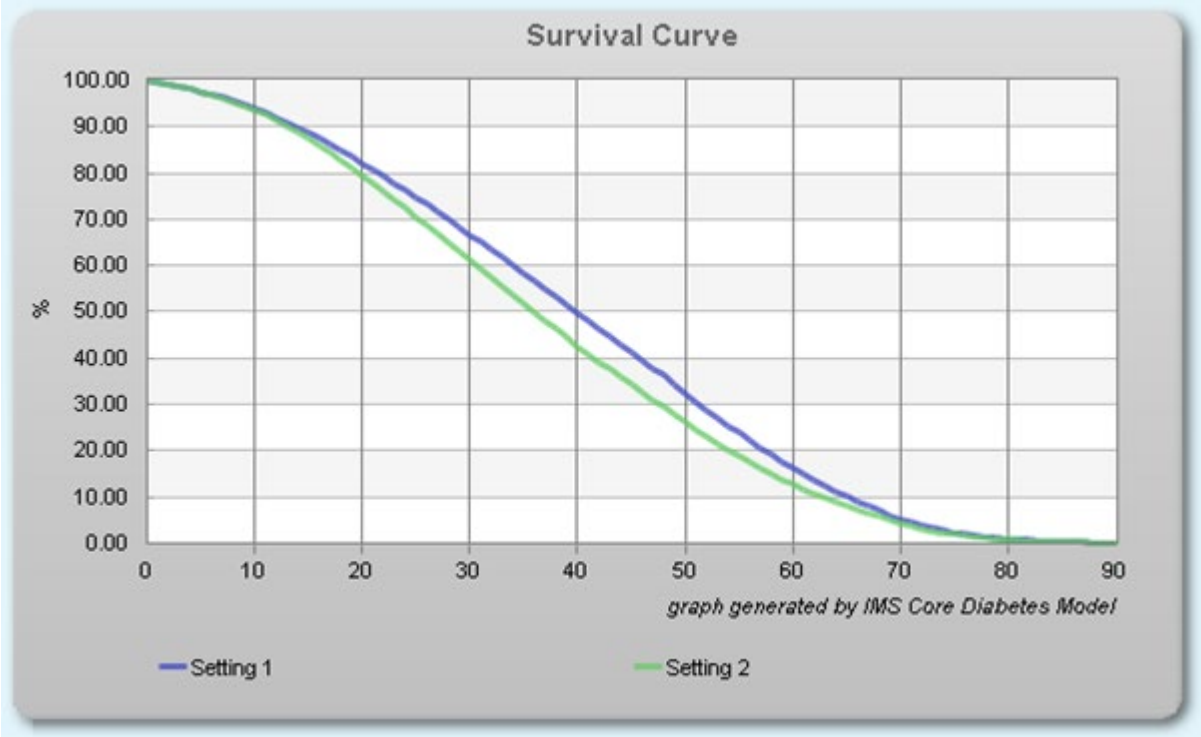


Figure 13: Cumulative patient survival over time



19.3.2.5 Discussion

Driving the results of this model is the treatment effect derived from a single US study (Adhikari 2009) showing a significant reduction in HbA1c with MDI compared with 2- to 3-times daily injections in children and young people with newly diagnosed type 1 diabetes at 1 year after baseline. The model assumes that the resulting differential in HbA1c will be lifelong (see Figure 3). If the differential is eroded over time then this model will tend to overstate the cost effectiveness of MDI. Also, the study has a high risk of bias because patients were allocated to the study groups based on physician preferences and therefore confounding variables may also explain some or part of the treatment effect observed.

In this context it should also be noted that the evidence review conducted for this guideline failed to find evidence of benefit of MDI in those with a diagnosis of over 1 year, although it may be that MDI works better in the newly diagnosed when a change of injection strategy is not an issue.

It should be remembered that the different cumulative incidence of particular events is a function of life expectancy as well as diabetic control and so, as in the case of CVD for example, the overall cumulative incidence is higher with MDI because of higher life expectancy (see Figure 10 and Figure 11).

19.3.2.6 Conclusion

The results of this analysis strongly suggest that MDI is cost effective relative to a 3-times daily (mixed) regimen. With base-case inputs the model suggested that MDI gave net QALY gains when compared with 3-times daily injections. Furthermore, PSA suggested that there was a high probability that MDI, despite its higher treatment cost, would lead to lower health service costs as a result of reduced incidence of long-term complications.

The model results are based on a population of children and young people starting treatment with newly diagnosed type 1 diabetes. The clinical review did not find evidence of benefit of MDI compared with regimens with fewer than 4 injections per day in a population of children and young people with type 1 diabetes who began using MDI treatment 1 year after diagnosis (see Section 6.1.2.6.8). Therefore, the analysis presented here does not demonstrate the cost effectiveness of MDI in such populations. The rationale for not restricting the recommendation to just those with newly diagnosed type 1 diabetes is presented in Section 6.1.2.6.8.

19.4 Cost effectiveness of different frequencies of capillary blood glucose monitoring in children and young people with type 1 diabetes

The 2004 guideline recommended that children and young people with type 1 diabetes and their families should be encouraged to perform frequent blood glucose monitoring as part of a continuing package of care. One of the review questions considered for the 2015 update was 'How frequently should finger-prick blood glucose testing be performed in children and young people with type 1 diabetes?'. This can be considered in terms of the point at which the harm and/or costs of doing an additional test outweigh the additional benefit derived from the extra test. Although there are unlikely to be major clinical harms or adverse events arising from increased frequency of capillary blood glucose (finger-prick) testing, it might be considered inconvenient for the children and young people affected. Therefore, a reasonable presumption is that the frequency of finger-prick testing should not exceed an amount for which there is no evidence of benefit. Furthermore, it may be the case that beyond a certain point the additional benefits of finger-prick testing, though positive, may not be sufficiently large to justify the additional costs.

In discussing this issue it is important to remember that the demands of a child or young person's lifestyle at certain times maybe such that it makes sense to test more frequently than routinely recommended in the guideline.

19.4.1 Methods

19.4.1.1 A 'what-if analysis'

The clinical evidence review did not find any randomised studies that compared different frequencies of finger-prick testing. Therefore, data from observational studies were included and these largely reported outcomes in terms of correlation statistics. However, finding a correlation between increased frequencies of finger-prick testing does not imply causation. It may be that more frequent monitoring leads to better control of blood glucose, as the patient has more data points on which to base action to control blood glucose. On the other hand, it is possible that better motivated patients test more frequently as they have a greater interest in achieving adequate long-term blood glucose control. In that case a positive relationship between the frequency of testing and outcomes may simply reflect that better motivated patients with better blood glucose control test more often and their better blood glucose control reflects their motivation in all aspects of their self-management rather than the extra information derived from the increased finger-prick frequency.

Given this limitation in the data it was decided that a 'what-if' analysis would be undertaken. The base-case analysis assumes that any correlation observed between lower HbA1c and increased finger-prick testing is indeed causal and the cost effectiveness of different frequencies is evaluated on that basis. Given the uncertainty as to whether this is a truly or wholly causal effect, additional sensitivity analyses were undertaken to assess how sensitive any conclusion about cost effectiveness is to the magnitude of the observed correlation. The

sensitivity analysis took the form of a threshold analysis to determine how much an additional finger-prick test would have to reduce HbA1c for it to be considered cost effective.

19.4.1.2 IMS Core Diabetes Model

The modelling was undertaken using the IMS core diabetes model. This model is described in Section 19.3.2 and its use within the context of this guideline is explained in the analysis comparing the cost effectiveness of MDI with 3 times daily (mixed) injections. The inputs and assumptions used in this model are the same as those used in the MDI versus mixed insulin model unless otherwise stated.

19.4.1.3 Treatment

Studies included in the clinical evidence review for blood glucose monitoring were considered to inform the impact of finger-prick testing frequency for this analysis. A decision was made not to use data from studies containing less than 1000 participants, given the much larger numbers present in other included studies.

Upon reviewing the literature, a decision was made to assess the frequency of monitoring blood glucose levels up to 5 times per day as evidence from a large German database (n=26,723) suggested no further improvement in metabolic control occurs beyond testing 5 times per day (Ziegler 2011).

In the base-case analysis data from a US study were used to estimate the change in blood glucose levels from increased monitoring (Miller 2013). Evidence from participants aged up to 18 years are included (n=11,641) with results presented for children and young people in the following age categories:

- 1 to less than 6 years
- 6 to less than 13 years
- 13 to less than 18 years.

The mean HbA1c across these age categories for different frequencies of SMBG were reported as shown in Table 97.

Table 97: Reported association between daily frequency of self-monitoring of blood glucose and mean HbA1c by age[a]

Age category	Mean HbA1c				
	SMBG 0 to 2 times daily	SMBG 3 to 4 times daily	SMBG 5 to 6 times daily	SMBG 7 to 9 times daily	SMBG 10 or more times daily
1 to <6 years	-	8.5	8.4	8.1	7.8
6 to <13 years	-	8.7	8.4	8.1	7.8
13 to <18 years	10.3	9.0	8.5	8.2	8.0
Mean[b]	10.3	8.9	8.4	8.1	7.8

SMBG self-monitoring blood glucose
a. Source: Miller 2013
b. Mean values across age categories are a weighted mean average based on the number of children in the respective age and frequency categories.

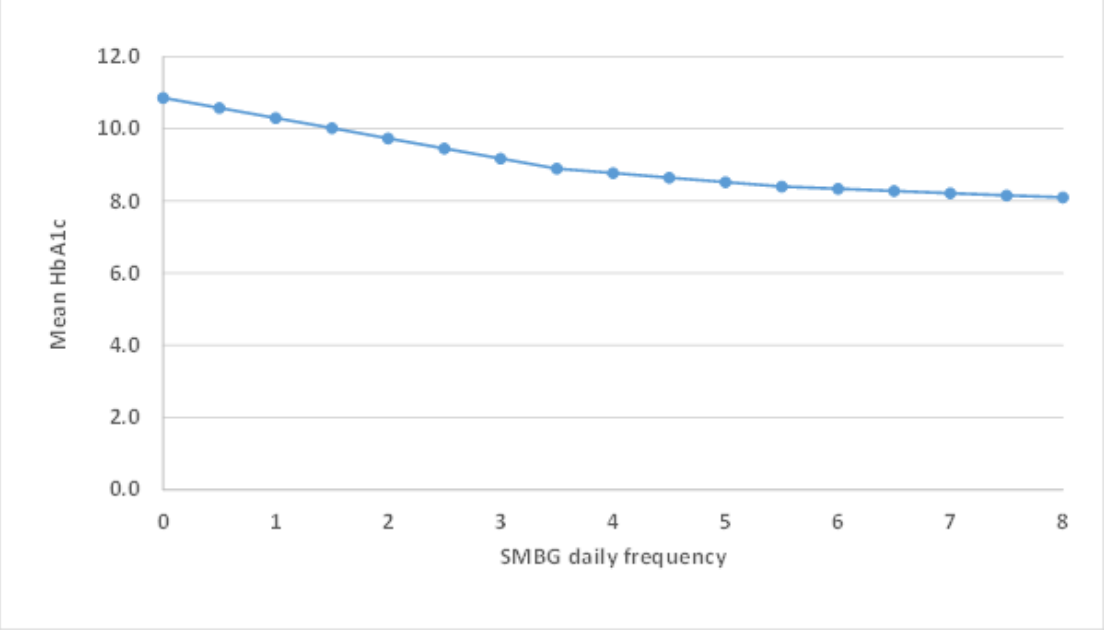
The mean value of HbA1c across age categories was used and was assumed to apply to the mid-point of the reported SMBG ranges. Linear interpolation was then applied to estimate the mean HbA1c for each daily finger-prick test increment as shown in Table 98 and Figure 14.

Table 98: Estimated change in mean HbA1c from increased daily frequency of self-monitoring of blood glucose

Estimated daily SMBG frequency	Estimated mean HbA1c	Reduction in HbA1c from an additional finger-prick test
0	10.86	NA
0.5	10.58	
1.0[a]	10.30	0.56
1.5	10.02	
2.0	9.74	0.56
2.5	9.46	
3.0	9.18	0.56
3.5[a]	8.90	
4.0	8.78	0.40
4.5	8.65	
5.0	8.53	0.25
5.5[a]	8.40	
6.0	8.34	0.19
6.5	8.28	
7.0	8.22	0.12
7.5	8.16	
8.0[a]	8.10	0.12
8.5	8.03	
9.0	7.95	0.15
9.5	7.88	
10.0[a]	7.8	0.15

HbA1c glycated haemoglobin, SMBG self-monitoring blood glucose
a. Mid-point of SMBG range (see Table 97)

Figure 14: Graph to show estimated association between HbA1c and daily self-monitoring blood glucose (SMBG) frequency



Source: Estimated from Miller 2013

The reduction in HbA1c is summarised in Table 99.

Table 99: Estimates of reduction in blood glucose level from increased monitoring per day

Monitoring frequency	0 to 1	1 to 2	2 to 3	3 to 4	4 to 5
% point reduction in blood glucose levels	0.56	0.56	0.56	0.40	0.25

a. Source Miller 2013

19.4.1.4 Costs

The costs of different frequencies of finger-prick testing used in the model are shown in Table 100. These are based on the costs estimated in Section 219.3.1.1.2.3.1.1.3 (Table 71 and Table 82) for the model comparing the cost effectiveness of MDI versus mixed insulin injection regimens.

Table 100: Costs of finger-prick testing per year

Frequency	Year 1	Subsequent years
0 times per day	£0	£0
1 times per day	£61.40	£61.40
2 times per day	£122.80	£122.80
3 times per day	£184.20	£184.20
4 times per day	£245.60	£245.60
5 times per day	£307.00	£307.00

In addition to the treatment costs the model also estimates lifetime complication costs. Costs in the model were taken from an NHS and Personal Social Services (PSS) perspective as per the NICE Reference Case.

19.4.2 Sensitivity analysis

For the guideline development group the key decision centred on whether to recommend testing 4 or 5 times daily because the previous 2004 guideline had, at least implicitly, set 4 times daily as the minimum desirable frequency by suggesting that children and young people trying to optimise their blood glucose control and/or with intercurrent illness should be encouraged to test more than 4 times daily. Therefore, a 'what-if' analysis was undertaken to assess the minimum percentage point reduction in HbA1c that would be needed to make 5-times daily testing cost effective relative to 4-times daily testing.

In the base-case analysis a reduction in HbA1c of 0.25 percentage points was assumed in moving from 4 finger-prick tests daily to 5 finger-prick tests daily. In the 'what-if' analysis hypothetical 0.20 percentage point, 0.14 percentage point and 0.11 percentage point reductions in HbA1c from the additional fifth test were assessed.

19.4.3 Results

19.4.3.1 Comparison across self-monitoring of blood glucose frequencies from 0 to 5 times daily

The results from the base-case analyses are shown in Table 101 and Table 102, and Figure 15 and Figure 16.

Table 101: Total costs and quality adjusted life years with different daily finger-prick testing frequency

Daily finger-prick testing frequency	Costs (95% CI[a])	QALYs (95% CI[a])
0	£43,280 (£42,393 to £44,166)	14.61 (14.51 to 14.71)
1	£40,610 (£39,751 to £41,462)	15.17 (15.07 to 15.27)
2	£37,842 (£37,020 to £38,664)	15.68 (15.59 to 15.77)
3	£35,369 (£34,584 to £36,153)	16.15 (16.06 to 16.24)
4	£34,040 (£33,291 to £34,790)	16.47 (16.39 to 16.55)
5	£33,902 (£33,180 to £34,624)	16.65 (16.58 to 16.72)

CI confidence interval, QALY quality adjusted life year
a. Confidence intervals represent patient 'random walks' in different iterations rather than second order uncertainty

Table 102: Incremental costs and effects of increasing frequency of blood glucose testing

Comparison daily finger-prick testing frequency	Incremental costs	Incremental effects (QALYs)	ICER
0 to 1	−£2,670	0.56	1 test dominates no testing
1 to 2	−£2,767	0.51	2 tests dominates 1 test
2 to 3	−£2,474	0.47	3 tests dominates 2 tests
3 to 4	−£1,328	0.32	4 tests dominates 3 tests
4 to 5	−£138	0.18	5 tests dominates 4 tests

ICER incremental cost effectiveness ratio, QALY quality adjusted life year

Figure 15: Graph to show costs associated with different frequencies of finger-prick testing

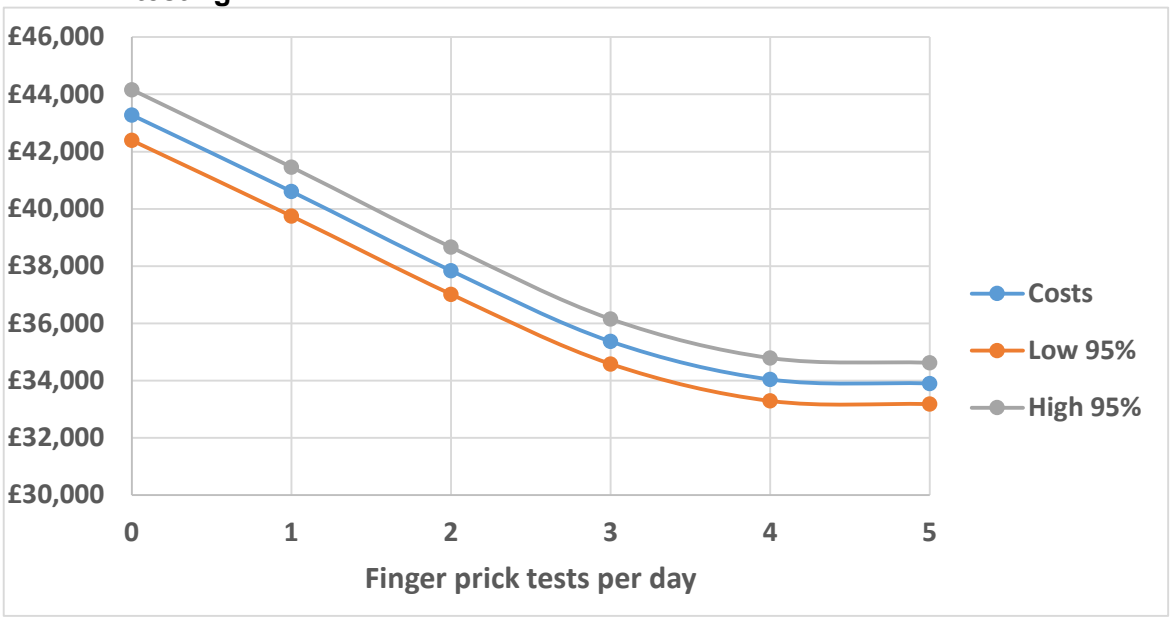
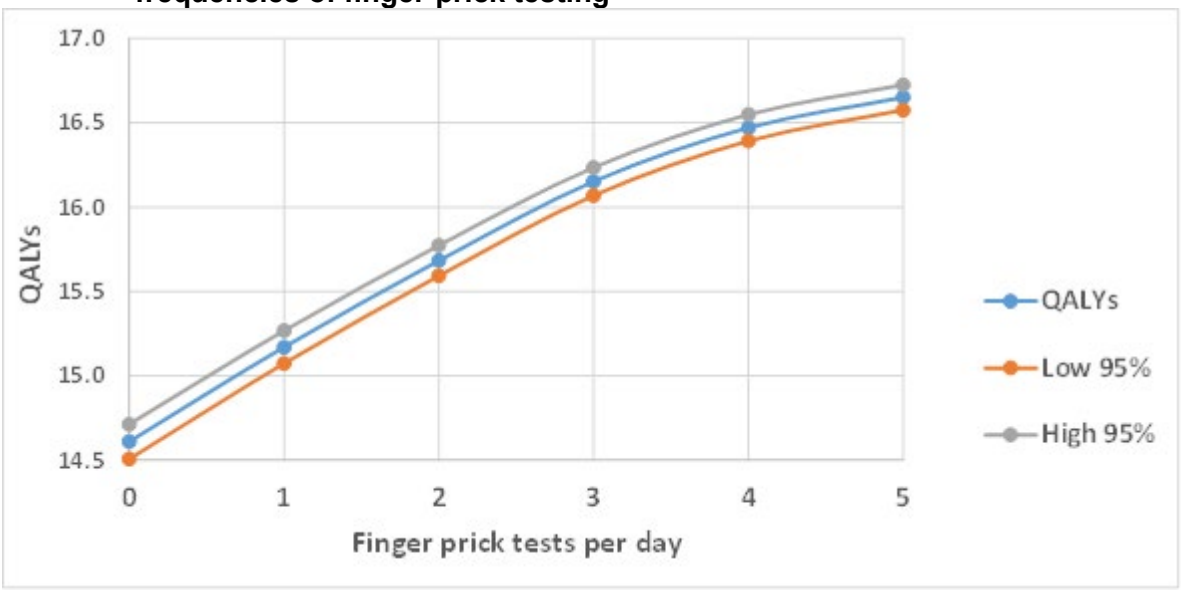


Figure 16: Graph to show quality adjusted life years associated with different frequencies of finger-prick testing



19.4.3.2 Comparison of 4-times daily self-monitoring of blood glucose with 5-times daily self-monitoring of blood glucose

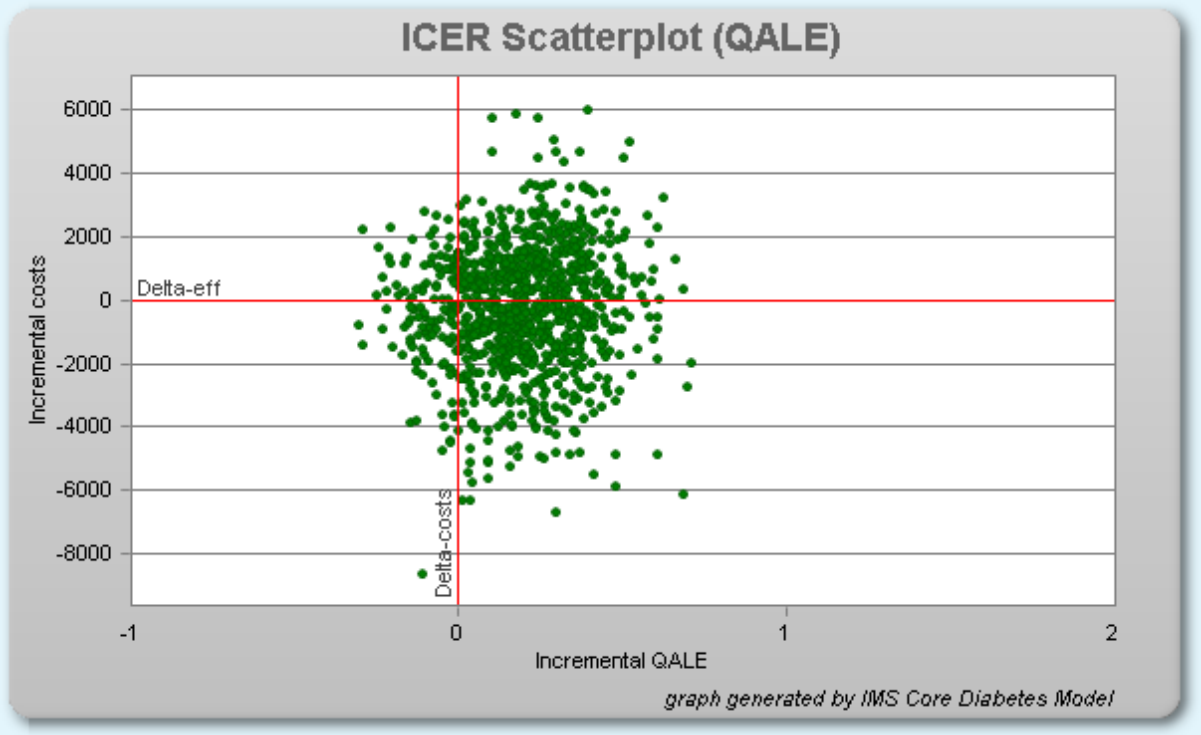
Figure 20 summarises key discounted results and Figure 17 shows the results of all 1000 simulations displayed on the cost effectiveness plane. This suggests that 5-times daily finger-prick testing dominates 4 times daily finger-prick testing, being cheaper and producing longer life expectancy and QALYs.

Table 103: Summary results

Output	Four times daily[a]	Five times daily[a]
Life expectancy[b]	21.70 (21.62 to 21.78)	21.887 (21.80 to 21.95)
QALYs	16.47 (16.39 to 16.55)	16.65 (16.58 to 16.72)
Costs	£34,040 (£33,291 to £34,790)	£33,902 (£33,180 to £34,624)

QALY quality adjusted life year
a. 95% confidence intervals in parentheses
b. Life expectancy is measured from age 12 years

Figure 17: Cost effectiveness plane (origin 4-times daily testing)



QALE quality adjusted life expectancy

A breakdown of costs is displayed in Table 104, showing that the higher monitoring costs of 5-times daily finger-prick testing are more than offset by a reduction in lifetime complication costs, even allowing for the increased life expectancy with 5-times daily testing.

Table 104: Breakdown of total costs

Category	Four times daily	Five times daily
Treatment	£5,386	£6,785
Management	£2,489	£2,509
Cardiovascular disease	£1,548	£1,524
Renal	£4,250	£3,692
Ulcer/amputation/nephropathy	£11,510	£10,929
Eye	£7,011	£6,626
Hypoglycaemia	£524	£528
Ketoacidosis/lactic acidosis	£0	£0
Anti-depression treatment	£1,323	£1,309
Total costs	**£34,040**	**£33,902**

A range of other outputs from the model are presented in Figure 18 to Figure 24. Setting 1 denotes 4-times daily finger-prick testing and setting 2 denotes 5-times daily finger-prick testing.

Figure 18: Breakdown of total costs

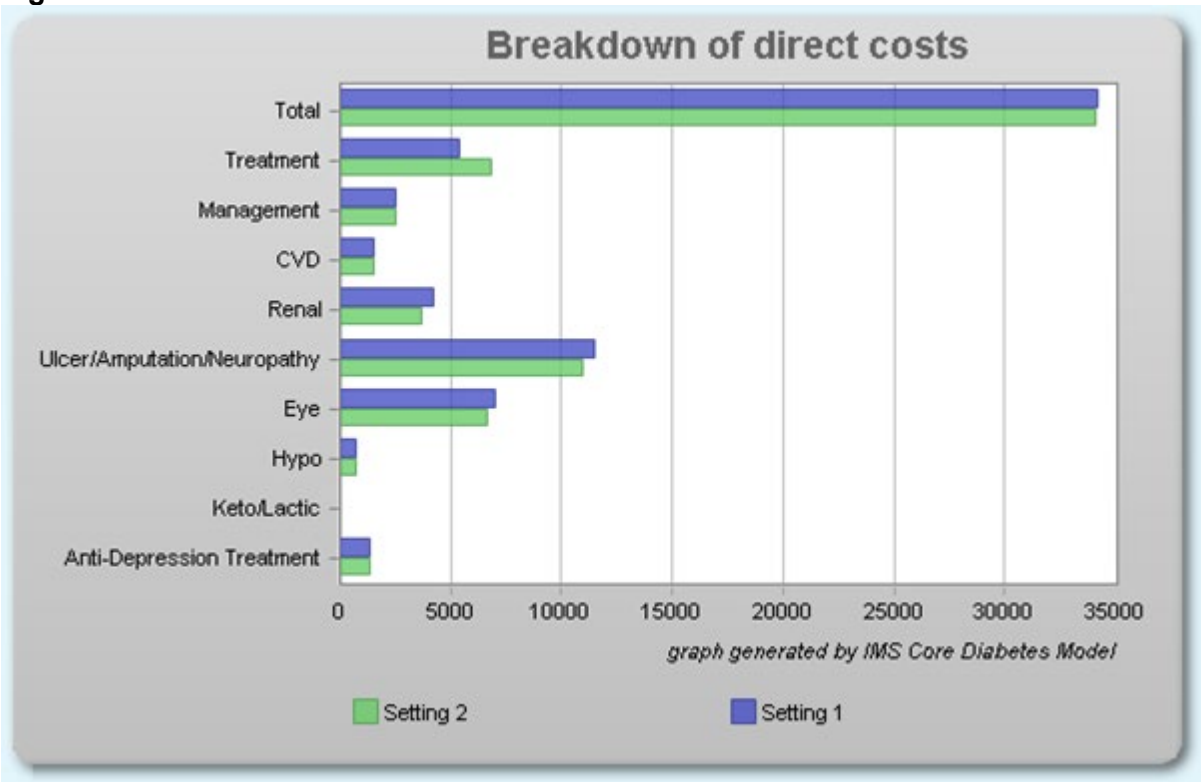


Figure 19: Cumulative incidence of eye disease

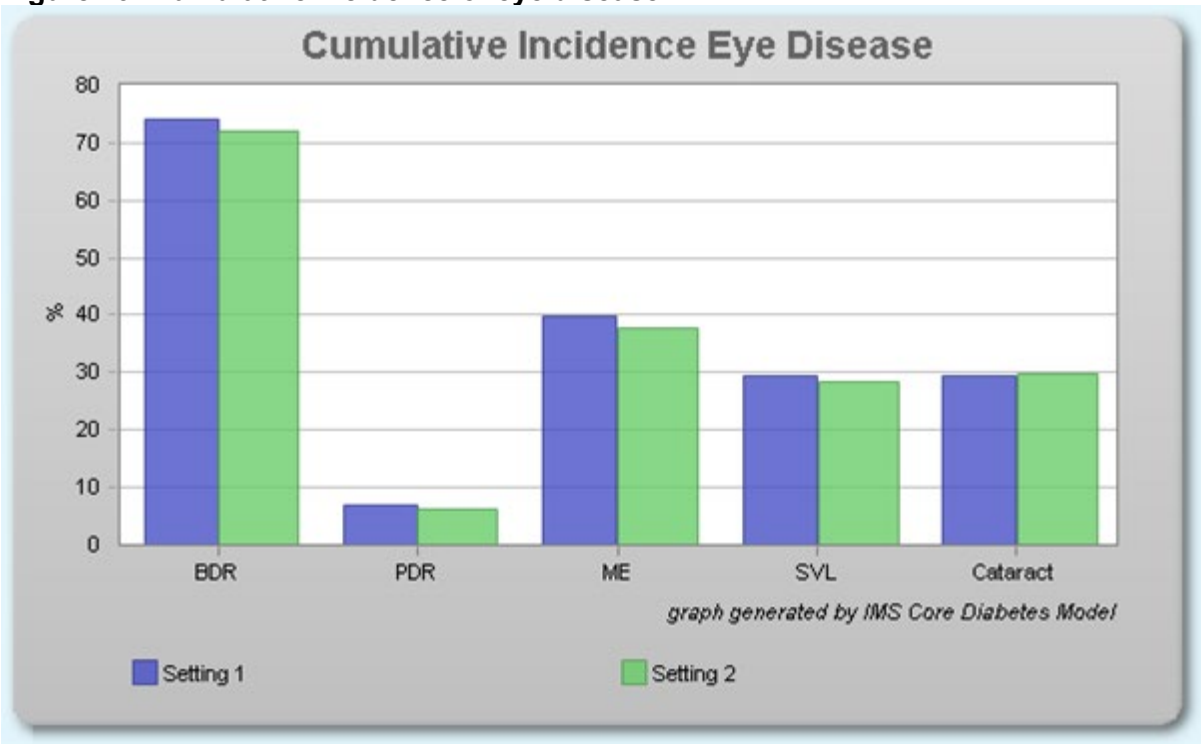


Figure 20: Cumulative incidence of renal disease

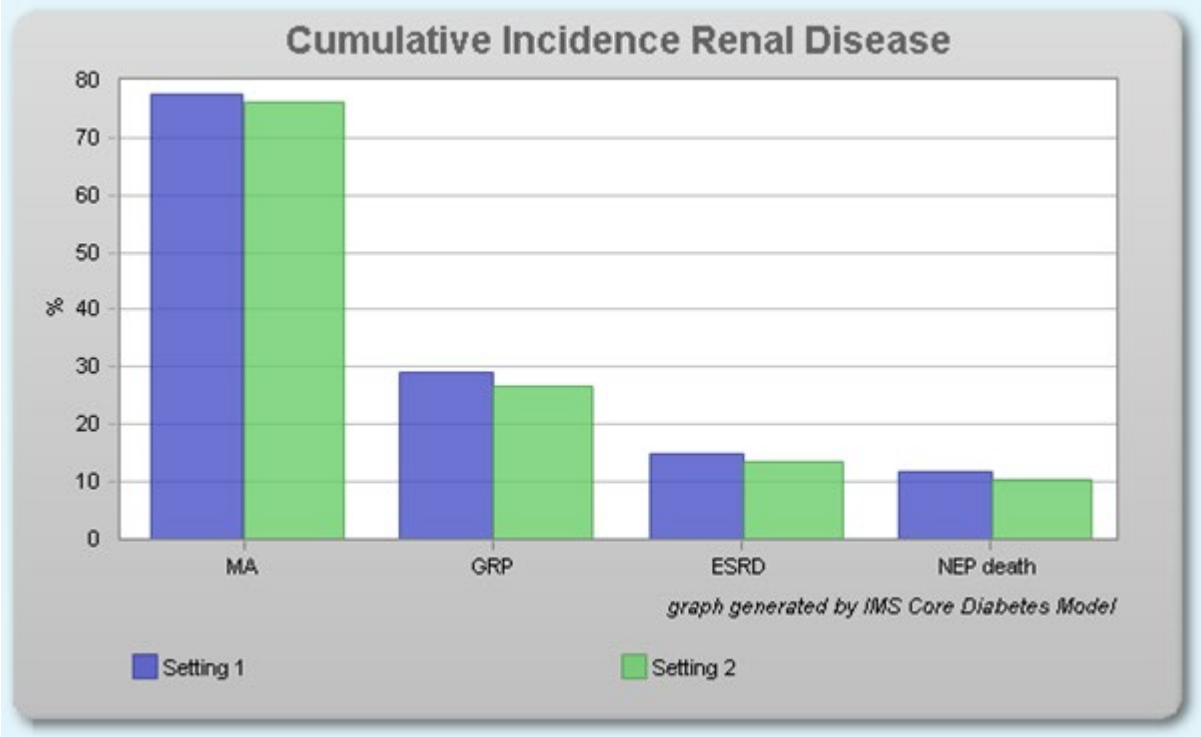


Figure 21: Cumulative incidence of ulcer

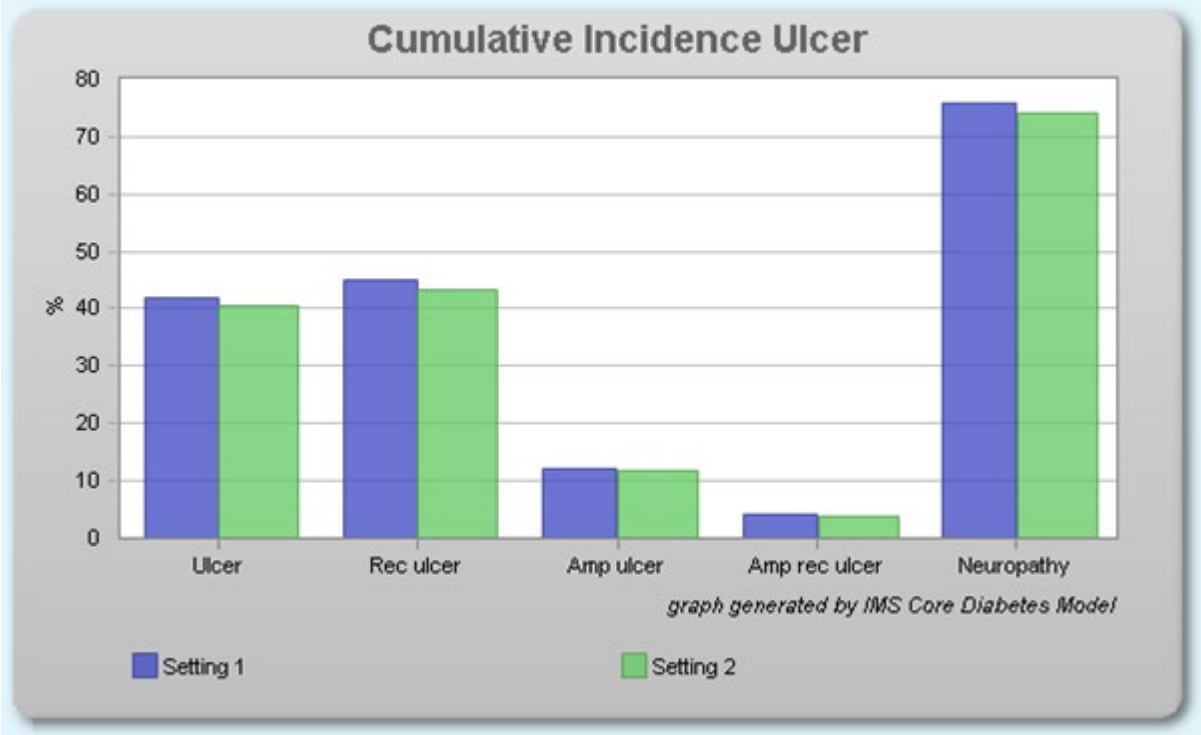


Figure 22: Cumulative incidence of cardiovascular disease

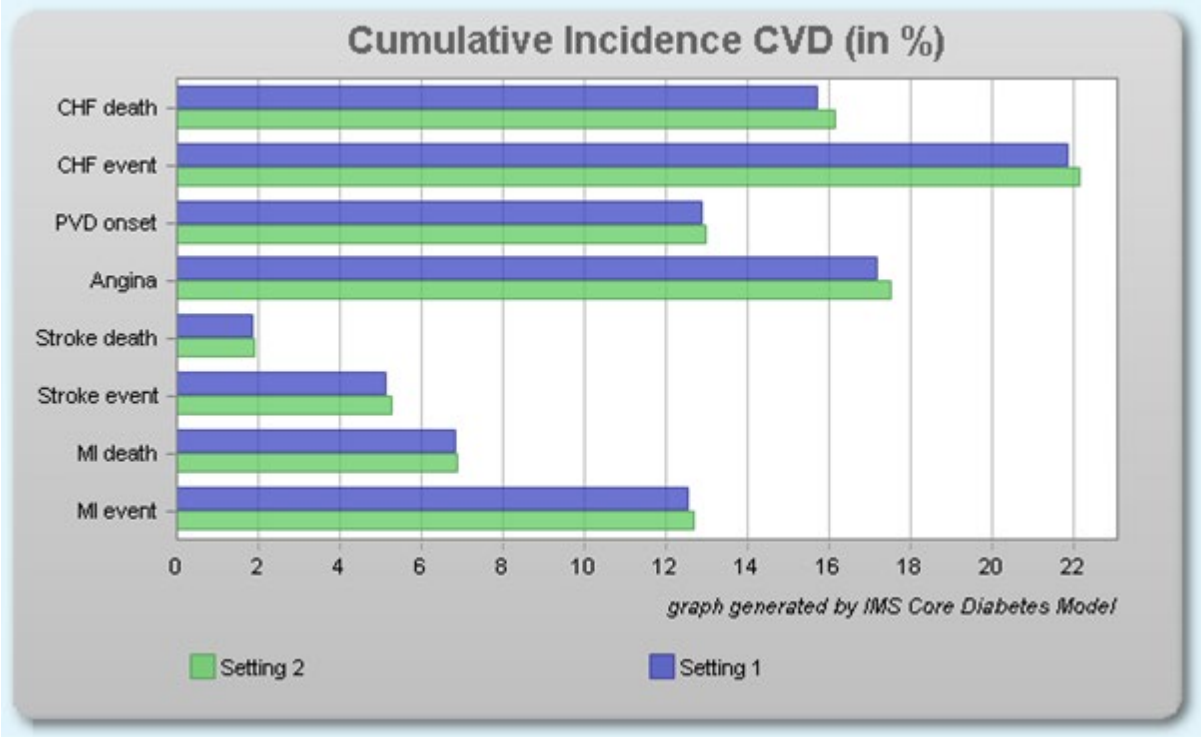


Figure 23: Survival curve

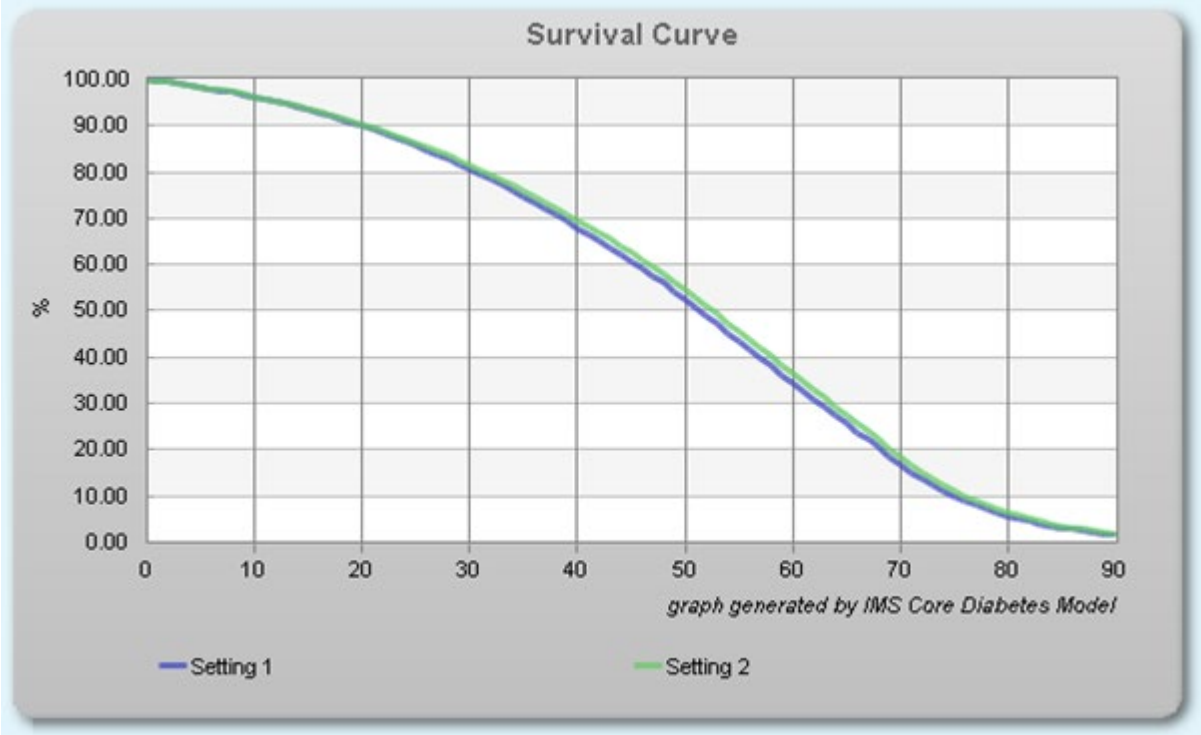
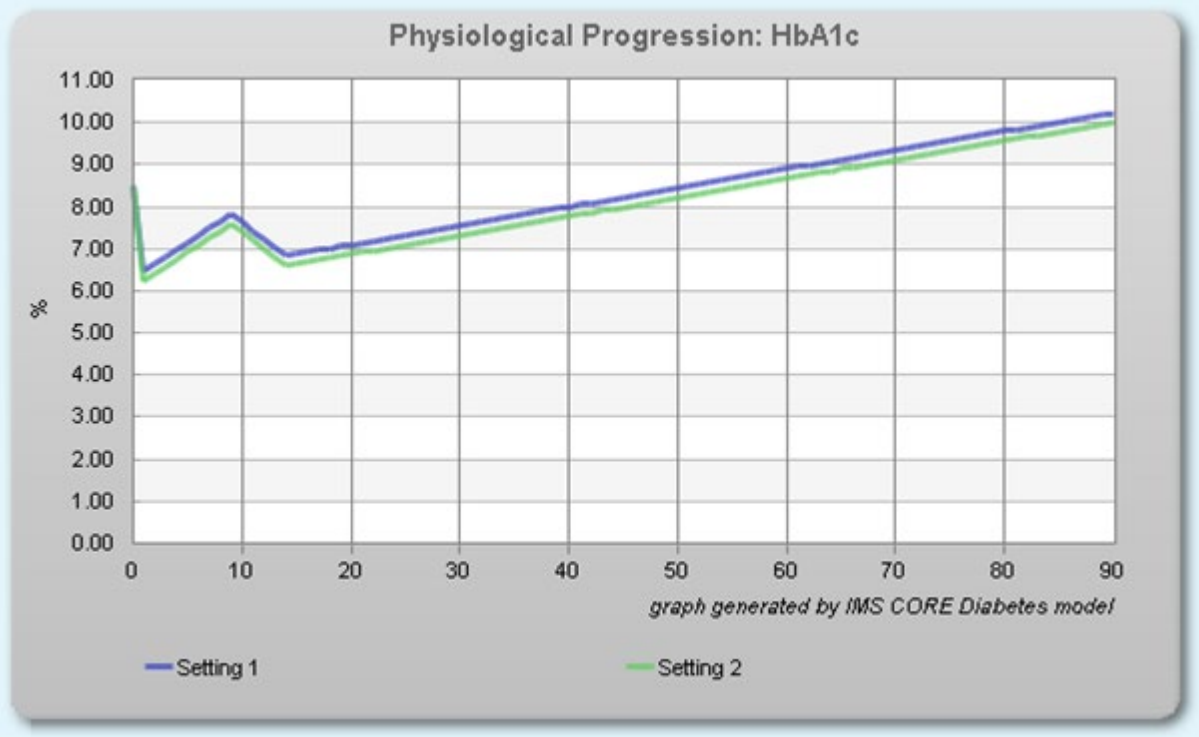


Figure 24: HbA1c progression over time



19.4.3.3 What-if analysis

Table 105 shows the incremental costs and QALYs of 5-times daily finger-prick testing relative to 4-times daily finger-prick testing, varying the percentage point reduction in HbA1c as a result of the increased testing. This suggests that 5-times daily finger-prick testing is cost effective compared with 4-times daily finger-prick testing, provided that the additional test leads to a greater than 0.06 percentage point reduction in HbA1c when assessing cost effectiveness at a willingness to pay threshold of £20,000 per QALY.

Table 105: Incremental costs and quality adjusted life years of 5-times daily finger-prick testing relative to 4 times per day finger-prick testing varying the reduction in HbA1c

Percentage point reduction in HbA1c	Incremental costs	Incremental QALYs	ICER
0.25 (base case)	−£138	0.18	5 tests dominates 4 tests
0.12	£664	0.09	£7,811 per QALY
0.06	£977	0.04	£27,139 per QALY
0.03	£1,204	0.02	£70,824 per QALY

HbA1c glycated haemoglobin, ICER incremental cost effectiveness ratio, QALY quality adjusted life year

19.4.4 Discussion

Evidence from the DCCT showed that reductions in HbA1c had important implications for the natural history of type 1 diabetes, with lower levels consistently reducing complications of the disease. Therefore, it is not surprising that interventions which produce improvements in HbA1c can represent an efficient use of scarce healthcare resources. Not only are there large health gains from avoiding the complications of diabetes but there are potentially large

savings as diabetic complications can be expensive to treat and manage. In all the base case analyses the 'downstream' savings always more than offset the higher monitoring costs of increased testing frequency. However, in this analysis it must be remembered that if there are certain characteristics associated with increased testing frequency, then the frequency of testing could be acting as a confounder to some extent for other influences on HbA1c, meaning that the cost effectiveness of increased testing is overstated in this analysis.

The life expectancy reported in Table 103 is less than that reported in MDI versus 3-times daily injection analysis (see Section 19.3.2.4). This is mostly explained by this model using the same cohort as that analysis, which is based on a child aged 12 years at diagnosis. Therefore, the HbA1c at baseline and progression over time does not allow for the treatment effects of insulin therapy (see Figure 24). As this is applied across all comparators this is unlikely to alter the cost effectiveness conclusion, but it does mean that life expectancy is likely to be significantly underestimated.

19.4.5 Conclusion

A model of this sort can only offer limited evidence in support of a recommendation that children and young people with type 1 diabetes should undertake SMBG 5 times per day. This is because the finding that finger-prick testing 5 times per day is cost effective relative to 4 times per day rests heavily on the assumption that the observed reduction in HbA1c with more frequent testing is a result of increased testing and not some other characteristic associated with higher levels of SMBG.

However, the 'what-if' analysis established that the threshold for cost effectiveness required a much smaller reduction in HbA1c than was used in the base-case analysis. This suggested that as long as the fifth daily test yielded a 0.06 percentage point reduction in HbA1c then the additional costs associated with testing were worth the additional benefit.

19.5 Cost effectiveness of blood ketone monitoring compared with urine ketone monitoring in children and young people with type 1 diabetes

This section was updated in 2015.

The 2004 guideline recommended that children and young people with type 1 diabetes should have short-acting insulin or rapid-acting insulin analogues and blood and/or urine ketone testing strips available for use during intercurrent illness. However, when faced with alternative courses of action it is important that the cost effectiveness of those alternatives is considered in the context of competing uses for scarce healthcare resources. A consideration of cost effectiveness may lead to one form of monitoring being considered preferable to another.

19.5.1 Review of the literature

A health economics search of the literature did not identify any studies comparing the cost effectiveness of urine ketone monitoring and blood ketone monitoring in children and young people with type 1 diabetes. Therefore a new health economic model was developed for the purposes of the 2015 guideline update using data from the single study included in the clinical review (Laffel 2005). This model is described below.

19.5.2 Methods

19.5.2.1 Population

The model is developed for a population of children and young people with type 1 diabetes.

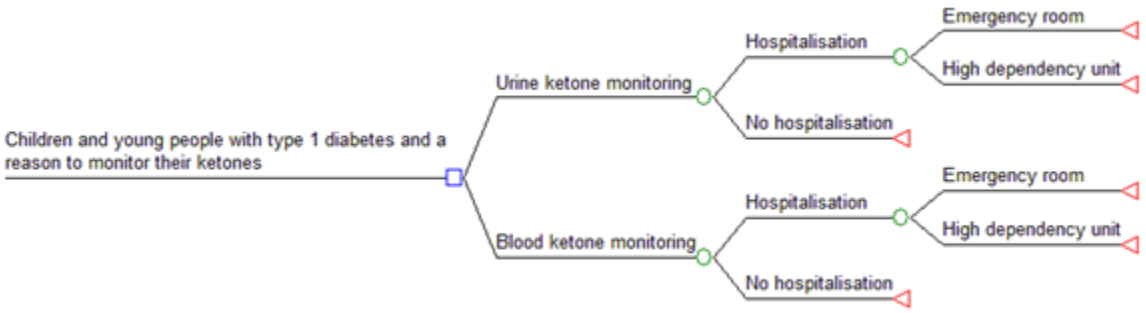
19.5.2.2 Comparators

Usually it would be important to establish that any form of monitoring represented a cost effective use of resources, but since monitoring of ketones is considered good practice for the prevention of DKA monitoring and forms part of current clinical practice, the 2015 update does not need to include an option for no monitoring. Therefore, this model is restricted to a comparison of urine and blood ketone monitoring.

19.5.2.3 Analysis type

Only 1 of the guideline development group's priority outcomes was reported in the included study (Laffel 2005) and this related to hospital admission. This meant it was not possible to undertake a cost-utility analysis, which is the preferred NICE approach: a cost minimisation approach was undertaken instead based on treatment costs and the costs of hospitalisation. A schematic of the model is presented in Figure 25.

Figure 25: Decision tree for urine ketone monitoring versus blood ketone monitoring



19.5.2.4 Hospitalisation events

Table 106 presents DKA-related hospital admissions for a 6-month period using data from 1 US study (Laffel 2005). The guideline development group was of the opinion that these hospital admission rates were higher than would be experienced in England and Wales. From their own experience and the National Paediatric Diabetes Audit Report 2011-12, Part 2, Hospital Admissions and Complications, they thought that an admission rate of 5% to 10% per year (or equivalently 5 to 10 per 100 patient years) would be more typical in patients for whom this guideline is intended. The guideline development group considered that there might be lower rates in England and Wales compared with the USA because of easier access to advice. Most paediatric units in England and Wales offer 24-hour advice and so when children and young people are ill they can often be cared for at home. Geography may also play a part as distance from home to diabetes units is shorter in England and Wales than in the USA. There is also an option of GP involvement in the care of children and young people at an early stage of illness. Additionally, the costs of medical care in the USA may act as a deterrent to advice being sought at an early stage. The effects of lower admission rates are explored in a sensitivity analysis (Section 19.5.3.3.1).

Table 106: Hospital admission for 6 months

Variable	Blood ketone monitoring	Urine ketone monitoring
Patients	62	61
Emergency room	8	14
Hospitalisation	3	8

Table 107 shows the model parameters derived from the data, including those used for PSA.

Table 107: Model hospitalisation parameters

Variable	Value	Distribution	Alpha	Beta
Emergency admission rate (blood)	0.26	Beta	8	54
Hospitalisation rate (blood)	0.10	Beta	3	59
Emergency admission rate (urine)	0.46	Beta	14	47
Hospitalisation rate (urine)	0.26	Beta	8	53

19.5.2.5 Costs

The costs are based on an NHS perspective and are for a cost year of 2012/13.

Cost inputs relate to the cost of ketone testing and different forms of hospital admission. For costing purposes the guideline development group suggested that a hospitalisation admission should be considered as a stay in a high dependency unit of 2 to 3 days and that an emergency room admission should be considered as a 24-hour stay on a paediatric ward. The model allows for the costs of a follow-up consultation to be included, although this does not form part of the base-case analysis. The model also allows the user to choose alternative types of paediatric intensive care, but the base-case is set to high dependency paediatric intensive care. A cost for a paediatric ward stay was not found in NHS Reference Costs and therefore the NHS Reference Cost for 'Diabetic mellitus with ketoacidosis or coma' was used as a proxy. The unit costs are summarised in Table 108.

Table 108: Unit costs

Item	Value	Distribution	SE	Source
Urine reagent strips (pack of 50)[a]	£2.50	N/A	N/A	NHS Drugs Tariff
Blood ketone detection strips (pack of 10)[b]	£20.75	N/A	N/A	NHS Drugs Tariff
Intensive care, ECMO[c]/ECLS[d]	£4,391	Normal	£11.58	NHS Reference Costs 2012/13
Intensive care, advanced enhanced	£2,409	Normal	£1.41	NHS Reference Costs 2012/13
Intensive care, advanced	£2,017	Normal	£5.57	NHS Reference Costs 2012/13
Intensive care, basic enhanced	£2,210	Normal	£0.74	NHS Reference Costs 2012/13
Intensive care, basic	£1,743	Normal	£2.60	NHS Reference Costs 2012/13
High dependency, advanced	£1,335	Normal	£2.05	NHS Reference Costs 2012/13
High dependency	£886	Normal	£1.67	NHS Reference Costs 2012/13
Diabetic mellitus with ketoacidosis or coma	£654	Normal	£6.89	NHS Reference Costs 2012/13

Item	Value	Distribution	SE	Source
Paediatric intensive care outpatient follow-up[e]	£173	Normal	-	NHS Reference Costs 2012/13
Paediatric outpatient follow-up	£190	Normal	£0.65	NHS Reference Costs 2012/13

SE standard error
a. www.ppa.org.uk/edt/October_2014/mindex.htm - Mission Ketone
b. www.ppa.org.uk/edt/October_2014/mindex.htm - GlucoMen LX ketone test strips
c. Extracorporeal membrane oxygenation (ECMO)
d. Extracorporeal life support (ECLS)
e. A standard error (SE) could not be estimated as NHS Reference Costs reported the same value for the lower and upper limits of the interquartile range

Table 109 presents further assumptions with respect to resource use.

Table 109: Ketone monitoring pack use and hospital length of stay

	Value	Source
Blood ketone detection packs per year	3	Guideline development group
Urine ketone detection packs per year	4	Guideline development group
Paediatric intensive care length of stays (days)	3	Guideline development group

19.5.2.6 Sensitivity analyses

To assess the robustness of the base-case results and to take account of data uncertainty, a number of sensitivity analyses were undertaken. These involved a mixture of 1-way sensitivity analyses (where a single model parameter is changed), 2-way sensitivity analyses and PSA using Monte Carlo simulation methods. PSA was undertaken for base-case data inputs and for each 1-way sensitivity analysis. Each PSA calculates the probability that blood ketone monitoring will be cost effective compared with urine ketone monitoring.

A ‘what-if’ analysis was used to assess the impact of assigning a QALY loss to an emergency room admission and hospitalisation.

19.5.3 Results

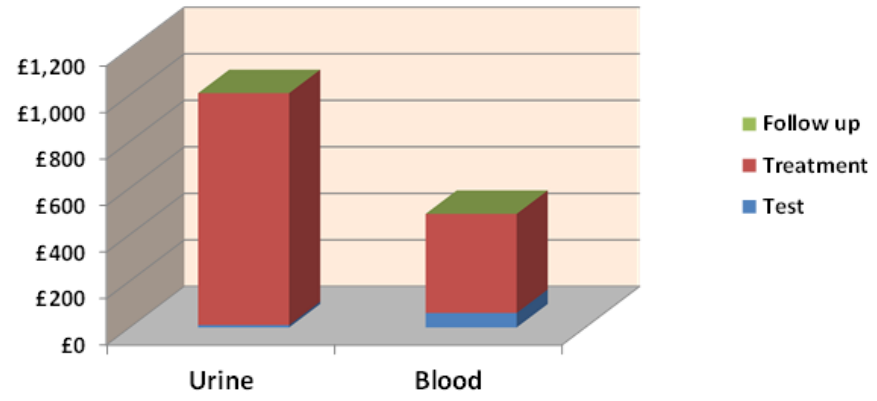
19.5.3.1 Base-case analysis

The base-case deterministic results are summarised in Table 110and depicted graphically inFigure 26. The results suggest that blood ketone monitoring is £519 cheaper per patient than urine ketone monitoring.

Table 110: Costs of blood and urine ketone monitoring

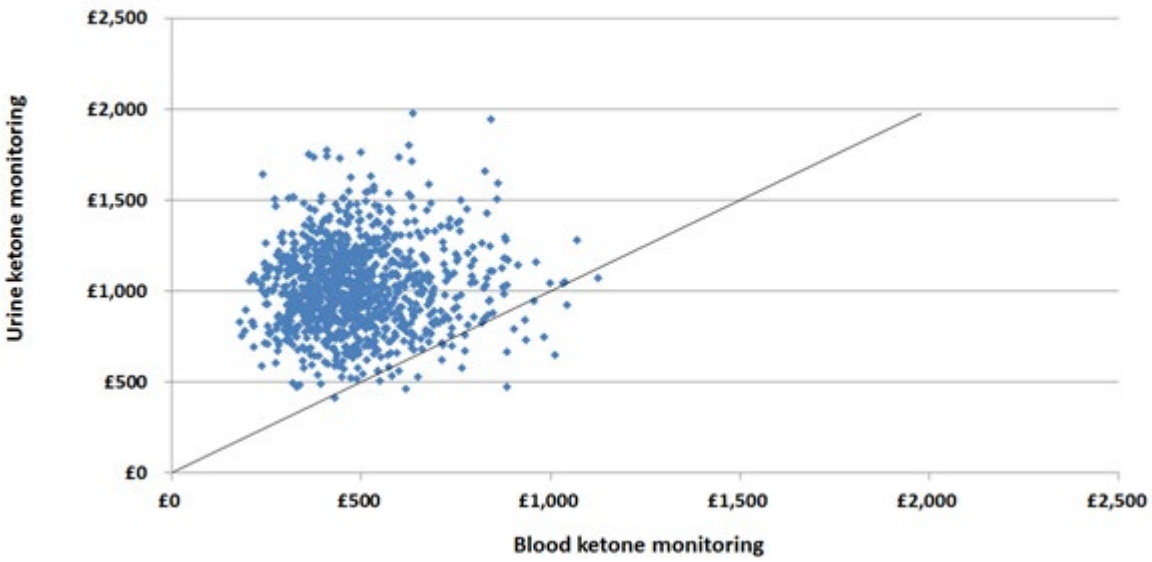
Cost category	Blood	Urine
Test	£62	£10
Treatment	£426	£997
Follow-up	-	-
Total	£488	£1,007

Figure 26: Graph comparing costs of blood and urine ketone monitoring



A PSA of 1000 simulations suggested that blood ketone monitoring was cheaper than urine ketone monitoring in 97.8% of simulations (see Figure 27). The diagonal line in Figure 27 indicates the threshold of equal cost for both monitoring strategies.

Figure 27: Probabilistic sensitivity analysis results based on base-case inputs



19.5.3.2 One-way sensitivity analyses

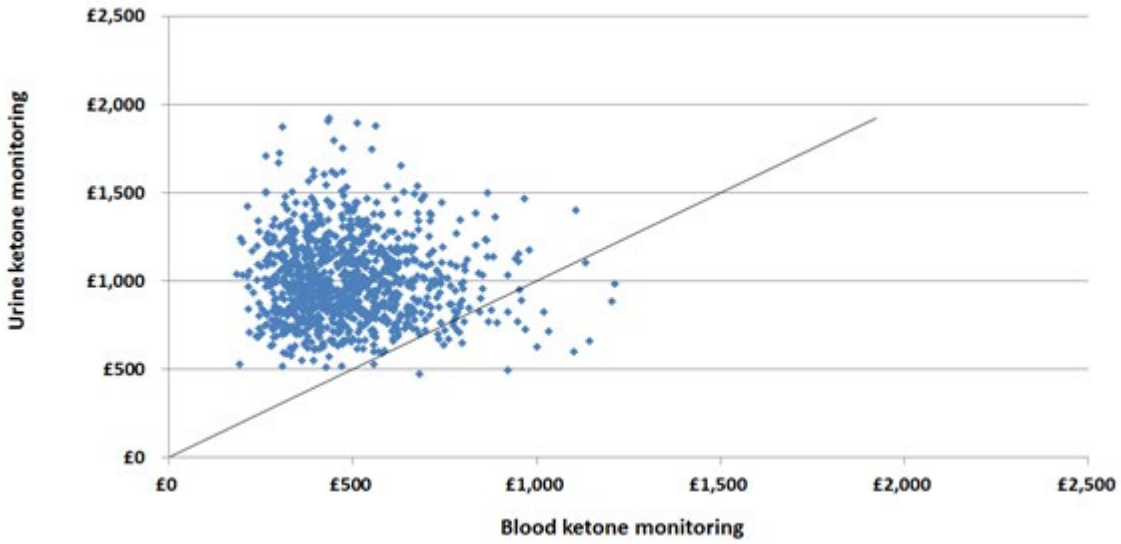
19.5.3.2.1 Including outpatient follow-up

The results of 1-way sensitivity analysis including outpatient follow-up are shown in Table 111 and, for the PSA, in Figure 28 The probability that blood ketone monitoring was cheaper than urine ketone monitoring was 96.9% in this PSA.

Table 111: Costs of blood and urine ketone monitoring when including the costs of an outpatient follow-up appointment

Cost category	Blood	Urine
Test	£62	£10
Treatment	£426	£997
Follow-up	£18	£50
Total	£507	£1057

Figure 28: Probabilistic sensitivity analysis based on base case inputs and including outpatient follow-up



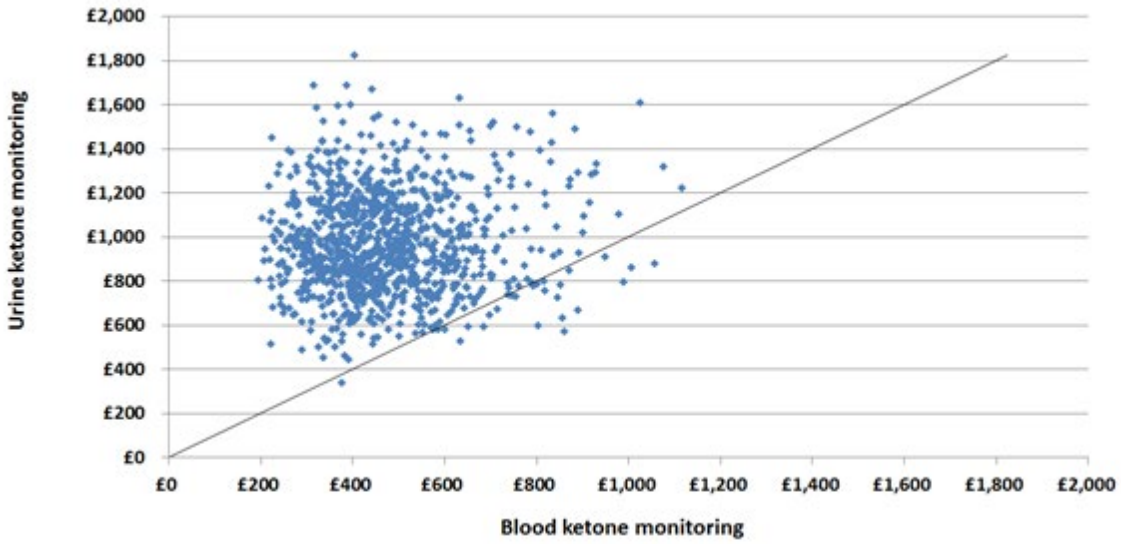
19.5.3.2.2 Including paediatric intensive care follow-up

The results of 1-way sensitivity analysis including paediatric intensive care follow-up are shown in Table 112 and, for the PSA, in Figure 29. The probability that blood ketone monitoring was cheaper than urine ketone monitoring was 97.5% in this PSA.

Table 112: Costs of blood and urine ketone monitoring when including the costs of a paediatric intensive care follow-up appointment

Cost category	Blood	Urine
Test	£62	£10
Treatment	£426	£997
Follow-up	£45	£79
Total	£533	£1,087

Figure 29: Probabilistic sensitivity analysis based on base-case inputs and including paediatric intensive care follow-up



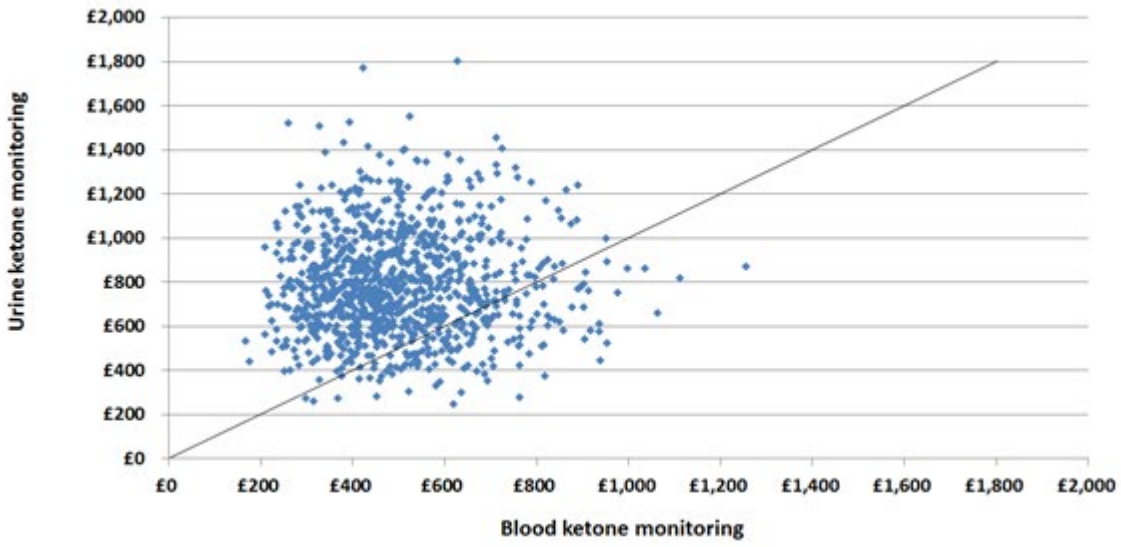
19.5.3.2.3 Reducing the rate of emergency admission with urine ketone monitoring to 13% per year

In this analysis the rate of emergency admission with urine ketone monitoring is reduced to 13%, approximately half that of blood ketone monitoring while maintaining all other inputs at their default values. The results of this analysis are shown in Table 113 and, for the PSA, in Figure 30. The probability that blood ketone monitoring was cheaper than urine ketone monitoring was 85.4% in this PSA.

Table 113: Costs of blood and urine ketone monitoring when reducing the rate of emergency admission with urine ketone monitoring

Cost category	Blood	Urine
Test	£62	£10
Treatment	£426	£783
Follow-up	-	-
Total	£488	£793

Figure 30: PSA based on base-case inputs but reducing the rate of emergency admission with urine ketone monitoring



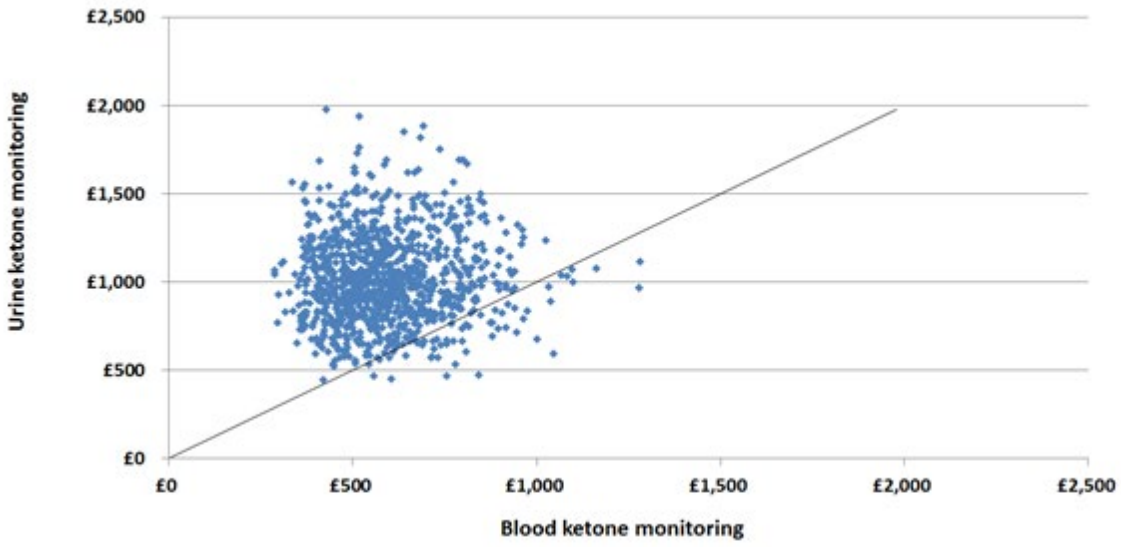
19.5.3.2.4 Eight blood ketone monitoring packs per year

This sensitivity analysis more than doubles blood ketone monitoring costs while maintaining other inputs at their default values. The results are given in Table 114 and, for the PSA, in Figure 31. The probability that blood ketone monitoring was cheaper than urine ketone monitoring was 94.5% in this PSA.

Table 114: Costs of blood and urine ketone monitoring when doubling the number of blood ketone monitoring packs

Cost category	Blood	Urine
Test	£166	£10
Treatment	£426	£997
Follow-up	-	-
Total	£592	£1007

Figure 31: PSA based on base-case inputs but doubling the number of blood ketone monitoring packs per year



19.5.3.3 Two-way sensitivity analysis

Although 1-way sensitivity analysis is useful in demonstrating the impact of varying 1 parameter in the model, changing 2 variables simultaneously and examining their relationship may aid interpretation when investigating uncertainty around the estimated results. It can be used to show a threshold where blood or urine ketone monitoring becomes cheaper and a view can be made as to whether the threshold value could plausibly be crossed given existing uncertainty.

The model allows 2 parameters to be varied simultaneously. Using a Visual Basic® macro 10,000 combinations of these parameters were compared. A lower and upper limit is set for each parameter and 100 equally spaced parameter values between these limits are evaluated (100×100).

Results are shown graphically as a threshold analysis for each combination of values within a given range. Any 2 of the following parameters can be selected for 2-way sensitivity analysis:

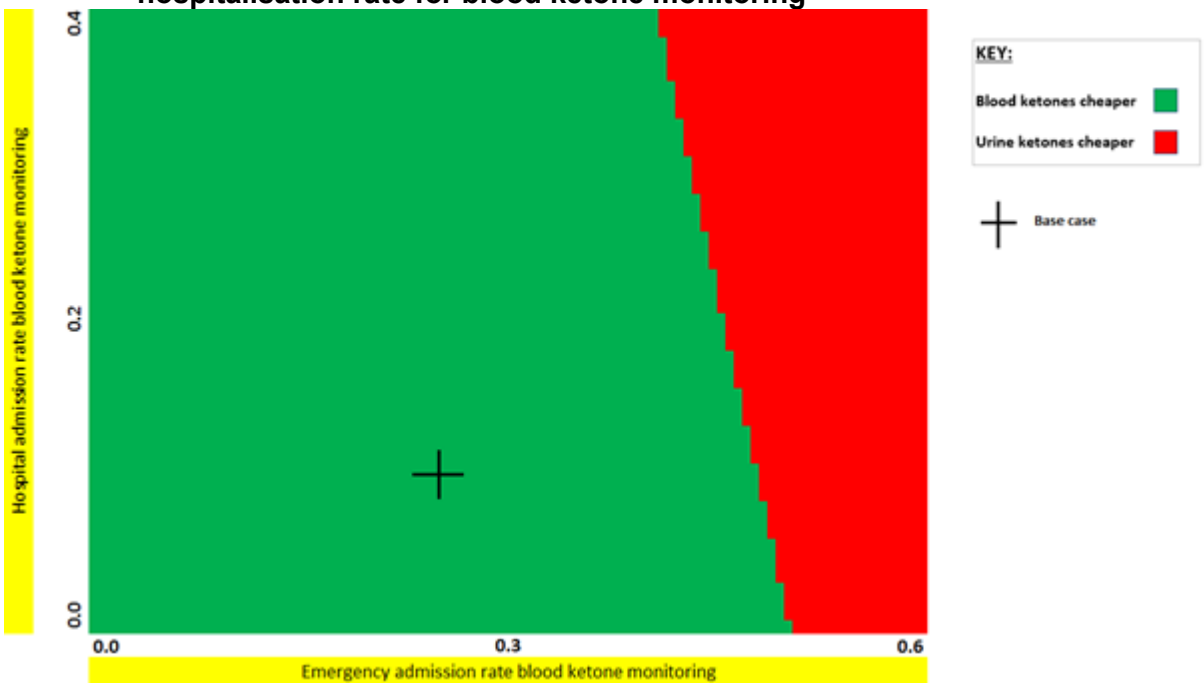
- rate for emergency room admission – blood
- rate for emergency room admission – urine
- rate for hospitalisation – blood
- rate for hospitalisation – urine
- number of test packs – blood
- number of test packs – urine
- cost per pack of test strips – blood
- cost per pack of test strips – urine
- high dependency unit cost
- length of stay.

A number of 2-way sensitivity analyses are described below.

19.5.3.3.1 *Varying the emergency room admission and hospitalisation rate for blood ketone monitoring*

The results for this 2-way sensitivity analysis are shown in Figure 32. It shows the combinations of emergency room admission rates and hospitalisation rates with blood ketone monitoring compared with blood ketone monitoring holding all other inputs constant at their base-case values. The base-case inputs for these 2 variables falls well within the green shaded cost effectiveness region.

Figure 32: Graph of 2-way sensitivity varying emergency room admission and hospitalisation rate for blood ketone monitoring

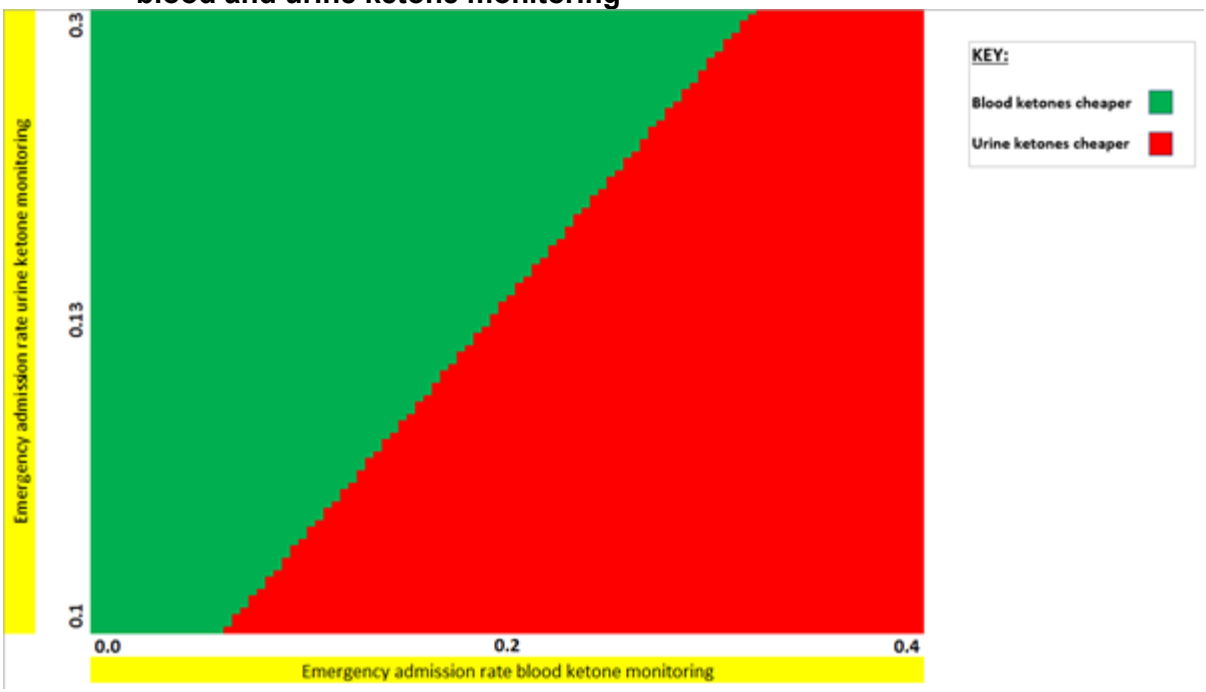


In addition, further probabilistic sensitivity analysis demonstrated that the probabilities of ketone monitoring being cost effective relative to urine ketone monitoring were 72.2% and 68.4% if both emergency room and hospitalisation rates were assumed to be 25% and 20% of the levels reported in the trials, respectively.

19.5.3.3.2 *Varying the emergency room admission rate for blood and urine ketone monitoring*

Figure 33 shows the impact of varying the emergency room admission rate for blood and urine ketone monitoring. Again, the default emergency admission rates lie well within the green shaded area for cost effectiveness.

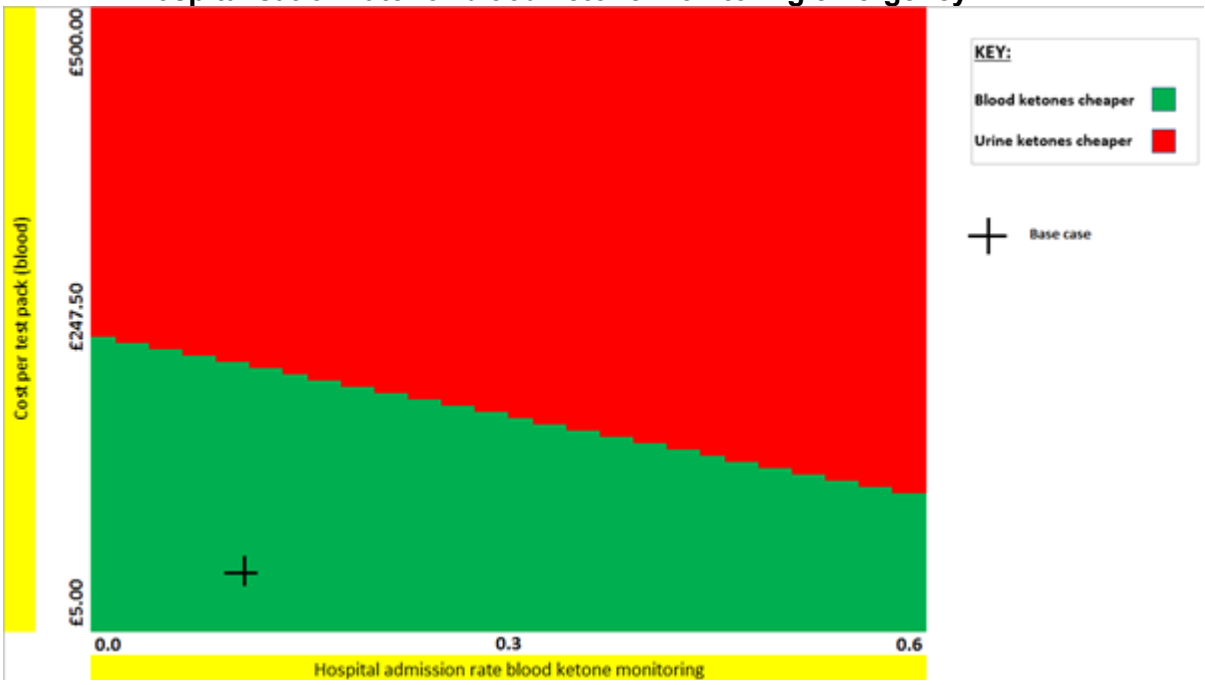
Figure 33: Graph of 2-way sensitivity varying emergency room admission rates for blood and urine ketone monitoring



19.5.3.3.3 Varying the cost of a blood ketone pack and the hospitalisation rate for blood ketone monitoring

In this sensitivity analysis the cost of a pack of blood monitoring ketone strips is varied along with the blood ketone monitoring hospitalisation rate and the results are displayed in Figure 10. It should be noted that the upper limit of the cost of a pack of blood monitoring ketone strips has been set to a level well in excess of the default value (over which there is no uncertainty). However, the analysis does show the trade-off between these variables necessary to retain cost effectiveness.

Figure 34: Graph of 2-way sensitivity varying the cost of a blood ketone pack and the hospitalisation rate for blood ketone monitoring emergency



19.5.3.4 'What-if' quality adjusted life year analysis

A QALY loss of 0.003 was assigned to a hospitalisation and an emergency room admission, while keeping all other inputs at their base-case values. The value of this QALY is not evidence based but is designed to reflect the fact that DKA is a short-lived medical emergency. The value of the 'what-if' QALY loss used in this sensitivity analysis might be interpreted as upper bound estimate of the QALY loss associated with a DKA hospital admission. It is based on a health state utility equivalent to death but experienced only for a period of 24 hours.

The results of this analysis are shown in Table 115.

Table 115: Incremental cost effectiveness of blood ketone monitoring assuming a quality adjusted life year loss is attributable to an admission

Monitoring method	Cost	QALY	Incremental cost	Incremental QALY	ICER
Urine	£1,545	−0.0022	-	-	-
Blood	£786	−0.0011	−£760	0.0011	Dominant

ICER incremental cost-effectiveness ratio, QALY quality adjusted life year

19.5.4 Discussion

Although the initial test cost for blood ketone monitoring exceeded the urine test cost per year, the total cost for urine ketone monitoring was almost twice that of blood ketone monitoring in the base-case analysis. The main driver of this differential is the increased treatment costs associated with urine ketone monitoring as a result of increased hospitalisation (see Figure 26).

Although cost effectiveness is based only on costs, it would be expected that any mortality and morbidity would be positively correlated with hospitalisation. Therefore, were it possible

to attach utilities to patient outcomes it would be expected that this would strengthen the results of the cost minimisation analysis as exemplified in the 'what-if' analysis.

All of the sensitivity analyses reported here suggest that the finding that blood ketone monitoring is cost effective relative to urine ketone monitoring is robust.

It should be noted that there are limitations with this analysis. In particular it is based on a single small study from the US (Laffel 2005), which was the only evidence that met the inclusion criteria for the clinical review related to this question.

19.5.5 Conclusion

Subject to the caveats about the quality of the data, this analysis suggests that there is a very high probability that blood ketone monitoring is cost effective compared with urine ketone monitoring.

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20.2 2015 update

This section was updated in 2015.

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21 Abbreviations

Abbreviations from the 2004 guideline

Abbreviation	
CI	Confidence interval
CGMS	Continuous glucose monitoring system
CSII	Continuous subcutaneous insulin infusion
DCCT	Diabetes Control and Complications Trial
GDG	Guideline Development Group
GPP	Good practice point
GRP	Guideline Review Panel
HbA1, HbA1c	Glycated haemoglobin
IQ	Intelligence quotient
LSHTM	London School of Hygiene and Tropical Medicine
NCB	National Children's Bureau
NCC-WCH	National Collaborating Centre for Women's and Children's Health
NICE	National Institute for Clinical Excellence
NICE TA	NICE Technology Appraisal
NNT	Number needed to treat
OGTT	Oral glucose tolerance test
OR	Odds ratio
QALY	Quality-adjusted life year
RCT	Randomised controlled (clinical) trial
RR	Relative risk (or risk ratio)
SD	Standard deviation
SE	Standard error
WMD	Weighted mean difference

Abbreviations and acronyms from the 2015 update

Abbreviation/acronym	Definition
3-OHB	3-hydroxybutyrate
Ab+	Antibody positive
ACE	Angiotensin converting enzyme
ACR	Albumin:creatinine ratio
ADA	American Diabetes Association
AER	Albumin excretion rate
AGREE	Appraisal of Guidelines for Research and Evaluation
BDR	Background diabetic retinopathy
BFST	Behavioural family systems therapy
BMI	Body mass index
BMI-SDS	Body mass index – standard deviation score
BSPED	British Society for Paediatric Endocrinology and Diabetes
CASCADE	Child and Adult Structured Competencies Approach to Diabetes Education
CBT	Cognitive behavioural therapy

Abbreviation/acronym	Definition
CGMS	Continuous glucose monitoring system
CHF	Chronic heart failure
CI	Confidence interval
CO^2	Carbon dioxide
CSII	Continuous subcutaneous insulin infusion
CST	Coping Skills Training
CVD	Cardiovascular disease
DCCT	Diabetes Control and Complications Trial
DKA	Diabetic ketoacidosis
QOLY-SF	Diabetes Quality of Life for Youth – Short Form
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
EDIC	Epidemiology of Diabetes Interventions and Complications
EED	Economic Evaluation Database
eGFR	Epidermal growth factor receptor
ESRD	End-stage renal disease
FPG	Fasting plasma glucose
GAD	Anti-glutamic acid decarboxylase
GAD65, GAD65+	Glutamic acid decarboxylase autoantibody 65 (positive)
GADA	Anti-glutamic acid decarboxylase antibody
GP	General practitioner
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GRP	Guideline review panel
HAEM	Haemoglobin
HbA1c	Glycated haemoglobin
HDL	High-density lipoprotein
HR	Hazard ratio
HTA	Health Technology Assessment
IAA	Insulin autoantibody
IA-2	Insulinoma-associated autoantibody
IA-2A+	Insulinoma-associated autoantibody-positive
IA-2β-A	Insulinoma-associated beta autoantibody
ICA	Islet-cell antibodies
ICA512	Anti-islet cell antibody 512
ICER	Incremental cost effectiveness ratio
ICU	Intensive care unit
IFCC	International Federation of Clinical Chemistry
IGRP	Islet-specific glucose-6-phosphatase catalytic subunit
IQR	Interquartile range
ISPAD	International Society for Pedatric and Adolescent Diabetes
ITU	Intensive care unit
KICk-OFF	Kids In Control OF Food
LADA	Latent autoimmune diabetes of adulthood
LDL	Low-density lipoprotein
LVH	Left ventricular hypertrophy

Abbreviation/acronym	Definition
MA	Microalbuminuria
MCMC	Markov chain Monte Carlo
MD	Mean difference
MDI	Multiple daily injection
ME	Macular oedema (edema)
MI	Myocardial infarction; Multiple injections (see context)
MID	Minimally important difference
MIMS	Monthly Index of Medical Specialities
MMTT	Mixed meal tolerance test
MODY	Maturity onset diabetes of the young
MRI	Magnetic resonance imaging
MST	Multisystemic therapy
NA	Not applicable
NC	Not calculable
NCC	National Collaborating Centre
NCC-WCH	National Collaborating Centre for Women's and Children's Health
NCGC	National Clinical Guideline Centre
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NPH	neutral protamine Hagedorn
NPSA	National Patient Safety Agency
OR	Odds ratio
PDR	Proliferative diabetic retinopathy
PDSN	Paediatric diabetes specialist nurse
PedsQL	Paediatric quality of life
PSA	Probabilistic sensitivity analysis
PVD	Peripheral vascular disease
QALY	Quality adjusted life years
QUADAS	Quality Assessment of Studies of Diagnostic Accuracy
RCT	Randomised controlled trials
RR	Relative risk
SBP	Systolic blood pressure
SD	Standard deviation
SDS	Standard deviation score
SMBG	Self-monitoring of blood glucose
SMD	Standardised mean difference
SVL	Severe visual loss
T1D	Type 1 diabetes
T2D	Type 2 diabetes
TRIG	Triglycerides
UCPCR	Urine C-peptide:creatinine ratio
UKPDS	UK Prospective Diabetes Study
VTE	Venous thromboembolism
WBC	White blood cells

Appendices

This section was updated in 2015.

Appendices A to N are presented in separate files. The individual appendices are listed below for reference.

Appendix A: Recommendations from NICE clinical guideline 15 (2004) that have been deleted or changed

Appendix B: 2015 update scope

Appendix C: Stakeholder organisations

Appendix D: Declarations of interest

Appendix E: Review protocols

Appendix F: Search strategies

Appendix G: Summary of identified studies

Appendix H: Excluded studies

Appendix I: Evidence tables

Appendix J: Forest plots

Appendix K: GRADE tables

Appendix L: Research recommendations

Appendix M: Young people's consultation day

Appendix N: Superseded text from 2004 guideline