NICE National Institute for Health and Care Excellence

Surveillance proposal consultation document

2019 surveillance of 4 diabetes guidelines

Surveillance proposal

We propose to update the following guidelines on diabetes at this time:

- Type 1 diabetes in adults: diagnosis and management (NICE guideline NG17). The proposed update will focus on insulin therapy and management of complications.
- Type 2 diabetes in adults: management (NICE guideline NG28). The proposed update will focus on blood glucose management and management of complications.
- Diabetes (type 1 and type 2) in children and young people: diagnosis and management (NICE guideline NG18). The proposed update will focus on measures to encourage screening for diabetic retinopathy and fluid and insulin therapy for diabetic ketoacidosis.

We propose to not update the guideline on Diabetic foot problems: prevention and management (NICE guideline NG19).

Reasons for the proposals

This section provides a summary of the reasons for the proposals.

Type 1 diabetes in adults: diagnosis and management

Blood glucose management

Telemedicine

Evidence was identified to support the use of telemedicine to manage blood glucose. Telemedicine interventions such as remote monitoring devices linked to clinicians for review, online education platforms and teleconference sessions were all found to significantly reduce HbA1c levels. Digital interventions that enable care to be delivered remotely feature heavily in the NHS Long-Term Plan. Currently the guideline only mentions structured education as a way of empowering people to self-monitor (recommendation 1.6.16). Taken together, most of the evidence suggests there may be a benefit of telemedicine interventions in improving blood glucose management, which is consistent with the NHS Long Term Plan. Therefore, it is proposed that this area is reviewed.

Smartphone applications and online platforms

Evidence was identified to support the use of a smartphone application to enhance self-monitoring. This area is relevant to the diabetes work running in the NHS England Test Bed programme, where digital platforms are being evaluated in real-world settings to enhance self-management. There are no published findings yet available from this work, however the NHS Long Term Plan does mention expanding the NHS Test Bed programme as one its objectives. A topic expert also raised digital platforms as an area that is in need of review. Considering the ongoing work in this area, the new evidence on smartphone applications and the importance of digital platforms emphasised in the NHS Long-Term Plan, it is proposed that this area is reviewed.

Flash glucose monitoring

Evidence was identified to support the use of Flash glucose monitoring in people with well-controlled diabetes. Topic experts also highlighted this as an area in need of review. Currently the guideline does not contain any recommendations on Flash glucose monitoring, however some of the evidence identified has already been considered in the NICE medtech innovation briefing on Freestyle Libre for glucose monitoring (MIB110) which covers people with type 1 and type 2 diabetes, as well as pregnant women with diabetes. This area is also relevant to a recent policy change in the NHS, ensuring access to Flash glucose monitoring on prescription in the NHS if patients meet various eligibility criteria such as: people who are clinically indicated as requiring intensive monitoring (more than 8 times a day); people unable to self-monitor; those with recurrent severe hypoglycaemia (if they have ruled out other options recommended in NICE guideline NG17 with their clinician); as well as other criteria listed in this statement. The new evidence does not cover these populations because the studies only include people with well-controlled diabetes, however given that the evidence on this device has not yet been considered since this guideline was published, it is proposed that this area is reviewed.

Insulin therapy

Long-acting insulin

Evidence was identified which supports the use of the ultra-long-lasting insulin degludec. This was also an area raised by topic experts, who highlighted that the evidence on new insulins needs reviewing. Whilst the original guideline committee noted that *how* insulins are used is more important than *which specific insulin within class* is used, there are still recommendations offering insulin detemir or insulin glargine in adults with type 1 diabetes (recommendation 1.7.4). Given the expert advice and the new evidence supporting ultra-long-lasting insulin, we propose this area is reviewed. The safety profiles and dosage conversions will also need careful consideration, given the advice in the corresponding drug safety update.

Biosimilar insulins

Evidence was identified to suggest that various biosimilar insulins may be non-inferior to original insulin formulations such as lispro and glargine. The guideline currently recommends offering insulin detemir or insulin glargine in adults with type 1 diabetes (recommendation 1.7.4). This was also an area raised by topic experts, who highlighted the potential cost savings available when switching to cheaper (but clinically comparable) insulins. Furthermore, recommendation 1.7.5 currently states "When choosing an alternative insulin regimen, take account of the person's preferences and acquisition cost" which reinforces the need to review cheaper alternatives. In light of the new evidence, it is proposed that this area is reviewed.

Adjuncts to insulin

We identified several trials examining the effect of SGLT2 inhibitors as an adjunct to insulin therapy. Topic experts also highlighted this as a possible area for update. Many of the studies were related to NICE technology appraisals currently in development, so cannot be considered in this surveillance review. However, there was some evidence to suggest that canagliflozin significantly improved HbA1c levels and body weight compared to placebo. Canagliflozin is a SGLT2 Inhibitor currently licensed for use in type 2 (but not type 1) diabetes. Given that the guideline does not currently have any recommendations on offering SGLT2 inhibitors, we propose that the impact of the NICE technology appraisals is assessed when the decisions are finalised. However, careful consideration will need to be given to the indication of adjunct therapy with SGLT2 inhibitors, whether this be glycaemic control or weight loss.

Managing complications

Eye disease

New evidence was identified on the treatment of diabetic eye disease, including retinopathy and macular oedema. The evidence supports the use of anti-VEGF treatment and intravitreous injection of aflibercept for diabetic retinopathy and laser therapy for diabetic macular oedema. Currently the guideline has recommendations on screening and referral, but no recommendations on specific treatments. However, there are many treatments covered in NICE technology appraisal guidance, suggesting that there may be a gap in the recommendations of NICE guideline NG17. Given the growing evidence base and the related NICE technology appraisal guidance, we propose that this area is reviewed.

Topic experts also highlighted new evidence on the optimum frequency of diabetic eye screening. This area was not considered in the surveillance review because it falls under the remit of the NHS Diabetic Eye Screening Programme who cover screening and referral criteria for people with diabetes. However, to avoid an overlap in guidance we plan to withdraw the recommendations on screening and referral.

Areas not proposed for update

Evidence was identified on education and information, dietary management and control of cardiovascular risk which directly supports or is consistent with existing recommendations and therefore has no impact on NICE guideline NG17.

Evidence was also identified on care of adults with type 1 diabetes in hospital which indicates that while basal-bolus insulin might result in better short-term glycaemic control than sliding scale insulin, it could also increase the risk for severe hypoglycaemic episodes. However, the new evidence was inconclusive about which insulin strategy has the best patient outcomes so further research is required before any impact on the guideline, which recommends using the basal-bolus strategy, can be concluded.

Evidence was also identified on areas not currently covered in NICE guideline NG17 which supports the use of closed-loop insulin delivery systems and sensor-augmented pump therapy in adults with type 1 diabetes, however further evidence from larger randomised control trials, with long-term follow-up and examining safety outcomes is required to confirm these findings.

For further details and a summary of all evidence identified in surveillance, see appendix A1 (NG17- type 1 diabetes in adults evidence summary).

Type 2 diabetes in adults

Blood glucose management

First intensification

Clinical characteristics

Evidence indicates that important clinical characteristics need to inform the choice of first intensification medication, after failure to control blood glucose with metformin and lifestyle interventions. These include:

- The presence of established atherosclerotic cardiovascular disease (CVD), for which there is now evidence to support the use of SGLT2 inhibitors and GLP1 agonist classes. However, some studies of individual drugs within these classes have demonstrated superiority over placebo (Harmony Outcomes [albiglutide], LEADER [liraglutide]) whereas others have not (ELIXA [lixisenatide] and EXSCEL [exenatide] suggesting that this may not be a class effect.
- Other comorbidities, such as heart failure or chronic kidney disease
- Risk of specific adverse medicine effects, particularly hypoglycaemia and weight gain.
- Safety and tolerability.

Cost effectiveness

At the time of the 2017 NICE review of SGLT-2 inhibitors and GLP-1 mimetics, the committee noted that there were no cost effectiveness studies on these classes based directly on cardiovascular outcomes reported in randomised trials. In the absence of robust cost effectiveness evidence, the committee agreed it would not be appropriate to make specific recommendations about the place of SGLT-2 inhibitors and GLP-1 mimetics in the diabetes management pathway, as to do so would involve a comparison to all the other available antidiabetic drug options, something that was not possible to do based on cardiovascular outcomes.

The committee therefore agreed it was appropriate that a larger scale update of the antidiabetic drug pathway in NICE NG28 be undertaken, and that this should be timed to also take in to account the evidence from several large trials, which were ongoing at the time, so all the relevant drugs from these classes can be considered:

These key CVD outcome trials, have now published:

DECLARE-TIMI 58 (dapagliflozin), HARMONY Outcomes (albiglutide),

EXSCEL (exenatide)

REWIND (dulaglutide – preliminary results).

It is therefore proposed that a review be undertaken as recommended by the committee, of the antidiabetic drug pathway in NICE NG28. This should include:

- Consideration of the concurrent review of related technology appraisals (TAs) and ongoing development of new TAs for SGLT2 inhibitors and GLP1 analogues. These will incorporate new evidence for canagliflozin, dapagliflozin, empagliflozin and ertugliflozin in the SGLT-2 class, and semaglutide and dulaglutide in the GLP-1 class. Both dual (first intensification) and triple (second intensification) therapy are covered within the scope of these TAs.
- Clinical characteristics detailed above and the potential need to adopt a risk stratification approach to sequencing of treatment.
- Safety and tolerability, taking into account the latest MHRA safety warning for SGLT-2 inhibitors.
- Patient adherence, taking into account frequency of monitoring and route of administration.
- Acquisition costs of individual drugs and cost effectiveness of drug combinations from different classes. The 2017 review committee noted that SGLT2 inhibitors had the same price per dose in 2017. No cost studies were identified on this class, but new evidence for GLP-1 analogues is conflicting on the comparative cost effectiveness of liraglutide and exenatide. A review of the health economic model is proposed.

Second intensification

The guideline recommends that if dual therapy with metformin and another oral drug has not continued to control HbA1c to below the person's individually agreed threshold for intensification, then triple therapy should be considered comprising metformin, a sulfonylurea and either a DPP-4 inhibitor or pioglitazone. Alternatively, insulin-based treatments can be considered.

If this is not effective, not tolerated or contraindicated, a GLP-1 mimetic can be considered in combination with metformin and a sulfonylurea.

Insulin-based treatments are advised if metformin is contraindicated or not tolerated, and if dual therapy with 2 oral drugs has not continued to control HbA1c to below the person's individually agreed threshold for intensification.

The guideline refers to DPP-4 inhibitors, GLP-1 mimetics and sulfonylureas at a class level in the recommendations, and to SGLT-2 inhibitors in additional text added since publication. However, cardiovascular outcomes were not considered in the guideline and therefore the same rationale for a comprehensive review of the antidiabetic drug pathway applies to second intensification as for first intensification (as detailed above). The review of second intensification should also consider:

- The evidence indicating that GLP-1 mimetics as a class may be cost-effective, with additional drug costs offset by diabetes-related complication decreases, leading to slightly lower direct medical costs.
- Evidence supporting the use of liraglutide for T2D in combination with insulin, particularly for improving glucose control, cardiovascular outcomes and weight loss.

Insulin-based treatments

The guideline recommends that when insulin therapy is necessary, it should be started from a choice of a number of insulin types and regimens. Neutral Protamine Hagedorn (NPH) insulin injected once or twice-daily according to need is the preferred option. Insulin detemir or insulin glargine can be considered as an alternative in certain circumstances (see recommendations 1.6.34 and 1.6.35 for details). There are several insulin glargine products available including Lantus, the biosimilar Abasaglar or high-strength Toujeo.

New evidence was identified showing that biosimilars Abasaglar, SAR342434 and MYL-1501D are non-inferior to glargine in reducing HbA1c, with similar safety profiles.

The price reduction of Tresiba (degludec) and evidence indicating its cost effectiveness, in addition to the emergence of cheaper biosimilars, following expiry of the patent for insulin glargine, have implications for the health economics of insulin-based treatments. Further biosimilars are also in development. The choice between these longer-acting basal insulins may be determined by factors such as access and cost, alongside clinical considerations.

There is a potential impact on the guideline to review the increasing range of biosimilar and analogue insulins now available. The acquisition costs, safety profiles and dosage conversions will need to be taken into consideration.

Insulin monotherapy compared with the addition of oral antidiabetic drugs

The new systematic review evidence supports the addition of several classes oral glucose-lowering agents to insulin in T2D patients requiring insulin therapy, but that additional weight gain is only avoided by adding metformin. This is largely consistent with recommendation 1.6.33, which advises continuing to offer metformin with insulin therapy in adults with T2D, and to review the continuing need for other blood glucose lowering therapies.

The supplementary text in the guideline stating that treatment with combinations of medicines including SGLT-2 inhibitors may be appropriate for some people with T2D remains valid but should be reviewed as part of the proposed broader review of the antidiabetic drug pathway to clarify the sequencing of particular drug classes, and individual drugs.

Managing complications

Eye disease

The same reason for updating and proposed review of recommendations for diabetic eye disease as stated for NG17 applies to NG28. New evidence was identified on the treatment of diabetic eye disease, including retinopathy and macular oedema. Given the growing evidence base and the related NICE technology appraisal guidance, we propose that this area is reviewed.

Areas not proposed for update

Evidence was identified on individualised care, patient education and antiplatelet therapy which directly supports or is consistent with existing recommendations and therefore has no impact on NICE guideline NG28.

New evidence was identified concerning dietary advice and the effectiveness of low or very low-calorie diets on short-term remission of type 2 diabetes in adults, however it is proposed that further evidence of long-term effectiveness of these diets is required before this is considered as an area for update. It is also felt that advising on low-calorie diets would not be at odds with the current recommendations to provide adults with type 2 diabetes individualised advice for carbohydrate intake and meal patterns.

New evidence was also identified concerning the use of motivational interviewing techniques for changing diet in adults with type 2 diabetes, results of which were inconclusive, with variation in trial and interventions design (components and intensity) making it difficult to identify best practice strategies. There are currently no recommendations on motivational interviewing, but it is proposed that further research identifying the effective components of motivational interviewing would be required for this to be considered as an area for update.

For further details and a summary of all evidence identified in surveillance, see appendix A2 (NG28 – type 2 diabetes in adults).

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

Diabetic retinopathy in children and young people with type 1 or type 2 diabetes

Evidence was identified indicating that compared with usual care, quality improvement initiatives incorporating behaviour change techniques such as goal-setting and additional social support lead to a substantial increase in diabetic retinopathy screening attendance and are likely to be cost-effective. While uptake data for NICE guideline NG18 indicates that there have been annual increases between 2015 and 2017 in the percentage of children aged 12 years or older with type 1 diabetes having an eye screening or a referral for eye screening, there remains room for improvement with the figure in 2017 at 74.4%; and the uptake data for children aged 12 years or older who have type 2 diabetes indicates that only just over half (54.8%) attended an annual eye screening appointment in 2017. The current recommendations 1.2.1 to 1.2.11 and 1.3.1 to 1.3.7 on education and information for children and young people with type 1 or type 2 diabetes respectively, discuss the need to provide a continuing, tailored programme of education but do not mention any behaviour change techniques that may improve actions such as attendance at screening appointments. It is therefore proposed that investigating the effectiveness of incorporating behaviour change techniques into services for children with diabetes is an area for review.

Fluid and insulin therapy for diabetic ketoacidosis

Evidence was identified which indicates that rapid fluid infusion at volumes higher than those currently recommend in recommendation 1.4.31 is not associated with an increased risk of cerebral oedema in children and young people with diabetic ketoacidosis; and that in the case of severe diabetic ketoacidosis, more rapid fluid infusion rates may be associated with faster improvements in mental status. This evidence, along with international guidance reported by the International society for pediatric and adolescent diabetes (ISPAD) and topic expert opinion, indicates that this should be an area for review.

Areas not proposed for update

New evidence that directly supports or is consistent with existing recommendations and therefore has no impact on NICE guideline NG18 includes: evidence related to aspects of insulin therapy (offering multiple daily injections, basal-bolus insulin regimens from diagnosis, followed by offering continuous subcutaneous insulin infusion or pump if injections aren't appropriate), dietary management, blood glucose targets and monitoring, psychological and social issues in children and young people with type 1 diabetes; education and information and the use of metformin in children and young people with type 2 diabetes; service provision and transition from paediatric to adult care for children and young people with type 1 or type 2 diabetes.

Areas for which new evidence was identified, but the evidence base remains limited: the use of automated tools or systems to assist in the identification and diagnosis of type 2 diabetes in children and young people; insulin therapy for children and young people with type 1 diabetes which supports the use of the long-acting insulin in reducing HbA1c and the use of hybrid closed-loop therapy in controlling glucose and reducing the risk of hypoglycaemia; oral medicines for children and young people with type 1 diabetes which supports the use of metformin as an adjunct to insulin in improving HbA1c levels in the short-term. Further evidence from larger randomised control trials is required in order to consider whether these should be areas for update.

For further details and a summary of all evidence identified in surveillance, see appendix A3 (NG18 – Type 1 and type 2 diabetes in children evidence summary).

Diabetic foot problems

The majority of evidence was found to be consistent with the current guideline recommendations. Improvements were seen in the area of wound dressings for several wound healing outcomes, however there was a lack of comparison between interventions. The evidence found supports the use of wound dressings as an intervention rather than highlighting a specific product. Evidence for new treatment options was thinly spread across multiple products, with no evidence of product superiority found. This is in line with topic expert feedback which suggested the new trials available would be unlikely to impact the current guideline recommendations. We did not look for evidence relating to the use of systemic antibiotics for the treatment of diabetic foot infection as an antimicrobial prescribing guideline is in production in this area.

For further details and a summary of all evidence identified in surveillance, see appendix A4 (NG19 – diabetic foot problems).

Overview of 2019 surveillance methods

NICE's surveillance team checked whether recommendations in the following guidelines remain up-to-date:

- Type 1 diabetes in adults: diagnosis and management (NICE guideline NG17)
- Type 2 diabetes in adults: management (NICE guideline NG28)
- Diabetes (type 1 and type 2) in children and young people: diagnosis and management (NICE guideline NG18)
- Diabetic foot problems: prevention and management (NICE guideline NG19)

For all guidelines, the surveillance process consisted of:

- Feedback from topic experts via a questionnaire.
- A search for new or updated Cochrane reviews.

- Examining related NICE guidance and quality standards and NIHR signals.
- A search for ongoing research.
- Examining the NICE event tracker for relevant ongoing and published events.
- Literature searches to identify relevant evidence.
- Assessing the new evidence against current recommendations to determine whether or not to update sections of the guideline, or the whole guideline.
- Consulting on the proposal with stakeholders (this document).

For further details about the process and the possible update decisions that are available, see ensuring that published guidelines are current and accurate in developing NICE guidelines: the manual.

Evidence considered in surveillance

Search and selection strategy

For details of the individual search and selection strategies used please refer to the following appendices:

- Appendix A1 (NG17 - Type 1 diabetes in adults)
- Appendix A2 (NG28 - Type 2 diabetes in adults)
- Appendix A3 (NG18 - Type 1 and type 2 diabetes in children)
- Appendix A4 (NG19 – Diabetic foot problems)

Intelligence gathered during surveillance

Views of topic experts

We considered the views of topic experts, including those who helped to develop the guideline. For this surveillance review, topic experts completed a questionnaire about developments in evidence, policy and services related to each of the 4 guidelines.

The following responses were received from 20 topic expert questionnaires sent for each guideline:

- NICE guideline NG17- Six responses were received, 5 of the experts felt an update was needed and 1 was unsure.
- NICE guideline NG28 – Seven responses were received, all 7 of the experts agreed that an update is needed.

- NICE guideline NG18 – Five responses were received, 4 of the experts felt an update was needed and 1 was unsure.
- NICE guideline NG19 – Seven responses were received, all 7 of the experts agreed that no update is required at this time.

For full details of the topic expert feedback for these 4 guidelines, please see appendices A1-A4.

Views of stakeholders

See ensuring that published guidelines are current and accurate in developing NICE guidelines: the manual for more details on our consultation processes.

Equalities

No equalities issues were identified during the surveillance process.

Editorial amendments

During surveillance of the guidelines we identified the following points in each of the 4 guidelines that should be amended.

Type 1 diabetes in adults

Recommendation 1.15.43: The hyperlink to NG69 needs updating to link to the latest version of the guideline.

Recommendation 1.15.42: The cross referral to NICE guideline CG113 should be changed to the most recent title: "Generalised anxiety disorder and panic disorder in adults: management".

Type 2 diabetes in adults

Antihypertensive drug treatment

NICE guideline CG127 on hypertension in adults, recommendation 1.6.15 states that low cost angiotensin-II receptor blocker (ARB) should be used in preference to an ACE inhibitor in all African or Caribbean people because of the low risk of angioedema. However, NG28 Recommendation 1.4.8 currently states the first line treatment should be an ACE inhibitor for a person of African or Caribbean family origin. Recommendation 1.4.10 advises that for a person with continuing intolerance to an ACE inhibitor (other than renal deterioration or hyperkalaemia), substitute an ARB for the ACE inhibitor.

It is proposed that the NICE NG28 recommendations in question be reviewed by the update committee and aligned appropriately with the NICE guideline on hypertension in adults, with revised text. A cross referral from NG28 section 1.4 to CG127 section 1.6 should be considered following the planned update of NICE CG127.

Cross-referrals

Recommendation 1.3.10: the cross referral to smoking: brief interventions and referrals and stop smoking services should be replaced with Stop smoking interventions and services. This should be done following the forthcoming review of the suite of NICE guidelines on smoking, to ensure the cross referral is current.

Recommendations 1.6.24 and 1.6.26: the following text will be added at the end to replace existing text cross referring to TAs: "Following the development of this guideline, new TAs are available that are relevant to this section. Please see the Type 2 diabetes in adults' pathway for further information."

Recommendations 1.6.24 and 1.6.26, 1.6.31 and 1.6.37: the following text will be added in the paragraph at the end to replace existing text cross referring to TAs: "Treatment with combinations of medicines including SGLT-2 inhibitors may be appropriate for some people with type 2 diabetes. Following the development of this guideline, new TAs are available that are relevant to this section. Please see the Type 2 diabetes in adults' pathway for further information."

Recommendation 1.7.22 requires the following footnote adding: "screening for diabetic retinopathy falls under the remit of the NHS Diabetic Eye Screening Programme."

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

Recommendation 1.2.32 lists the 'sulphonylureas', these are now spelled 'sulfonylureas', so should be changed to this new spelling. 'glyburide' is listed but that name isn't used in the UK and is a synonym for 'glibenclamide', which is already listed. 'glyburide' should therefore be removed from this recommendation.

Recommendations 1.2.110 and 1.3.43 require the following footnote adding: "screening for diabetic retinopathy falls under the remit of the NHS Diabetic Eye Screening Programme."

Recommendation 1.3.14 the cross-referrals to NICE guideline NG7 on 'preventing excess weight gain' and NICE guideline CG189 on 'obesity: identification, assessment and management' should be replaced with cross-referrals to the NICE physical activity, obesity and diet pathways

Diabetic foot problems

Section 1, Recommendations: The text box highlighting the certainty of recommendations contains an incorrect hyperlink. The following link "See about this guideline for details" goes to 'changes after publication'. It should be updated to About this guideline.

Overall surveillance proposal

After considering all evidence and other intelligence and the impact on current recommendations, we propose the following guidelines should be updated:

- Type 1 diabetes in adults: diagnosis and management (NICE guideline NG17).

- Type 2 diabetes in adults: management (NICE guideline NG28).
- Diabetes (type 1 and type 2) in children and young people: diagnosis and management (NICE guideline NG18).

We propose to not update the guideline on Diabetic foot problems: prevention and management (NICE guideline NG19).

Surveillance proposal consultation document

Appendix A3: Summary of evidence from surveillance

2019 surveillance of Diabetes (type 1 and type 2) in children and young people: diagnosis and management (2015) NICE guideline NG18

Contents:

- Evidence considered in surveillance
- Intelligence gathered during surveillance
- Summary of evidence from surveillance

Evidence considered in surveillance

Search and selection strategy

We searched for new evidence related to the whole guideline.

We found 31 studies in a search for randomised control trials (RCTs) and Cochrane reviews published between 1 June 2014 and 7 December 2018 for children and young people with type 1 diabetes and published between 26 August 2014 and 19 February 2019 for children and young people with type 2 diabetes.

The search dates differ as the literature search for evidence on children and young people with type 1 diabetes was part of a wider search for populations of any age with type 1 diabetes which was developed to identify evidence relevant to both NICE guideline NG17 on type 1 diabetes in adults and NICE guideline NG18. The second search strategy was developed specifically for evidence on children and young people only with type 2 diabetes. The start dates reflect the last date of searches performed for the evidence reviews of NICE guideline NG17 and NG18 respectively, and the end dates reflect differences in when work on each surveillance review started.

We also included:

- One relevant RCT from a total of 3 identified by topic experts, plus 6 additional non-RCT publications

- Two RCTs and 1 additional publication identified through comments received after publication of the guideline

From all sources, we considered 31 studies and 7 additional publications to be relevant to the guideline.

See summary of evidence from surveillance below for details of all evidence considered, and references.

Selecting relevant studies

Studies were included if they met the following criteria:

- they included children and young people with type 1 or type 2 diabetes. There was some flexibility given to studies that included young people older than 18 years old: these were included if the sample also clearly included children aged younger than 18 years old.
- were RCTs with a sample size of at least 40 or
- a Cochrane review.

Ongoing research

We checked for relevant ongoing research. Of the ongoing studies identified, 3 were assessed as having the potential to change recommendations, however the medications listed are not currently licenced for use in children and young people with type 1 or type 2 diabetes. These will be considered as relevant evidence if these medications gain a licence for use in this population. We plan to check the publication status regularly and evaluate the impact of the results on current recommendations as quickly as possible. These studies are:

- A Study to Investigate the Efficacy and Safety of Canagliflozin in Children and Adolescents (>=10 to <18 Years) With Type 2 Diabetes Mellitus
- Phase 3 Alogliptin Pediatric Study
- A Study of SIMPONI® to Arrest Beta-cell Loss in Type 1 Diabetes (T1GER).

Intelligence gathered during surveillance

Views of topic experts

For this surveillance review, topic experts completed a questionnaire about developments in evidence, policy and services related to NICE guideline NG18.

We sent questionnaires to 20 topic experts and received 5 responses. The topic experts were recruited to the NICE Centre for Guidelines Expert Advisers Panel to represent their specialty.

Four of the experts felt that the guideline should be updated, whereas one was unsure. Areas identified for update included: the effectiveness of newer insulins and cheaper biosimilar insulins for type 1 diabetes, the use of FreeStyle Libre for glucose monitoring (Flash), the definition of hypoglycaemia, changing the frequency of diabetic retinopathy screening, fluid therapy for children and young people with diabetic ketoacidosis, and the use of new technologies such as online education as an alternative to current structured education offerings. Further details are provided in the relevant 'Intelligence gathering' sections below.

Summary of evidence from surveillance

Studies identified in searches are summarised from the information presented in their abstracts.

Feedback from topic experts who advised us on the approach to this surveillance review, was considered alongside the evidence to reach a view on the need to update each section of the guideline.

A full list of guideline recommendations can be found on the website at the following link: https://www.nice.org.uk/guidance/ng18

1.1 Diagnosis

Surveillance proposal

This section should not be updated.

2019 surveillance summary

Diagnosis of type 1 diabetes (T1D) in children and young people

No relevant evidence was identified.

Diagnosis of type 2 diabetes (T2D) in children and young people

One cluster RCT (n=1,369) assessed the effectiveness of an automated T2D screening module added to a computerised clinical decision support tool (CDST) compared to a standard CDST on screening for T2D and diagnosing T2D in paediatric patients at high risk for T2D. The tool led to a significant improvement in screening of patients who met the American Diabetes Association criteria for T2D and in them attending scheduled follow-up appointments with primary care clinicians. [1]

See Table 1 for study details.

Diagnosis of other types of diabetes

No relevant evidence was identified.

Intelligence gathering

A topic expert highlighted the use of new technologies such as a new diabetes platform and online education as an alternative to the current structured education offerings, however no evidence was provided by topic experts and none was identified in the literature search.

Impact statement

There are no recommendations concerning the use of automated tools or systems to assist the identification and diagnosis of children and young people with T2D. While the new evidence indicates that an automated T2D screening module added to a CDST improves attendance at a screening appointment, the impact on diagnosis is not stated. It is therefore proposed that this is not an area for update. Further research in this area will be looked for in the next surveillance review.

New evidence is unlikely to change guideline recommendations.

1.2 Type 1 diabetes

Surveillance proposal

This section should be updated.

Editorial amendments

Recommendation 1.2.32 lists the 'sulphonylureas', these are now spelled 'sulfonylureas', so should be changed to this new spelling. 'Glyburide' is listed but that name isn't used in the UK and is a synonym for 'glibenclamide', which is already listed. 'Glyburide' should therefore be removed from this recommendation.

In recommendation 1.2.110 requires the following footnote adding: "screening for diabetic retinopathy falls under the remit of the NHS Diabetic Eye Screening Programme."

2019 surveillance summary

Study details for the evidence in this section are provided in Table 2.

Education and information for children and young people with type 1 diabetes

No relevant evidence was identified.

Smoking and substance misuse

No relevant evidence was identified.

Immunisation

No relevant evidence was identified.

Insulin therapy for children and young people with type 1 diabetes

Four RCTs assessed different insulin regimen in children with T1D. Three RCTs reported that the following regimens were non-inferior at reducing HbA1c:

- a co-formulation of basal and bolus insulin (insulin degludec/insulin aspart) injected once-daily with insulin aspart for remaining meals compared to insulin detemir (IDet) injected once-daily or twice-daily plus mealtime insulin aspart (n=362) [2]
- insulin degludec injected once-daily compared with IDet injected once or twice-daily, with prandial insulin aspart [3]
- continuous subcutaneous insulin infusion (CSII) compared to multiple daily injections (MDI) initiated within 14 days of T1D diagnosis (n=293); however, CSII was more expensive than MDI, with no additional QALY gains, indicating that it is not cost-effective. [4]

One RCT compared 48 to 72 hours IV insulin therapy to multiple subcutaneous injections at diagnosis of T1D and found a significant improvement in mean plasma glucose after the first 2 full days of insulin therapy but no differences at 24 months follow-up (n=54). [5]

One RCT investigated the psychosocial benefits of CSII compared to MDI for 6 months followed by CSII in children with T1D and their families (n=211). Results indicated that children with T1D aged 8-11 years old had a significantly improved diabetes-specific health-related quality of life (DHRQOL) in the CSII group compared to MDI group but that adolescents (aged 12-16 years old) did not. There was also a significant decline of overall diabetes burden reported by caregivers in the CSII compared to MDI group. [6]

One RCT assessed the effectiveness of different types of insulin pump therapy: hybrid closed-loop therapy compared to sensor-augmented pump therapy in children with sub-optimally controlled T1D (n=86). It was reported that the hybrid closed-loop therapy led to significant improvements in glucose control and reduced the risk of hypoglycaemia. [7]

Oral medicines for children and young people with type 1 diabetes

Two RCTs compared metformin to placebo in children with T1D as an adjunct to insulin. One RCT (n=90) reported that HbA1c levels significantly improved when metformin was given for 12 months compared to placebo [8]; while the other RCT (n=140) reported significant improvements in HbA1c levels with metformin compared to placebo at 13 weeks follow-up but not at 26 weeks follow-up. [9] Significant improvements in vascular function, insulin dose and body mass index (BMI) score were also reported in the metformin compared to placebo groups; and both RCTs reported that there were no significant differences in gastrointestinal side effects between those receiving metformin compared to those given a placebo.

Dietary management for children and young people with type 1 diabetes

A cluster RCT (31 UK paediatric centres; n=396) reported that compared to usual care, a 5-day structured dietary education course led to significant improvements in quality of life at 6 and 12 months but no differences in HbA1c at 24 months in children and young people with T1D. [10]

Exercise for children and young people with type 1 diabetes

No relevant evidence was identified.

Blood glucose targets

A Cochrane review of 12 RCTs (n=2,230) assessed the effects of intensive versus conventional glycaemic targets in patients with T1D. Only 1 RCT included children (n=not reported in the abstract). Results from this trial were not reported separately. Overall, the authors concluded that tight blood sugar control reduces the risk of developing microvascular diabetes complications such as retinopathy, nephropathy and neuropathy in younger patients at early stages of T1D, with the effects becoming weaker once complications have manifested; but that 'there is no firm evidence for specific blood glucose targets' and 'treatment goals need to be individualised taking into account age, disease progression, macrovascular risk, as well as the patient's lifestyle and disease management capabilities'. [11]

Blood glucose monitoring

An RCT (n=90) reported that compared to no incentive, a 3-month financial incentive intervention that rewarded daily blood glucose monitoring of 4 or more checks per day, led to significant improvements in adherence to glucose monitoring at the end of the 3-month intervention, but not at 3 months follow-up in young people with T1D. The intervention had no effect on changes in HbA1c levels at either the end of the intervention or 3 months follow-up [12]

One RCT in young people with poorly controlled T1D and who were poorly compliant with blood glucose self-monitoring (n = 182) compared an intervention involving an experimental blood glucose meter which integrates blood glucose testing with a smartphone (iBGStar™ + DMApp) with a standard glucose monitor. There were no significant differences in HbA1c levels, self-monitoring compliance or quality of life after 6 months between the intervention and control groups. [13]

HbA1c targets and monitoring

See [12, 13] above and Table 2 for study details.

Hyperglycaemia, blood ketone monitoring and intercurrent illness in children and young people with type 1 diabetes

No relevant evidence was identified.

Hypoglycaemia in children and young people with type 1 diabetes

No relevant evidence was identified.

Difficulties with maintaining optimal blood glucose control in children and young people with type 1 diabetes

No relevant evidence was identified.

Surgery for children and young people with type 1 diabetes

No relevant evidence was identified.

Psychological and social issues in children and young people with type 1 diabetes

Three RCTs assessed the impact of psychological interventions on mental wellbeing and/or HbA1c levels. Compared with usual care, a clinic-based structured educational group incorporating psychological approaches (n=362) and motivational interviewing and problem-solving skills training (n=258) for children with T1D were found to have no significant impact on HbA1c levels at follow-up of between 12 to 24 months [14, 15]. While no significant improvements in HbA1c levels were found when cognitive behavioural therapy (CBT) was compared to non-directive supportive counselling (n=85), children in the CBT group maintained HbA1c levels, while those in the non-directive supportive counselling showed a significant deterioration in HbA1c levels at the 12 months follow-up; CBT was also reported to significantly improve psychological outcomes compared to non-directive supportive counselling. [16]

Monitoring for complications and associated conditions of type 1 diabetes

No relevant evidence was identified.

Diabetic retinopathy in children and young people with type 1 diabetes

No relevant evidence was identified.

Diabetic kidney disease in children and young people with type 1 diabetes

No relevant evidence was identified.

Intelligence gathering

Insulin therapy for children and young people with type 1 diabetes

Topic experts said that evidence for newer ultra-long-acting insulins such as degludec (Tresiba) should be reviewed. No evidence in children was provided.

Other analogue and biosimilar insulins were highlighted by topic experts, however only medicines licenced for children and evidence which included children as participants were considered in this surveillance review.

Initial intelligence identified MiniMed 640G system with SmartGuard for managing blood glucose levels in people with type 1 diabetes (February 2016) MIB51. The MiniMed 640G integrated sensor-augmented pump therapy system with SmartGuard is a continuous glucose monitoring and insulin delivery system for people with type 1 diabetes. It can automatically suspend insulin delivery if blood glucose is predicted to drop below a pre-set level within

30 minutes. The Medtech Innovation Briefing indicates that the evidence is still in proof of concept phase.

Blood glucose monitoring

Initial intelligence identified FreeStyle Libre for glucose monitoring (July 2017) MIB110. This MIB summarises the evidence on FreeStyle Libre (Flash glucose monitor) which measures glucose levels from a sensor applied to the skin as an alternative to routine finger-prick blood glucose testing. It is intended as a replacement for glucose monitoring via the fingertip prick test.

Topic experts also asked that evidence on this be considered as NHS England have released guidance on Flash Glucose Monitors for Type 1 diabetes patients in March 2019 which highlights which people with T1D should receive a Flash glucose monitor – specific ages are not provided. Topic experts also highlighted the November 2018 Regional Medicines Optimisation Committee FreeStyle Libre Position Statement. The advice of this group to Area Prescribing Committees is that: "Until further trial data is available, it is recommended that audit data on the use of FreeStyle Libre® is collected through its use in limited and controlled settings where patients are attending for Type 1 diabetes care. It is recommended that FreeStyle Libre® should only be used for people with Type 1 diabetes, aged 4 and above, attending specialist Type 1 care using multiple daily injections or insulin pump therapy, who have been assessed by the specialist clinician" and meet specific criteria.

Hypoglycaemia in children and young people with type 1 diabetes

A topic expert noted that they thought the definition of hypoglycaemia should be updated. They highlighted a discussion paper that described internationally agreed upon definitions for hypoglycaemia and discussed potential regulatory approaches for recognising and labelling diabetes therapies in order to facilitate personalised care.

Diabetic retinopathy in children and young people with type 1 diabetes

Topic experts highlighted new evidence that indicates screening for diabetic retinopathy could take place less frequently than annually without leading to a delay in diagnosing clinically significant disease:

- Screening Intervals for Diabetic Retinopathy and Implications for Care
- Frequency of Evidence-Based Screening for Retinopathy in Type 1 Diabetes.

Initial intelligence gathering identified that screening for diabetic retinopathy falls under the remit of the NHS Diabetic Eye Screening Programme.

Initial intelligence gathering also identified an NIHR Health Technology Assessment (HTA) on What works to increase attendance for diabetic retinopathy screening? An evidence synthesis and economic analysis. This reported that quality improvement incorporating behaviour change techniques such as goal-setting and providing additional social support increased diabetic retinopathy screening attendance by 12% on average compared with usual

care, with a high probability of being cost-effective at a societal willingness to pay threshold of £20,000/QALY.

Uptake data for NICE guideline NG18 derived from the Royal College of Paediatrics and Child Health National Paediatric Diabetes Audit indicates that between 2015 and 2017 there have been annual increases in the percentage of children aged 12 years or older with T1D having an eye screening or a referral for eye screening (64.9%, 66.2% and 74.4%).

Impact statement

Insulin therapy for children and young people with type 1 diabetes

Evidence was identified which supports the existing recommendation 1.2.19 to offer children and young people with T1D MDI basal-bolus insulin regimens from diagnosis, and to then offer CSII or pump if injections aren't appropriate. While it was reported in 1 RCT that there are psychosocial benefits of CSII compared to MDI for children with T1D and benefits for carers of children with T1D, the current recommendations make it clear that patient choice is taken into consideration when advising on and choosing an insulin regimen (recommendation 1.2.18).

New evidence was also identified which supports both the use of the long-acting insulin degludec in children with T1D, which can be delivered as a once-daily injection, or alternatively the use of detemir injected once- or twice-daily. Evidence on degludec was not reviewed during the original guideline development of NICE guideline NG18 but evidence for other long-acting insulins (glargine and detemir) was searched for; however at the time there were no published studies investigating the effectiveness of insulin glargine or insulin detemir specifically in children and young people and it was concluded that further research was needed. The committee also noted that 'there is no substantive evidence to suggest that any particular type of intermediate or long-acting insulin has greater clinical effectiveness than any other'. The evidence base remains limited, with only 2 published RCTs investigating long-acting insulin use in children and young people with T1D, as such it is proposed that this is not currently an area for update.

Recommendation 1.2.30 advises that if a child or young person with T1D does not have optimal blood glucose control, that if necessary, they can be offered an alternative insulin regimen, including an insulin pump. New evidence from 1 RCT was identified concerning pumps that use new technology which automatically adjusts the delivery of insulin (hybrid closed-loop therapy). The results indicate that these newer devices may be superior to sensor-augmented pump therapy in controlling glucose and reducing the risk of hypoglycaemia in people with T1D of all ages, including children with sub-optimally controlled T1D. As the evidence base for this new technology is still emerging it is proposed that this is not currently an area for update.

New evidence is unlikely to change guideline recommendations.

Oral medicines for children and young people with type 1 diabetes

Recommendation 1.2.31 advises that metformin in combination with insulin is only given in the context of research studies 'because the effectiveness of this combined treatment in improving blood glucose control is uncertain'. New evidence from 2 RCTs indicates that compared with placebo, metformin given to children and young people with T1D as an adjunct to insulin does result in improved HbA1c levels, although the results were mixed concerning the long-term effectiveness. Given that the evidence base remains limited, with only 2 published RCTs, and the use of metformin in children and young people with T1D is off-label, it is proposed that this is not currently an area for update.

New evidence is unlikely to change guideline recommendations.

Dietary management for children and young people with type 1 diabetes

New evidence from 1 cluster RCT reported that a dietary education course led to significant improvements in quality of life but no differences in HbA1c. This does not have an impact on current recommendations which highlight the need for children and young people with T1D to be aware of the importance of healthy eating on their health, and that they should be supported in making changes to their food choices.

New evidence is unlikely to change guideline recommendations.

Blood glucose targets and monitoring

In line with current recommendations, a Cochrane review assessing the effects of intensive versus conventional glycaemic targets in patients with T1D concluded that 'treatment goals need to be individualised taking into account age, disease progression, macrovascular risk, as well as the patient's lifestyle and disease management capabilities'. Financial incentives for achieving daily blood glucose monitoring are not discussed in NICE guideline NG18 and the evidence from 1 RCT indicates that this is only effective while incentives are in place, indicating that this is not an effective long-term strategy for getting young people to monitor their blood glucose. The use of monitors integrated with smartphone technology are also not discussed in NICE guideline NG18, however current evidence from 1 RCT indicates that a blood glucose meter that integrates blood glucose testing with a smartphone App does not lead to additional improvements in blood glucose monitoring in comparison to using a traditional glucose meter in young people with T1D.

In relation to equipment for monitoring blood glucose, NICE guideline NG18 recommends offering a choice of equipment in order to optimise blood glucose control in response to adjustment of insulin, diet and exercise (recommendation 1.2.60). It also recommends offering ongoing real-time continuous glucose monitoring with alarms to children and young people with T1D who have frequent severe hypoglycaemia, or impaired awareness of hypoglycaemia associated with adverse or an inability to recognise, or communicate about, symptoms of hypoglycaemia (recommendation 1.2.62); and recommends considering ongoing real-time continuous glucose monitoring for neonates, infants and pre-school children,

children and young people who undertake high levels of physical activity, children and young people who have comorbidities or are receiving treatments that can make blood glucose control difficult (recommendation 1.2.63). There are no recommendations specifically on the use of a Flash glucose monitor but the MIB describing the technology is available in the NICE Diabetes in Children and Young people interactive flowchart. The new NHS England guidance on prescribing this technology is not at odds with the recommendation to offer a choice of equipment; and as no evidence concerning the effectiveness of a Flash glucose monitor was identified in this surveillance review, it is proposed that is not an area for update.

New evidence is unlikely to change guideline recommendations.

HbA1c targets and monitoring

New evidence from 1 RCT indicates that financial incentives given to young people with T1D have no impact on HbA1c levels, as such this evidence has no impact on existing recommendations.

New evidence is unlikely to change guideline recommendations.

Hypoglycaemia in children and young people with type 1 diabetes

A discussion paper on internationally agreed upon definitions for hypoglycaemia and proposed regulatory approaches for recognising and labelling diabetes therapies in order to facilitate personalised care was identified by a topic expert, however development and regulatory issues are not within scope for NICE guideline NG18. No definitions of hypoglycaemia are specified in the guideline recommendations 1.2.76 to 1.2.86 but reference is made to mild, moderate and severe hypoglycaemia. The full guideline reports that "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."

New evidence is unlikely to change guideline recommendations.

Psychological and social issues in children and young people with type 1 diabetes

While evidence form 3 RCTs indicates that psychological interventions have little impact on HbA1c levels in children and young people with T1D, there is evidence that CBT improves mental wellbeing. This is in line with the current recommendation to consider providing a programme of behavioural intervention therapy or behavioural techniques in order to

improve health-related quality of life but does not indicate that such programmes necessarily help with treatment adherence or improved HbA1c levels (recommendation 1.2.103).

New evidence is unlikely to change guideline recommendations.

Diabetic retinopathy in children and young people with type 1 diabetes

While topic experts highlighted new evidence on the optimum frequency of screening for diabetic retinopathy, this area falls under the remit of the NHS Diabetic Eye Screening Programme and is therefore not considered in the surveillance review. The current recommendations to offer children and young people with T1D (or T2D) monitoring for diabetic retinopathy annually from 12 years of age is in line with the recommendations from the NHS Diabetic Eye Screening Programme. A footnote will be added to clarify that screening for diabetic retinopathy falls under the remit of the NHS Diabetic Eye Screening Programme. We will ensure that we keep up-to-date with any changes made by the NHS Diabetic Eye Screening Programme that may impact on existing recommendations and review accordingly.

There was however evidence from an NIHR HTA that indicates attendance at screening for retinopathy could be improved by incorporating behaviour change techniques such as goal-setting and providing additional social support into services.

New evidence identified that may change current recommendations.

1.3 Type 2 diabetes

Surveillance proposal

This section should be updated.

Editorial amendments

Recommendation 1.3.14 highlights that in children or young people who have type 2 diabetes (T2D) and are overweight or obese, the benefits of physical activity and weight loss are addressed, and children supported in making lifestyle changes. There are cross-references to NICE guideline NG7 on 'preventing excess weight gain' and NICE guideline CG189 on 'obesity: identification, assessment and management'; however given that there are several relevant NICE guidelines in these areas, it is proposed that cross-references are made instead to the NICE physical activity, obesity and diet pathways.

In recommendation 1.3.43 on offering children and young people with type w diabetes annual monitoring, the bullet point that recommends 'diabetic retinopathy from 12 years'

should have a footnote added noting that screening for diabetic retinopathy falls under the remit of the NHS Diabetic Eye Screening Programme.

2019 surveillance summary

Study details for the evidence in this section are provided in Table 3.

Education and information for children and young people with type 2 diabetes

One RCT (n=90) reported that a nursing intervention in children with T2D resulted in significant improvements in compliance with dietary control, exercise, and drug use and significantly better blood glucose, blood lipids, blood pressure and body mass when compared to those receiving usual care. [17]

Smoking and substance misuse

No relevant evidence was identified.

Immunisation

No relevant evidence was identified.

Dietary management for children and young people with type 2 diabetes

See [17] above and Table 3 for study details.

Metformin

Three RCTs report on data from the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) trial, a large trial (n=699) comparing the efficacy and safety of 3 interventions: metformin, metformin plus rosiglitazone or metformin with an intensive lifestyle intervention incorporating nutrition, physical activity, and behaviour modification in children and young people aged 10-17 year olds with T2D. The following results were reported:

- A significant improvement in glycaemic control in the metformin with rosiglitazone compared to the metformin group [18]
- A non-significant improvement in glycaemic control in the metformin with lifestyle intervention compared to the metformin group [18]
- No difference in weight in the metformin with lifestyle intervention compared to the metformin or metformin with rosiglitazone group [19]
- No differences in metabolic syndrome between the 3 intervention groups. [20]

One RCT (n=91) also compared outcomes in 10-19 year olds with impaired glucose tolerance or T2D given metformin alone for 12 months or 3 months of insulin glargine followed by 9 months of metformin. No significant differences were found between the groups in HbA1c, fasting glucose, oral glucose tolerance test 2-h glucose results, beta-cell function or BMI percentile. [21]

HbA1c targets and monitoring for children and young people with type 2 diabetes

See [17] above and Table 3 for study details.

Surgery for children and young people with type 2 diabetes

No relevant evidence was identified.

Psychological and social issues in children and young people with type 2 diabetes

No relevant evidence was identified.

Monitoring for complications and associated conditions of type 2 diabetes

No relevant evidence was identified.

Hypertension in children and young people with type 2 diabetes

No relevant evidence was identified.

Dyslipidaemia in children and young people with type 2 diabetes

No relevant evidence was identified.

Diabetic retinopathy in children and young people with type 2 diabetes

No relevant evidence was identified.

Diabetic kidney disease in children and young people with type 2 diabetes

No relevant evidence was identified.

Intelligence gathering

Diabetic retinopathy in children and young people with type 2 diabetes

Initial intelligence gathering identified that screening for diabetic retinopathy falls under the remit of the NHS Diabetic Eye Screening Programme. An NIHR HTA on What works to increase attendance for diabetic retinopathy screening? An evidence synthesis and economic analysis was also identified. This reported that quality improvement incorporating behaviour change techniques such as goal-setting and providing additional social support increased diabetic retinopathy screening attendance by 12% on average compared with usual care, with a high probability of being cost-effective at a societal willingness to pay threshold of £20,000/QALY.

Uptake data for NICE guideline NG18 derived from the Royal College of Paediatrics and Child Health National Paediatric Diabetes Audit indicates that for children aged 12 years or older with T2D 64.9% had an eye screening or a referral for eye screening in 2015, 47.2% had retinopathy in 2016, which increased to 54.8% in 2017.

Impact statement

Education and information for children and young people with type 2 diabetes

Recommendations 1.3.1 and 1.3.2 highlight the importance of providing children and young people with T2D and their family members or carers a continuing programme of tailored education on HbA1c monitoring and targets, the effects of diet, physical activity, body weight and intercurrent illness on blood glucose control. The findings from 1 RCT on a nursing intervention in children with T2D that led to improvements in diet, exercise, drug use, blood glucose, blood lipids, blood pressure and body mass when compared to those receiving usual care, supports this recommendation.

New evidence is unlikely to change guideline recommendations.

Metformin

Overall, the evidence supports recommendation 1.3.22 to offer standard-release metformin from diagnosis to children and young people with T2D. While there is evidence that compared to metformin alone, glycaemic control is significantly improved if rosiglitazone and metformin are prescribed, rosiglitazone has been suspended in the UK and as such it would not be appropriate to consider its use in children with T2D. There is evidence from 1 RCT on the use of insulin and metformin in children and young people with T2D. This RCT reported no differences in blood glucose measurements between those receiving insulin followed by metformin, compared to those given metformin alone. As evidence is based on 1 relatively small RCT, it is proposed that NICE guideline NG18 is not updated in relation to evidence concerning the use of metformin and insulin in children and young people with T2D.

New evidence is unlikely to change guideline recommendations.

Diabetic retinopathy in children and young people with type 2 diabetes

A footnote will be added to recommendation 1.3.43 to clarify that screening for diabetic retinopathy falls under the remit of the NHS Diabetic Eye Screening Programme. We will ensure that we keep up-to-date with any changes made by the NHS Diabetic Eye Screening Programme that may impact on existing recommendations and review accordingly.

Evidence was identified that indicates attendance at screening for retinopathy could be improved by incorporating behaviour change techniques such as goal-setting and providing additional social support into services. Uptake data indicates that eye screening attendance is at a low rate in children aged 12 years or older who have T2D. As current recommendations do not discuss how attendance could be encouraged, this should be considered as an area for update.

New evidence identified that may change current recommendations.

1.4 Diabetic ketoacidosis

Surveillance proposal

This section should be updated.

2019 surveillance summary

Study details for the evidence in this section are provided in Table 4.

Recognition, referral and diagnosis of diabetic ketoacidosis

No relevant evidence was identified.

Initial management of diabetic ketoacidosis

No relevant evidence was identified.

Fluid and insulin therapy

A Cochrane review of 5 RCTs (n=201) assessed the effects of subcutaneous rapid-acting insulin analogues for the treatment of diabetic ketoacidosis (DKA) in any people with T1D or T2D and DKA. Only 1 of the trials (n=60) included younger diabetic participants and children. This trial found no significant difference in the time to reach a glucose level of 250 mg/dL between insulin lispro and intravenous (IV) regular insulin in children with DKA. This was in line with the overall findings of the Cochrane review that there were 'neither advantages nor disadvantages when comparing the effects of subcutaneous rapid-acting insulin analogues versus intravenous regular insulin for treating mild or moderate DKA'. The authors reported the evidence was mostly low- to very low-quality. [22] Five RCTs compared different doses and rates of administration of oral fluids and insulin therapy for the treatment of DKA:

- One RCT (n=50) reported that time to metabolic normalisation was significantly better in children and young people with T1D and DKA given IV fluid at high volume (20 mL/kg bolus + 1.5 × maintenance rate) compared to those given IV fluid at low volume (10 mL/kg bolus + 1.25 × maintenance rate), although there were no differences between the groups in overall hospital length of treatment. [23].
- Across the remaining 4 RCTs, there were no significant differences in outcomes reported between the following interventions:
  - a balanced salt solution (Hartmann's solution) versus 0.9% normal saline (n=77); but there was a significant improvement in time for plasma bicarbonate to reach 15 mmol/L in the children described as having 'severe' DKA who were given Hartmann's solution compared to 0.9% normal saline [24]
  - 3% saline versus 0.9% saline (n=40) [25]
  - different sodium chloride content of IV fluids (0.9% or 0.45%) and rate of administration (rapid or slow) (n=1,255) [26]

- low-dose insulin infusion (0.05 U/kg per hour) versus standard dose insulin infusion (0.1 U/kg per hour) (n=50). [27]

Monitoring during therapy

No relevant evidence was identified.

Complications of diabetic ketoacidosis

Hypokalaemia

One RCT reported no differences in hypokalaemia in children with DKA (n=50) given a low-dose insulin infusion (0.05 U/kg per hour) compared with a standard dose insulin infusion (0.1 U/kg per hour). [27]

Avoiding future episodes of diabetic ketoacidosis

No relevant evidence was identified.

Intelligence gathering

Initial intelligence gathering and topic experts identified guidance from the International society for pediatric and adolescent diabetes (ISPAD): ISPAD Clinical Practice Consensus Guidelines 2018: Diabetic ketoacidosis and the hyperglycemic hyperosmolar state which states that in children with DKA 'an assumed fluid deficit between 5% and 10% of body weight should be replaced over 24 to 48 hours along with maintenance fluids, using fluids with a sodium content between 0.45% and 0.9% saline. The risk of cerebral injury does not appear to be associated with differences in fluid protocols within these ranges. Therefore, clinicians should not unnecessarily restrict fluid administration if clinical signs suggest the need for circulatory volume expansion.' This recommendation is based on the findings of [26], a publication which topic experts also highlighted. One topic expert reported concern that current fluid therapy is "very conservative and my clinical impression is there are high rates of transient acute kidney injury with current recommendations." Published evidence concerning the impact on kidney injuries was not provided.

Topic experts also highlighted Fluid treatment for children with diabetic ketoacidosis: How do the results of the pediatric emergency care applied research network Fluid Therapies Under Investigation in Diabetic Ketoacidosis (FLUID) Trial change our perspective which discusses implications of the findings of [26] on fluid therapy on DKA. This report concludes that 'rapid fluid infusion does not cause brain injury (within the range of infusion rates evaluated). Furthermore, although the main trial results showed no significant differences in neurological outcomes in the study arms, subanalyses in children with the most severe DKA suggested more rapid improvements in mental status with more rapid fluid infusion rates. These findings emphasise that fluid infusion for DKA treatment should not be restricted because of concerns about causing brain injury. Most, if not all, children with DKA require a fluid bolus of 20 mL/Kg, and additional fluid boluses should be administered if peripheral perfusion remains poor or there are other clinical signs of circulatory compromise after the initial fluid bolus.'

Impact statement

Fluid and insulin therapy

The new evidence supports existing recommendations 1.4.22-49 in that there is evidence that both subcutaneous rapid-acting insulin analogues and IV regular insulin are effective for treating mild or moderate DKA and that 0.9% sodium chloride is an appropriate fluid. However, the new evidence, notably from [26], indicates that rapid fluid infusion at volumes higher than those recommend in recommendation 1.4.31 is not associated with an increased risk of cerebral oedema in children and young people with DKA; and that in the case of severe DKA, more rapid fluid infusion rates may be associated with faster improvements in mental status. This evidence, along with international guidance and topic expert opinion indicates that this should be an area for update.

New evidence identified that may change current recommendations.

1.5 Service provision

Surveillance proposal

This section should not be updated.

2019 surveillance summary

Study details for the evidence in this section are provided in Table 5.

Service provision

A Cochrane review of 93 RCTs (n=22,047) assessed the effects of telemedicine compared to usual care in people with various chronic conditions, including diabetes (21 RCTs, n=2,768), of which 3 studies included young people (n=217). Overall, it was reported that telemedicine can improve the control of blood glucose in those with diabetes. [28]

An RCT with adolescents with T1D or T2D (n=146) assessed the effectiveness of a multisystemic therapy involving an intensive, home and community-based family treatment on patient-provider relationships. It reported some improvements in aspects of patient-provider relationships. [29]

An RCT with children with T2D in India (n=90) reported that a nursing intervention resulted in significant improvements in drug compliance in comparison to usual care. [17]

Transition from paediatric to adult care

A Cochrane review of 4 RCTs (n=238) assessed the effectiveness of interventions designed to improve the transition of care for adolescents from paediatric to adult health services. All

chronic conditions that required ongoing clinical care were included. One trial assessed a structured comprehensive transition programme with a transition co-ordinator for adolescents with T1D (n=26). The trial found that at 12-month follow-up, there was no significant difference in rates of transfer from paediatric to adult diabetes services nor in risk of disease-related hospital admissions. The quality of the evidence was rated as low. Data from this trial was also combined with another trial which evaluated a technology-based intervention for adolescents with a range of different conditions on the use of health services. It was reported that these interventions may lead to slightly more young people taking positive steps to initiate contact with health professionals themselves, but the quality of the evidence was rated as low, and results were non-significant. [30]

There was also an RCT with young adults aged between 17 to 19 years old with T1D (n=120) that assessed the effect of an appointment-management intervention on clinic attendance and disengagement after transition of care from paediatric to adult services. They found no improvements in clinic attendance or disengagement from services 0-12 months post-transition from the intervention but did find significant improvements at 12-24 months after transition. [31]

Intelligence gathering

No evidence was identified.

Impact statement

The evidence supports existing recommendations that include the need for a multidisciplinary team to provide care (recommendation 1.5.1) and the provision of 24-hour telephone access (telemedicine; recommendation 1.5.4). While the evidence was mixed concerning the effectiveness of interventions on improving the transition from paediatric to adult care, the the quality of the evidence was rated as low in the Cochrane review and there is overall only a small number of trials in this area. The evidence does not indicate that the principles in recommendations 1.5.9-1.5.13 do not hold.

New evidence is unlikely to change guideline recommendations.

Research recommendations

Research recommendation	Summary of findings
What is the clinical and cost effectiveness of a programme of structured education from diagnosis for children and young people with type 1 diabetes?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
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?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
What is the effectiveness of education programmes in which young people with type 1 diabetes provide training for their peers?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
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.	There is new evidence from 1 RCT that indicates there is no difference in effectiveness between CSII and MDI in reducing HbA1c, but that CSII may not be cost-effective.
Research is needed to evaluate the effectiveness of long-acting insulin analogues in children and young people with type 1 diabetes.	The new evidence from 2 RCTs supports the use of the long-acting insulin degludec in children with T1D.
Further research is required to evaluate the effectiveness of insulin delivery systems in children and young people with type 1 diabetes.	The new evidence from 1 RCT indicates that pumps that use new technology may be superior to sensor-augmented pump therapy in children with sub-optimally controlled T1D in controlling glucose and reducing the risk of hypoglycaemia
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.	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
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?	The new evidence from 2 RCTs indicates that compared with placebo, metformin given to children and young people with T1D as an adjunct to insulin does result in improved HbA1c levels.

Research recommendation	Summary of findings
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?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
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?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
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?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
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.	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
Further research is needed to evaluate the effects of persistent hypoglycaemia and recurrent diabetic ketoacidosis on neurocognitive function.	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
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.	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
Further research is needed to evaluate the effectiveness of screening for cardiovascular risk factors in children and young people with type 1 diabetes.	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Research recommendation	Summary of findings
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?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
What is the long-term comparative clinical and cost effectiveness of different metformin preparations for treating type 2 diabetes in children and young people?	The new evidence shows that metformin administered in tablet form using a standard dosage improves glycaemic control: metformin was provided as 1000mg capsules in the TODAY trial [18-20] and the dosage/preparation was not described in the abstract of the other RCT [21]. Different metformin preparations were not compared with one another.
What is the clinical and cost effectiveness of psychological interventions for children and young people with type 2 diabetes?	There is new evidence from 3 RCTs which indicates that psychological interventions have little impact on HbA1c levels in children and young people with T1D, but that CBT improves mental wellbeing.
What is the optimal dosage of intravenous insulin for managing diabetic ketoacidosis (DKA) in children and young people?	The new evidence indicates that larger dosages of insulin than those recommended in NICE guideline NG18 are not associated with an increased risk of cerebral oedema in children with DKA. This should be considered in an update to the guideline.
Further research is needed to evaluate the effects of low blood glucose levels on learning, attendance at school and educational attainment.	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
Further research is needed to investigate young people's experiences of transition from paediatric to adult services for people with type 1 diabetes.	The new evidence from a Cochrane review and an RCT was mixed concerning the effectiveness of interventions on improving the transition from paediatric to adult care.

Data summary tables

Table 1. Diagnosis

Study	Type*	n	Population	Intervention	Comparator	Outcome	Result
Diagnosis of T2D in children and young people							
Hannon, T. S.; et al. (2017) [1]	cRCT	1,369	Children aged 10 years or older with T2D or at risk of T2D	T2D module to a computerised clinical decision support	usual computerised clinical decision support	screening for T2D	Improvement with intervention
						attending a scheduled follow-up appointment	Improvement with intervention

*Type of study cRCT = cluster randomised controlled trial

n = number of participants

T2D = type 2 diabetes

Table 2. Type 1 diabetes

Study	Type*	n	Population	Intervention	Comparator	Outcome	Result
Insulin therapy for children and young people with type 1 diabetes							
Battelino, T.; et al. (2018) [2]	RCT	362	1 - <18 years old with T1D	Insulin degludec/insulin aspart (IDegAsp) once-daily (OD) plus insulin aspart (Asp) for remaining meals	insulin detemir (IDet) OD or twice-daily plus mealtime Asp (Idet + Iasp)	HbA1c	No improvement with intervention (non-inferior)
Thalange, N., et al. (2015) [3]	RCT	350 (for 26 weeks), 280 (for 26 weeks extension)	1 – 17 years old with T1D	Insulin degludec (IDeg) OD	IDet once- or twice-daily, with prandial insulin aspart	HbA1c at 26 and 52 weeks	No improvement with intervention (non-inferior)
						change in mean fasting plasma glucose	Improvement with intervention
						hypoglycaemia	No improvement with intervention (non-inferior)
						hyperglycaemia with ketosis	Improvement with intervention

Study	Type*	n	Population	Intervention	Comparator	Outcome	Result
Blair, Joanne; et al. (2018) [4]	RCT	293	7 months - 15 years with T1D	Continuous subcutaneous insulin infusion (CSII) (SCIPI RCT)	Multiple daily injections (MDI) initiated within 14 days of T1D diagnosis	HbA1c (at 12 months follow-up)	No improvement with intervention
						Cost effectiveness	No improvement with intervention
Enander, R.; et al. (2018) [5]	RCT	54	2.8 - 14.9 years old with T1D	48 to 72 hours IV insulin therapy at diagnosis	multiple subcutaneous injections	mean plasma glucose (first 2 full days of insulin therapy)	Improvement with intervention
						HbA1c (at 24 months follow-up)	No improvement with intervention
						insulin doses (at 24 months follow-up)	No improvement with intervention
						maximal mixed-meal tolerance test (at 24 months follow-up)	No improvement with intervention
Mueller-Godeffroy, Esther; et al. (2018) [6]	RCT	211	6 - 16 years old with T1D (receiving MDI)	Immediate CSII (PUMPKIN trial)	MDI for 6 months before transferring to CSII	Patient-reported diabetes-specific quality of life for age group 12-16 years	No improvement with intervention
						Patient-reported diabetes-specific quality of life for age group 8-11 years	Improvement with intervention
						Diabetes burden of main caregiver	Improvement with intervention
Tauschmann, M.; et al. (2018) [7]	RCT	86 (33 were aged 6–12 years and 19 were aged 13–21 years)	>6 years old with sub-optimally controlled T1D (population had an insulin pump)	Hybrid closed-loop therapy	Sensor-augmented pump therapy	HbA1c	Improvement with intervention
						Proportion of time glucose concentration was within target range (glucose control)	Improvement with intervention
Oral medicines for children and young people with type 1 diabetes							
Anderson, J. J. A.; et al. (2017) [8]	RCT	90	8 - 18 years old with T1D	Metformin	Placebo	HbA1c at 3 and 12 months	Improvement with intervention

Study	Type*	n	Population	Intervention	Comparator	Outcome	Result
						Vascular function	Improvement with intervention
						Gastrointestinal side effects	No improvement with intervention
						Insulin dose	Improvement with intervention
Libman, I. M.; et al. (2015) [9]	RCT	140	12.1 - 19.6 years with T1D	Metformin	Placebo	HbA1c at 13 weeks follow-up	Improvement with intervention
						HbA1c at 26 weeks follow-up	No improvement with intervention
						Total daily insulin (per kg of body weight)	Improvement with intervention
						BMI score	Improvement with intervention
						Gastrointestinal side effects	No improvement with intervention
Dietary management for children and young people with type 1 diabetes							
Price, K. J.; et al. (2016) [10]	cRCT	396	11-16 years old with T1D	Structured education course (KICk-OFF: Kids in Control of Food)	Usual care	HbA1c	No improvement with intervention
						Generic quality of life scores at 6 and 12 months follow-up	Improvement with intervention
Blood glucose targets							
Fullerton, B.; et al. (2014) [11]	CR	12 RCTs (n=2,230; 1 RCT with children with T1D n=NR))	T1D (all ages)	tighter ('intensive') blood glucose control)	less intense treatment targets ('conventional' glucose control)	risk of developing microvascular diabetes complications	Improvement with intervention
Blood glucose monitoring, HbA1c targets and monitoring							
Wong, C. A.; et al. (2017) [12]	RCT	90	14 - 20 years old with T1D	Financial incentive ($60 monthly) (BE IN CONTROL)	No incentive	Adherence to glucose monitoring at end of intervention	Improvement with intervention

Study	Type*	n	Population	Intervention	Comparator	Outcome	Result
						Adherence to glucose monitoring at 3 months follow-up	No effect with intervention
						Change in HbA1c levels at end of intervention	No effect with intervention
						Change in HbA1c levels at 3 months follow-up	No effect with intervention
Di Bartolo, P.; et al. 2017 [13]	RCT	182	14 – 24 years old with poorly controlled T1D and poorly compliant with blood glucose self-monitoring	Experimental glucose meter with an App (iBGStar™ + DMApp) (i-NewTrend)	Standard glucose monitoring	Change in HbA1c at 6 months	No effect with intervention
						Achievement of compliance with self-monitoring of blood glucose at 6 months	No effect with intervention
						Quality of life at 6 months	No effect with intervention
Psychological and social issues in children and young people with type 1 diabetes							
Christie, Deborah; et al. (2016) [14]	cRCT	362	8 - 16 years old with T1D	Clinic-based structured educational group incorporating psychological approaches (CASCADE)	Standard care	HbA1c	No improvement with intervention
						HbA1c measured at 12 or 24 months	No improvement with intervention
						Diabetes-specific QoL	No improvement with intervention
Mayer-Davis, Elizabeth J.; et al. (2018) [15]	RCT	258	13 - 16 years old with T1D	Motivational interviewing and problem-solving skills training (FLEX)	Usual care	HbA1c at 18 months	No improvement with intervention
Wei, C.; et al. (2018) [16]	RCT	85	11 - 16 years old with T1D	Cognitive behavioural therapy	Non-directive supportive counselling	HbA1c at 24 months	No improvement with intervention
						Psychological outcomes	Improvement with intervention

*Type of study CR = Cochrane review; cRCT = cluster randomised controlled trial; RCT = randomised controlled trial.

n = number of participants. The number of participants was not always reported in the abstract (NR).

CSII = continuous subcutaneous insulin infusion; IDet = insulin detemir; MDI = Multiple daily injections; OD = once-daily; T1D = type 1 diabetes;

Table 3. Type 2 diabetes

Study	Type*	n	Population	Intervention	Comparator	Outcome	Result
Education and information for children and young people with type 2 diabetes							
Hezang, B.; et al. (2017) [17]	RCT	90	Children with T2D	nursing intervention	usual care	dietary control compliance	Improvement with intervention
						exercise treatment compliance	Improvement with intervention
						blood glucose, blood lipids, blood pressure and body mass	Improvement with intervention
Metformin							
Narasimhan, S.; Weinstock, R. S. (2014) [18]	RCT	699	Obese youth aged 10 - 17 years old with new-onset T2D	metformin with rosiglitazone	monotherapy with metformin	glycaemic control	Improvement with intervention
				metformin with an intensive lifestyle intervention (TODAY trial)	monotherapy with metformin	glycaemic control	No improvement with intervention
Marcus, M. D.; et al. (2017) [19]	RCT	595	11 - 17 years old with T2D	metformin with an intensive lifestyle intervention	monotherapy with metformin	Change in weight	No improvement with intervention
				metformin with an intensive lifestyle intervention (TODAY trial)	metformin with rosiglitazone	Change in weight	No improvement with intervention
Weinstock, R. S.; et al. (2015) [20]	RCT	679 at baseline; 625 at 6 months follow-up; 545 at 24 months.	Youth with T2D	metformin with rosiglitazone metformin with an intensive lifestyle intervention (TODAY trial)	monotherapy with metformin	metabolic syndrome	No improvement with intervention
Consortium, Rise (2018) [21]	RCT	91	Overweight or obese 10 - 19 years old with IGT or T2D	3 months insulin glargine followed by 9 months metformin (RISE)	12 months metformin alone	beta-cell function	No improvement with intervention
						BMI percentile	No improvement with intervention

Study	Type*	n	Population	Intervention	Comparator	Outcome	Result
						HbA1c, fasting glucose, oral glucose tolerance test 2-h glucose results	No improvement with intervention

*Type of study RCT = randomised controlled trial

n = number of participants.

IGT = impaired glucose tolerance; T2D = type 2 diabetes.

Table 4. Diabetic ketoacidosis (DKA)

Study	Type*	n	Population	Intervention	Comparator	Outcome	Result
Andrade-Castellanos, C. A.; et al. (2016) [22]	CR	5 RCTs (n=201; 1 RCT with children with DKA n=60)	People (all ages) with DKA	subcutaneous rapid-acting insulin analogues	standard IV insulin infusion	time to reach a glucose level of 250 mg/dL	No improvement with intervention
Bakes, K.; et al. (2016) [23]	RCT	50	0 - 18 years old with T1D and DKA	IV fluid at high volume (20 mL/kg bolus + 1.5 × maintenance rate)	IV fluid at low volume (10 mL/kg bolus + 1.25 × maintenance rate)	time to metabolic normalisation	Improvement with intervention
						Normalisation of PH	Improvement with intervention
						Normalisation of serum bicarbonate	No improvement with intervention
						length of hospital treatment and time to discharge	No improvement with intervention
Yung, M.; Letton, G.; Keeley, S. (2017) [24]	RCT	77	Children with DKA	a balanced salt solution (Hartmann's solution)	0.9% normal saline	time for plasma bicarbonate to reach 15 mmol/L	No improvement with intervention
Shaf, O.; Kumar, V. (2018) [25]	RCT	40	Children with moderate to severe DKA	3% saline	0.9% saline	hemodynamic improvement, the resolution of acidosis and the correction of hyperglycaemia	No improvement with intervention

Study	Type*	n	Population	Intervention	Comparator	Outcome	Result
Kuppermann, N.; et al. (2018) [26]	RCT	1,255	Children with DKA	sodium chloride content of IV fluids (0.9% or 0.45%) and rate of administration (rapid or slow)	sodium chloride content of IV fluids (0.9% or 0.45%) and rate of administration (rapid or slow)	neurological outcomes	No improvement with intervention (non-inferior)
Nallasamy, K.; et al. (2014) [27]	RCT	50	≤ 12 years old with DKA	low-dose insulin infusion (0.05 U/kg per hour)	standard dose insulin infusion (0.1 U/kg per hour)	rate of decrease in blood glucose until to 250 mg/dL or less	No improvement with intervention (non-inferior)
						time to resolution of acidosis	No improvement with intervention (non-inferior)
						episodes of treatment failures	No improvement with intervention (non-inferior)
						hypokalaemia	No improvement with intervention (non-inferior)
						hypoglycaemia	No improvement with intervention (non-inferior)
*Type of study CR = Cochrane review; RCT = randomised controlled trial n = number of participants. DKA = diabetic ketoacidosis; T1D = type 1 diabetes							

Table 5. Service provision

Study	Type*	n	Population	Intervention	Comparator	Outcome	Result
Service provision							
Flodgren, G., et al. (2015) [28]	CR	21 RCTs with people with diabetes (3RCTs with young people, n=217)	People with chronic conditions including diabetes	Telemedicine	Usual care	Blood glucose control	Improvement with intervention

Study	Type*	n	Population	Intervention	Comparator	Outcome	Result
Carcone, A. I.; et al. (2015) [29]	RCT	146	Adolescents with T1D or T2D	multisystemic therapy	telephone support	Patient-provider relationships: Coordinated and Comprehensive Care scale	Improvement with intervention
						Patient-provider relationships: Respectful and Supportive Care scale; Enabling and Partnership Scale; Providing Specific Information scales	No improvement with intervention
Hezang, B.; et al. (2017) [17]	RCT	90	Children with T2D	nursing intervention	usual care	drug compliance	Improvement with intervention
Transition from paediatric to adult care							
Campbell, F.; et al. (2016) [30]	CR	4 RCTs (n=238; 1 RCT with adolescents with T1D n=26)	Adolescents with chronic conditions including T1D	comprehensive transition programme	Usual care	rates of transfer from paediatric to adult diabetes services	No improvement with intervention
						risk of disease-related hospital admissions	No improvement with intervention
White, Mary; et al. (2017) [31]	RCT	120	17 - 19 years old with T1D	Transition from paediatric to adult care (TrACeD)	Standard care	Clinic attendance 0-12 months post-transition	No improvement with intervention
						Clinic attendance 12-24 months post-transition	Improvement with intervention
						Disengaged from services 0-12 months post-transition	No improvement with intervention
						Disengaged from services 12-24 months post-transition	Improvement with intervention

*Type of study CR = Cochrane review; RCT = randomised controlled trial.

n = number of participants.

T1D = type 1 diabetes; T2D = type 2 diabetes.

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