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).

Appendix A1: Summary of evidence from surveillance

2019 surveillance of Type 1 diabetes in adults: diagnosis and management (2015) NICE guideline NG17

Contents:

Evidence considered in surveillance

Search and selection strategy

We searched for new evidence related to the whole guideline.

We found 80 studies in a search for randomised controlled trials and Cochrane reviews published between 1 June 2014 and 7 December 2018.

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

Selecting relevant studies

Due to the large number of studies identified in the initial search, the following strategies were taken to ensure only relevant studies were selected:

- Studies with a sample size lower than 50 were excluded.
- Studies that included both type 1 and type 2 diabetes were excluded if they did not distinguish between the populations in the results.
- Pilot or proof-of-concept studies were excluded.
- Single studies already included in a Cochrane review were excluded.

Ongoing research

We checked for relevant ongoing research; of the ongoing studies identified, 8 studies were assessed as having the potential to change recommendations; therefore 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:

- Effectiveness of multimodal imaging for the evaluation of retinal odema and new vessels in diabetic retinopathy
- Circulating biomarkers to detect sight-threatening diabetic retinopathy
- A comparison of standard laser with micropulse laser for the treatment of diabetic macular oedema
- DAFNEplus cluster randomised controlled trial
- Optimising cardiac surgery outcomes in people with diabetes
- Lowering Events in Non-proliferative retinopathy in Scotland
- Performance Check of the Abbott FreeStyle Libre Flash Glucose Monitoring System
- Masked performance check of the Abbott FreeStyle Libre Flash Glucose Monitoring System.

Intelligence gathered during surveillance

Views of topic experts

Topic expert views have contributed to our proposal to update the following areas: smartphone applications and online platforms, Flash glucose monitoring, insulin therapy, SGLT2 inhibitors. See summary of evidence from surveillance below.

In addition, one expert called for more guidance around CVD risk assessment in type 1 diabetes; this is being considered in the update of the NICE guideline on lipid modification and we will assess impact when it is published.

A topic expert also highlighted new evidence around diabetic eye screening. However, this was not considered in this surveillance review as this 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.

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/ng17

1.1 Diagnosis and early care plan

Surveillance proposal

No new information was identified.

This section of the guideline should not be updated.

1.2 Support and individualised care

Surveillance proposal

No new information was identified.

This section of the guideline should not be updated.

1.3 Education and information

Surveillance proposal

This section of the guideline should not be updated.

2019 surveillance summary

One randomised controlled trial (RCT) was identified on a training programme to enhance self-management skills in type 1 diabetes (table 1). A guided self-determination intervention (delivered by group training) was found to have no effect on HbA1c levels compared to care as usual but did significantly improve diabetes distress scores after 9 months. (1) (n = 178).

Intelligence gathering

A topic expert noted that there have been advances in online platforms, which could be offered as an alternative to the current structured education programmes referenced in the guideline.

An ongoing trial (DAFNEplus) was identified which is examining the effect of a 5-day training course for healthy eating in adults with type 1 diabetes. We have added the trial to our event tracker and will assess the impact of the results when they are available.

Impact statement

Evidence was identified to suggest that a guided self-determination intervention had no effect on HbA1c levels compared to care as usual. This is consistent with the guideline, which does not make any recommendations on self-determination interventions. Ongoing research was identified on the DAFNE trial, which the guideline currently recommends (recommendation 1.3.1). We will assess the impact of these results when they are available.

New evidence is unlikely to change guideline recommendations.

1.4 Dietary management

Surveillance proposal

This section of the guideline should not be updated.

2019 surveillance summary

We identified 1 RCT (2) (n = 168) on dietary management interventions. The results indicate that carbohydrate counting with an automated basal calculator (to estimate insulin requirements outside of meal-times) is more effective than mental calculations in lowering HbA1c levels (table 2).

Intelligence gathering

No intelligence was identified for this section of the guideline.

Impact statement

New evidence was identified to support the use of an automated basal calculator in carbohydrate calculating compared to mental calculations. During guideline development, the committee noted that bolus calculators (to estimate one-off insulin requirements at meal-times) can be a useful addition to a patient's own carbohydrate counting. However, they also highlighted that a bolus calculator's effectiveness relies on carefully adjusted settings, ratios and blood glucose targets, and ability to carbohydrate count accurately. They noted that these are usually established with the help of skills learned in structured education, or in intensive one-to-one consultation with a suitably trained healthcare professional. As such, recommendations 1.4.1 and 1.4.2 advise carbohydrate counting training for adults with type 1 diabetes as part of structured education programmes (which may or may not cover the use of a bolus calculator). Therefore, no impact on the guideline is expected.

New evidence is unlikely to change guideline recommendations.

1.5 Physical activity

Surveillance proposal

No new information was identified.

This section of the guideline should not be updated.

1.6 Blood glucose management

Surveillance proposal

This section of the guideline should be updated.

2019 surveillance summary

Telemedicine

One Cochrane review and 3 RCTs were identified which examined the effect of telemedicine interventions on blood glucose management (table 3).

The Cochrane review (3) included 93 trials (n = 22,047) which examined the effectiveness, acceptability and costs of interactive telemedicine as an alternative to, or in addition to, usual care (i.e. face-to-face care, or telephone consultation). Telemedicine in this circumstance was defined as "the use of telecommunication systems to deliver health care at a distance". For the purposes of this surveillance review, only the impact on diabetes outcomes are summarised (16 studies; n = 2768). The telemedicine interventions included in these studies mainly consisted of remote monitoring devices that sent data to clinicians to review. Usually the remote monitoring was accompanied by additional education (delivered remotely) and/or a teleconference with the clinician. Results indicated that telemedicine was associated with significantly lower HbA1c levels at 9 months follow-up. Cholesterol and blood pressure were also found to significantly lower in people allocated to telemedicine interventions.

Later trials show more mixed results on telemedicine. An internet-based telematic system was found to be no different from face-to-face sessions in terms of the effect on HbA1c levels. The intervention required significantly less time investment from healthcare professionals (4) (n = 154). In contrast, one study in young adults found telemedicine to have no significant impact on HbA1c levels, self-monitoring compliance and quality of life, compared to standard glucose self-monitoring after 6 months (5) (n = 182).

Smart phone applications and online platforms

Results from one trial indicated that a smartphone application for self-monitoring was found to significantly reduce HbA1c levels compared to usual care after 3 months (6) (n = 100) (table 3).

Flash glucose monitoring

The IMPACT trial examined the effect of Flash glucose monitoring in people with well-controlled type 1 diabetes, compared to standard self-monitoring of capillary blood glucose (table 3). One study found that Flash glucose monitoring significantly reduced the time spent in hypoglycaemia (<3.9 mmol/L [70 mg/dL]), compared to standard monitoring (7) (n = 241). This effect was also found in adults using multiple daily injections insulin therapy (8) (n = 167).

Continuous glucose monitoring (CGM)

We identified evidence from 4 trials examining the use of CGM (table 3).

Both the DIAMOND and GOLD trials examined the effect of CGM in people who took multiple daily injections of insulin, compared to usual care (not specified in the abstracts). Results from both trials suggest that CGM significantly reduced HbA1c levels compared to usual care (9,10) (DIAMOND, n = 158; GOLD, n = 161). Further analyses found that the diabetes distress score (11) (DIAMOND, n = 158) and frequency of hypoglycaemic events (12) (DIAMOND, n = 158) were also improved with CGM compared to usual care.

Both the HypoDE and HypoCOMPaSS trials examined the effect of CGM on people who took multiple daily injections and had a history of impaired hypoglycaemia awareness or experienced severe hypoglycaemia in the previous year. Compared to self-monitoring of capillary blood glucose, CGM was found to significantly reduce the number of hypoglycaemic events at 26 weeks follow-up (13) (HypoDE, n = 149). However, another trial found there was no effect of CGM on hypoglycaemia awareness after 24 weeks (14) or at 2-year follow-up (15) (both HypoCOMPaSS, n = 96).

Intelligence gathering

Telemedicine

A key priority in the NHS Long Term Plan is the move to deliver more digitally-enabled care. It states that over the next 5 years, every patient will be able to access a GP digitally, and where appropriate, opt for a 'virtual' outpatient appointment. There is also mention of the NHS App which will link health records and have the potential to offer a 'digital triage' to help people find the most appropriate care. Virtual clinics are also discussed, as well as triaging for specialist referrals with the use of photographs and online questionnaires reviewed by a healthcare professional.

Smartphone applications and online platforms

A topic expert suggested that online platforms for education and self-management may be considered a suitable alternative to structured education programmes currently referenced in the guideline. In addition, the NHS England Test Bed programme brings NHS organisations and industry partners together to test combinations of digital technologies with pathway redesign in real-world settings. The programme has specific projects on diabetes (e.g. Diabetes Digital Coach) which are currently testing various digital platforms aimed 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.

Flash glucose monitoring

In November 2018, NHS England announced that Freestyle Libre (a Flash glucose monitoring system in the form of a wearable sensor) will be available on prescription for patients with type 1 diabetes who meet certain criteria. This policy will be rolled out from April 2019 and is expected to address the regional variation in Freestyle Libre availability that some patients are experiencing. The eligibility criteria for this technology are detailed in a recent statement from NHS England. The criteria for eligibility include: 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); as well as other criteria listed in the statement.

One of the trials (7) identified in this surveillance review has already been considered in the NICE medtech innovation briefing on Freestyle Libre for glucose monitoring (MIB110). Whereas the rest of the evidence considered in the medtech innovation briefing was in people with type 2 diabetes or pregnant women with diabetes, so not relevant to NICE guideline NG17.

In January 2019, the MHRA issued a medical device alert warning that some users of the Freestyle Libre device were experiencing skin reactions to the adhesive provided. This led to them applying barrier creams and sprays before attaching the sensor which may have affected the performance of the device. The manufacturer has confirmed that from April 2019, the formulation of the adhesive will be revised.

Topic experts also noted the change in policy around Freestyle Libre and highlighted the significant cost pressures that this may add to the NHS, calling for the guideline to be reviewed in this area.

We identified 2 ongoing trials (ISRCTN87654534 and ISRCTN12543702) examining the performance of Freestyle Libre in people with both type 1 and type 2 diabetes. These trials are being tracked and we will assess the impact of the results when they are available.

Impact statement

Telemedicine

Evidence from a Cochrane review suggests that telemedicine interventions, such as remote monitoring devices linked to health records, online software for education and teleconferences with a clinician improve blood glucose management. Evidence published after the review is mostly consistent with these findings, with a smartphone application appearing to improve HbA1c levels and an internet-based telematic intervention was found to be as effective as face-to-face sessions with a healthcare professional in terms of HbA1c levels. Although one trial was identified which found no difference in HbA1c levels, self-monitoring compliance and quality of life, from a policy perspective, 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.

New evidence identified that may change current recommendations.

Smartphone applications and online platforms

One study was identified to support the use of a smartphone application to enhance self-monitoring. This area relates 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 this as an area that is in need of review. Considering the ongoing work in this area and the importance of digital platforms emphasised in the NHS Long-Term Plan, it is proposed that this area is reviewed.

New evidence identified that may change current recommendations.

Flash glucose monitoring

New evidence was identified on the use of Flash glucose monitoring in people with well-controlled type 1 diabetes. Time spent in hypoglycaemia was significantly reduced with Flash glucose monitoring compared to standard self-monitoring of capillary blood glucose. This evidence relates to a recent policy change, which states that from April 2019, Freestyle Libre (a Flash glucose monitoring device) should be made available to patients on the NHS in England if they meet certain criteria. The NICE medtech innovation briefing on Freestyle Libre for glucose monitoring (MIB110) emphasises all evidence (at the time of publication in 2017) was limited to people with well-controlled diabetes and that the resource impact is unclear due to uncertainty around staff training and support requirements that may be needed. Long-term impact on patient outcomes is also uncertain, with the longest follow-up being 6 months. We are monitoring the progress of 2 ongoing trials in this area

(ISRCTN87654534 and ISRCTN12543702) which may shed more light on the long-term effectiveness of Freestyle Libre in patients with type 1 diabetes. We will review these results and assess impact on the guideline as soon as they are published. In the meantime, it is proposed that this area is reviewed to take into account the change in policy and the new evidence published since the release of the NICE medtech innovation briefing MIB110.

New evidence identified that may change current recommendations.

CGM

We identified new evidence which supports the use of CGM in people having multiple daily injection therapy, with and without impaired hypoglycaemia awareness or history of severe hypoglycaemia. This is broadly consistent with the guideline which recommends offering CGM to adults with complete loss of hypoglycaemia awareness or history of severe hypocglycaemia (recommendation 1.6.22). The guideline does not mention offering CGM to all people who have multiple daily injections, however it does advise that the principles of flexible insulin therapy with a multiple daily injection insulin regimen (or pump therapy) should be followed for people with CGM (recommendation 1.6.23). Therefore no impact on the guideline is expected.

New evidence is unlikely to change guideline recommendations.

1.7 Insulin therapy

Surveillance proposal

This section of the guideline should be updated.

2019 surveillance summary

Insulin therapy

We identified 1 Cochrane review and 15 RCTs comparing different insulin types and dosages (table 4).

We also identified evidence on insulin peglispro (16,17), however as this drug does not currently have a license to be used in the UK this evidence has not been considered in this surveillance review.

Insulin analogues compared to human insulins

A Cochrane review (18) of 9 studies (n = 2693) examined the effects of short-acting insulin analogues (such as insulin lispro, insulin aspart and insulin glulisine) compared to regular

human insulin. Results indicated that HbA1c levels were significantly lower in the insulin analogue group but there was no significant difference between groups for the risk of severe hypoglycaemia. A further study in people with recurrent severe hypoglycaemia found insulin analogues (detemir/aspart) to significantly reduce the number of severe hypoglycaemic episodes, compared to human insulin (19) (n = 159).

Long-acting insulins

Two trials (20,21) found that insulin degludec, an ultra-long-lasting insulin, may be superior to insulin glargine in terms of glucose-lowering effect (20) (n = 57) and hypoglycaemia outcomes (21) (n = 501). Insulin degludec was also found to be non-inferior to insulin detemir for changes to HbA1c levels (22) (n = 455).

Biosimilar insulins

Four biosimilar insulins were found to be non-inferior to the original formation, including SAR342434 (lispro) (23), LY296316 (glargine) (24), MK-1293 (glargine) (25), MYL-1501D (glargine) (26) for changes to HbA1c levels.

Rapid acting insulins

Results from the ONSET trials indicated that a faster-acting version of insulin aspart was non-inferior to conventional insulin aspart at 26 weeks ((27) n = 1143; (28) n = 1024) but superior at 52 weeks (29) (n = 381) for HbA1c levels. The same non-inferiority effect of faster-acting aspart was also found when delivered via a continuous subcutaneous insulin infusion (CSII), (30) (n = 472).

Dose comparisons

Results from the EDITION trial indicated that a higher dose of insulin glargine (300 units/ml) was non-inferior to a lower dose (100 units/ml) ((31) n = 243 (32) n = 549) in terms of HbA1c levels. However, a higher dose significantly reduced the rate of confirmed severe hypoglycaemic events ((33) n = 243).

Continuous subcutaneous insulin infusion or insulin pump therapy

Four studies (14,34–36) were identified which examined the effect of insulin pump therapy in adults with type 1 diabetes. These studies relate to the NICE technology appraisal guidance on continuous subcutaneous insulin infusion for the treatment of diabetes mellitus (NICE technology appraisal guidance 151) and will not be considered in this surveillance review.

Adjuncts to insulin

We identified 13 RCTs examining the effect of adjunctive treatment alongside insulin in type 1 diabetes (table 4). The following studies relate to NICE technology appraisal guidance in development and will not be considered in this surveillance review:

- Three studies on sotagliflozin (37–39) (GID-TA10376)
- Three studies on empagliflozin (40–42) (GID-TA10375)
- Three studies on dapagliflozin (43–45)(GID-TA10374)

Results from one RCT (46) (n = 351) indicated that adjunctive treatment with canagliflozin significantly improved HbA1c levels and body weight compared to placebo.

Results from the ADJUNCT trials show adjunctive treatment with liraglutide significantly improved HbA1c levels and body weight compared to placebo after 26 weeks (47) (n =835) and 1 year (48) (n = 1398). For a subset of overweight participants with insufficient glycaemic control, there was no effect of liraglutide on HbA1c levels but there were significantly fewer hypoglycaemic events compared to placebo (49) (n = 100).

We also identified evidence on Subetta (50) as an add-on to insulin therapy, however as this drug does not currently have a license to be used in the UK this evidence has not been considered in this surveillance review.

Intelligence gathering

Many topic experts highlighted that new insulins have become available since the guideline was published. They advised that as many have different pharmacological features, such as ultra-long lasting and fast-acting, there are now more options available in insulin therapy that should be considered in the guideline. The increased availability of biosimilar insulins was also raised as an area to review as these are cheaper versions of the insulins currently recommended in the guideline.

An expert also noted that the guideline may need to be reviewed to consider the place of sodium-glucose cotransporter 2 (SGLT2) inhibitors in the treatment of type 1 diabetes.

A drug safety update was identified relating to high-strength, fixed-combination and biosimilar insulin products. This gives an overview of the new insulin products available and advises on ways to minimise the risk of medication errors.

Impact statement

Insulin therapy

Insulin analogues compared to human insulins

A Cochrane review and a further trial were identified which support the use of short-acting insulin analogies over human insulin. This is consistent with the guideline, which currently recommends offering rapid-acting insulin analogues before meals (recommendation 1.7.7) and has no recommendations on human insulin use. Therefore, no impact on the guideline is expected.

New evidence is unlikely to change guideline recommendations.

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). In light of 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.

New evidence identified that may change current recommendations.

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 highlighted 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. It is proposed that this area is reviewed to consider the various biosimilar insulins now available.

New evidence identified that may change current recommendations.

Rapid-acting insulin

Results from one trial indicated that a faster-acting version of insulin aspart was non-inferior in the short term and superior in the long term to conventional insulin aspart. The guideline does not currently recommend using a particular type of rapid-acting insulin (recommendations 1.7.7-1.7.9), therefore it is unlikely that the guideline will be impacted.

New evidence is unlikely to change guideline recommendations.

Dose comparisons

Results from one trial suggest there may be some benefit to offering a higher dose of insulin glargine to improve hypoglycaemia outcomes. The guideline does not currently make any recommendations on dosage amounts, under the assumption that other NICE evidence sources (such as the British National Formulary) are up-to-date and can be used for such queries. Therefore, no impact on the guideline is expected.

New evidence is unlikely to change guideline recommendations.

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, given the rise in research for this population. 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.

Results from one trial suggest that adjunctive treatment with liraglutide may improve HbA1c levels and reduce body weight. However, the effect on HbA1c levels was not found in a subset of overweight participants with insufficient glycaemic control, despite improvement in hypoglycaemia outcomes. Liraglutide is a GLP-1 agonist currently licensed for use in type 2 diabetes. The guideline currently recommends adding metformin to insulin therapy if an adult with type 1 diabetes and a BMI of 25 kg/m^2 or above and wants to improve their blood glucose control whilst minimising their effective insulin dose (recommendation 1.7.14). Given the lack of benefit of liraglutide on overweight adults with type 1 diabetes, the guideline is unlikely to be affected at this point.

New evidence identified that may change current recommendations.

1.8 Insulin delivery

Surveillance proposal

No new information was identified.

This section of the guideline should not be updated.

1.9 Referral for islet or pancreas transplantation

Surveillance proposal

No new information was identified.

This section of the guideline should not be updated.

1.10 Awareness and management of hypoglycaemia

Surveillance proposal

No new information was identified.

This section of the guideline should not be updated.

1.11 Ketone monitoring and management of diabetic ketoacidosis (DKA)

Surveillance proposal

No new information was identified.

This section of the guideline should not be updated.

1.12 Associated illness

Surveillance proposal

No new information was identified.

This section of the guideline should not be updated.

1.13 Control of cardiovascular risk

Surveillance proposal

This section of the guideline should not be updated.

2019 surveillance summary

We identified 3 reports of 2 trials which examined different interventions to control cardiovascular disease (CVD) risk in type 1 diabetes (table 5).

One analysis of the ASCEND trial (51) (n = 15480) found that taking daily aspirin appeared to prevent serious vascular events in people who had diabetes and no evident CVD at the time of trial entry. However, major bleeding events were significantly more common with aspirin compared to placebo. In the same trial, another analysis (52) (n = 15,480) found no effect of

n-3 fatty acid supplementation on cardiovascular events over an average of 7.4 years, compared to an olive oil control.

One RCT (53) (n = 4732) found achieving a target systolic blood pressure of less than 120mmHg does not appear to mitigate risk of major adverse cardiovascular events whereas between 120-140mmHg does significantly reduce risk.

Intelligence gathering

A topic expert noted that further guidance on the cardiovascular risk assessment may be needed, particularly for younger adults with type 1 diabetes as the guidance advice on statins and angiotensin-converting-enzyme inhibitors is not appropriate for women of childbearing age.

Impact statement

Results from the ASCEND trial indicate that daily aspirin may prevent serious vascular events in people with type 1 diabetes and no current CVD, however aspirin also increased serious bleeding events. The guideline currently states "Do not offer aspirin for the primary prevention of cardiovascular disease to adults with type 1 diabetes" (recommendation 1.13.1). During guideline development, there was little evidence in this population however the committee noted that guidance from the MHRA suggests that the harms of aspirin for primary prevention outweigh the benefits. As mentioned in the study, the absolute benefits of aspirin in this case are largely counterbalanced by the bleeding hazard. Therefore, it is unlikely that the new evidence will impact the guideline. The guideline does contain other recommendations for the primary prevention of CVD, including recommendations on smoking cessation, lipid modification and lifestyle changes.

A topic expert highlighted the need for further guidance on cardiovascular risk assessment. Currently the guideline sign-posts to the NICE guideline on lipid modification for advice on tools for assessing risk of CVD in adults with type 1 diabetes (recommendation 1.13.3). The NICE guideline on lipid modification is currently undergoing update in the area of CVD risk assessment, following recent surveillance which identified new evidence on the QRISK3 tool to identify and assess CVD risk in people with type 1 diabetes. We will review this area and assess impact on NICE guideline NG17 once this evidence has been considered and the update has been published.

New evidence is unlikely to change guideline recommendations.

1.14 Care of adults with type 1 diabetes in hospital

Surveillance proposal

This section of the guideline should not be updated.

2019 surveillance summary

A Cochrane review of 8 studies (54) (n = 1048) examined the effects of sliding scale insulin for non-critically ill hospitalised adults with diabetes mellitus (table 6). The main comparison was between sliding scale insulin and basal-bolus insulin therapy. Results indicated that basal-bolus insulin therapy may be associated with an increased risk of severe hypoglycaemic episodes (defined as blood glucose levels below 40 mg/dL). Sliding scale insulin was associated with higher blood glucose levels compared to basal-bolus insulin therapy. There were no significant differences in mean length of hospital stay and post-operative infections. The authors concluded that the evidence was insufficient to draw any conclusions on the most effective insulin strategy in this population.

Intelligence gathering

No intelligence was identified for this section of the guideline.

Impact statement

We identified evidence that suggest basal-bolus insulin might result in better short-term glycaemic control but could increase the risk for severe hypoglycaemic episodes, compared to sliding scale insulin. The guideline currently recommends using the basal-bolus strategy (see recommendation 1.14.4). As the new evidence was inconclusive about which insulin strategy has the best patient outcomes, further research is required before any impact on the guideline can be assessed.

New evidence is unlikely to change guideline recommendations.

1.15 Managing complications

Surveillance proposal

This section of the guideline should be updated.

Editorial amendments

- 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”.

2019 surveillance summary

Eye disease

We identified 2 Cochrane reviews and 3 RCTs on interventions to manage eye disease in type 1 diabetes (table 7). Two Cochrane reviews (55,56) and 5 RCTs (57–61) focussed on the use of anti-vascular endothelial growth factor (anti-VEGF) for diabetic macular oedema which relate to the NICE technology appraisal guidance on Ranibizumab for treating diabetic macular oedema (TA274). Therefore, these studies will not be considered in this surveillance review.

Treatment of proliferative diabetic retinopathy

A Cochrane review (62) of 18 studies (n = 1005) examined the effectiveness and safety of anti-VEGF for proliferative diabetic retinopathy. The comparator in this case was panretinal photocoagulation (PRP) which is usual care. Results indicated that anti-VEGFs (bevacizumab, pegaptanib) significantly improved visual acuity compared to no anti-VEGF treatment. Any anti-VEGF treatment was also associated with significantly reduced risk of vitreous or pre-retinal haemorrhage and risk of losing 3 or more lines of visual acuity. Authors noted that the evidence was of very low quality and further trials are needed to inform treatment decisions.

One RCT (63) (n not reported in the abstract, 22 ophthalmic centres) found that intravitreous injection of aflibercept was more effective than standard care with photocoagulation at improving visual acuity.

Evidence was identified on the use of sulodexide in patients with non-proliferative diabetic retinopathy (64), however as this drug does not currently have a license to be used in the UK this evidence has not been considered in this surveillance review.

Treatment of diabetic macular oedema

A Cochrane review (65) of 24 studies (n = 4422 eyes) examined the efficacy and safety of laser photocoagulation as monotherapy in the treatment of diabetic macular oedema. Results indicated that compared to no intervention, those receiving laser treatment were significantly less likely to lose best-corrected visual acuity (BCVA) at one year. There was some indication that the less invasive laser techniques (e.g. subthreshold technique) may be as effective as standard laser therapy, however authors note that further evidence is required.

One RCT (66) (n = 125) found that compared to placebo, there was no effect of topical nepafenac on change in optical coherence tomography retinal volume.

Diabetic kidney disease

A Cochrane review of 44 studies (67) (128 records, n = 13,036) examined the efficacy and safety of insulin and other pharmacological interventions for lowering glucose levels in people with diabetes and chronic kidney disease (table 7). Studies were identified examining the following interventions: SGLT2 inhibitors, DPP-4 inhibitors, GLP-1 agonists and glitazones. Results indicated that compared to placebo, SGLT-2 inhibitors may significantly reduce HbA1c, fasting blood glucose, systolic blood pressure, systolic blood pressure and

weight. However, there was no significant effect on risk of cardiovascular death, hypoglycaemia and acute kidney injury. Compared to placebo, DPP-4 inhibitors may significantly reduce HbA1c but there was little or no effect on fasting blood glucose, risk of cardiovascular death and weight. Compared to placebo, GLP-1 agonists may significantly reduce HbA1c. The evidence on glitazones was uncertain and no conclusions could be drawn.

A long-term follow-up study of the Diabetes Control and Complications Trial (DCCT) (68) (n = 1441) found that intensive treatment (involving target levels of glycaemia as close to non-diabetic range as safely possible) significantly reduced the risk of developing albuminuria after 18 years.

Chronic painful neuropathy

We identified 3 studies related to diabetic peripheral neuropathic pain (table 7). One RCT (69) (n = 303) found that duloxetine is non-inferior to pregabalin in lowering average pain scores in people with diabetic peripheral neuropathic pain. Another trial (70) (n = 270) found that there was no difference in pain scores in people treated with gabapentin or pregabalin. However, an additional RCT (71) (n = 620) found that, compared to placebo, there was no effect of pregabalin on average pain scores for people with painful diabetic peripheral neuropathy.

Evidence was also identified on the use of mirogabalin (72), however as this drug does not currently have a license to be used in the UK, this evidence has not been considered in this surveillance review.

Gastroparesis

We identified 1 RCT (73) (n = 56) which found a small particle size diet to significantly reduce gastroparetic symptoms compared to a control diet in adults with gastroparesis. Another study (74) (n = 89) found that metoclopramide nasal spray was more effective at symptom control than metoclopramide in oral tablet form (table 7).

Evidence was also identified on the use of Relamorelin (75), however as this drug does not currently have a license to be used in the UK this evidence has not been considered in this surveillance review.

Psychological problems

We identified 2 studies examining interventions to treat psychological problems in adults with type 1 diabetes (table 7). One RCT (76) (n = 94) found that both mindfulness-based cognitive behaviour therapy (CBT) and regular CBT significantly reduced depression compared to no treatment. Another study (77) (n = 200) found that a self-management intervention significantly reduced depressive symptoms in people with serious mental illness and diabetes, compared to usual care.

Intelligence gathering

One topic expert noted that there is new evidence on the optimum screening strategy for retinopathy in type 1 diabetes.

We were also made aware of restrictions in the use of SGLT-2 inhibitors in people with impaired renal function. For example, the summary of product characteristics for dapagliflozin advises that it should not be initiated in patients with a glomerular filtration rate [GFR] < 60 mL/min and should be discontinued at GFR persistently below 45 mL/min.

We also identified several ongoing trials relevant to this section of the guideline which are detailed below:

- Effectiveness of multimodal imaging for the evaluation of retinal odema and new vessels in diabetic retinopathy
- Circulating biomarkers to detect sight-threatening diabetic retinopathy
- A comparison of standard laser with micropulse laser for the treatment of diabetic macular oedema
- Lowering Events in Non-proliferative retinopathy in Scotland

These trials are being tracked and we will assess the impact of the results when they are published.

Impact statement

Eye disease

Treatment of diabetic retinopathy

We identified new evidence on the treatment of proliferative diabetic retinopathy, supporting the use of anti-VEGF treatment and also intravitreous injection of aflibercept. The guideline currently only has recommendations on screening for diabetic retinopathy and referral criteria. During original guideline development, the committee only considered evidence on non-surgical treatment for diabetic retinopathy (which excludes the use of injections). Given the growing evidence base in this area and the related NICE technology appraisal guidance on treatments for diabetic macular oedema, we propose that this area is reviewed.

Topic experts also highlighted new evidence on the optimum frequency of screening for diabetic retinopathy. 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.

New evidence identified that may change current recommendations.

Treatment of diabetic macular oedema

We identified new evidence on the treatment of diabetic macular oedema. A Cochrane review supports the use of laser therapy compared to no intervention and suggested that less invasive techniques may be just as effective as the standard laser, however these results

were highly uncertain. A further study found no effect of nepafenac on change in optical coherence tomography retinal volume. As mentioned above, the guideline currently only has recommendations on screening for diabetic retinopathy and referral criteria. There are no recommendations on diabetic macular oedema and the original guideline committee did not consider surgical evidence in this area. Given the growing evidence base in this area and the related NICE technology appraisal guidance on treatments for diabetic macular oedema, there may be a need for new recommendations to be developed.

New evidence identified that may change current recommendations.

Diabetic kidney disease

New evidence was identified to support the use of glucose-lowering agents (SGLT2 inhibitors, DPP-4 inhibitors and GLP-1 agonists) in people with diabetes and chronic kidney disease. The guideline currently sign-posts to the NICE guideline on chronic kidney disease however it does not contain any recommendations on glucose-lowering agents for this population. The new evidence seems to suggest that SGLT2 could be effective in managing blood glucose levels in people with chronic kidney disease. However, the Cochrane review notes that the safety aspects of these treatments are uncertain and expert advice warns of the restrictions in using dapagliflozin in people with chronic kidney disease. Until there is further evidence on the safety of glucose-lowering agents in adults with diabetes and chronic kidney disease, it is unlikely that the guideline will be affected.

We identified evidence from a large long-term trial (DCCT) supporting the use of intensive diabetes treatment (with glycaemia targets) significantly reduced the risk of developing albuminuria at 18-year follow-up. The guideline currently recommends "Support adults with type 1 diabetes to aim for a target HbA1c level of 48 mmol/mol (6.5%) or lower, to minimise the risk of long-term vascular complications" (recommendation 1.6.6). During guideline development, the committee acknowledged the importance of the DCCT data as a large RCT of intensified therapy. After considering the results, they selected a target HbA1c value that is lower than the achieved HbA1c of the DCCT, recognising that achieving the value of 7%, as done in the DCCT, was more likely if the target was set lower than this. The new evidence supports the continued use of this target and therefore it is unlikely to impact recommendations.

New evidence is unlikely to change guideline recommendations.

Chronic painful neuropathy

We identified mixed evidence on the use of duloxetine, gabapentin and pregabalin for people with diabetic peripheral neuropathic pain. The guideline does not have any recommendations on pharmacological treatments for neuropathic pain, however it does signpost to the NICE guideline on neuropathic pain – pharmacological management (NICE guideline CG173) which recommends a choice of duloxetine, gabapentin or pregabalin as an initial treatment (recommendation 1.1.8). Whilst 2 of the identified trials were consistent with this

recommendation, the third study found no effect of pregabalin on pain scores. Until further evidence is identified to confirm these findings, no impact is expected at this point.

New evidence is unlikely to change guideline recommendations.

Gastroparesis

We identified evidence supporting the adoption of a small particle size diet for people with diabetes and gastroparesis. This is in line with recommendation 1.15.25 in the guideline which states "Advise a small-particle-size diet (mashed or pureed food) for symptomatic relief for adults with type 1 diabetes who have vomiting caused by gastroparesis". Evidence was also identified to suggest that metoclopramide as a nasal spray is more effective than oral tablets at controlling symptoms. The guideline does not currently have any recommendations on the use of metoclopramide for gastroparesis. Until there is further evidence in this area, the guideline will not be affected.

New evidence is unlikely to change guideline recommendations.

Psychological problems

We identified evidence to support the use of standard CBT, mindfulness-based CBT and a self-determination intervention in adults with diabetes and psychological problems. The guideline does not currently make any recommendations on interventions in this group, instead signposting to NICE guidelines on common mental health disorders, generalised anxiety disorder and panic disorder (with or without agoraphobia) in adults and depression in adults with a chronic health problem. The new evidence is in line with the advice in these guidelines so no impact is expected.

New evidence is unlikely to change guideline recommendations.

Areas not currently covered in the guideline

In surveillance, evidence was identified for areas not covered by the guideline. This new evidence has been considered for possible addition as a new section of the guideline.

New section considered in surveillance

Closed-loop systems

Surveillance proposal

This section should not be added.

Closed-loop insulin delivery

2019 surveillance summary

We identified 2 RCTs examining the effect of closed-loop insulin delivery systems (table 8). One study (78) (n = 86), in adults with sub-optimally controlled type 1 diabetes, found that 12 weeks of day and night hybrid closed-loop insulin delivery significantly reduced the risk of hypoglycaemia. The 'hybrid' nature of this intervention enabled participants to administer insulin boosts at meal times.

Another trial (79) (n = 75) found that 4 nights of closed-loop control (used at home) significantly reduced the time spent in hypoglycaemia. The closed-loop device in this trial had no input from the participant.

In both trials, the closed-loop delivery intervention was compared to sensor-augmented pump therapy. Although both therapies combine the use of CGM with an insulin pump, the closed-loop delivery is fully automatic, sometimes termed an "artificial pancreas" whereas the sensor-augmented pump therapy allows users to perform real-time adjustments to insulin therapy.

Intelligence gathering

NICE have produced guidance on integrated sensor-augmented pump therapy systems for managing blood glucose levels in type 1 diabetes (the MiniMed Paradigm Veo system and the Vibe and G4 PLATINUM CGM system) (Diagnostics guidance DG21). These systems combine continuous glucose monitoring and continuous subcutaneous insulin infusion, for people with type 1 diabetes.

Impact statement

New evidence was identified to suggest a benefit of closed-loop insulin delivery systems over sensor-augmented pump therapy, particularly in people with sub-optimally controlled diabetes. A closed-loop system is an emerging therapeutic approach for people with type 1 diabetes, combining a linked continuous glucose monitor with an insulin pump. Whilst the new evidence shows promising results in reducing the risk of hypoglycaemia during the night, more research is needed to understand the long-term effectiveness of closed-loop systems and to examine safety outcomes. Furthermore, only one of the studies focussed specifically on patients with sub-optimally controlled diabetes, so further evidence to confirm the findings in this group would be useful.

New evidence is unlikely to impact on the guideline.

New section considered in surveillance

Sensor-augmented pump therapy

Surveillance proposal

This section should not be added.

Sensor-augmented pump therapy

2019 surveillance summary

We identified one study (80) (n = 60) which examined the effect of sensor-augmented pump (SAP) therapy in people with type 1 diabetes, a history of albuminuria and were on stable renin-angiotensin system inhibition (table 8). Glucose variability, HbA1c levels and urine albumin creatine ratio all improved with SAP therapy compared to multiple daily injections.

Intelligence gathering

No topic expert feedback was relevant to this section.

Impact statement

New evidence supports the use of SAP therapy over multiple daily injections in people with a history of albuminuria and taking renin-angiotensin system inhibitors. Whilst the trial shows promising results for this population, the sample size was relatively small and confirmation in a larger trial is needed before impact on the guideline can be assessed.

New evidence is unlikely to impact on the guideline.

Research recommendations

Research recommendation	Summary of findings
In adults with diabetes, are diagnostic tests (autoimmune markers and biochemical tests such as urine C-peptide and urine C-peptide/creatinine ratio) useful for defining type 1 diabetes, and if so, what is the optimal time in which they should be measured in order to make the diagnosis?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Research recommendation	Summary of findings
In adults with type 1 diabetes, are diagnostic tests (autoimmune markers and biochemical tests such as urine C-peptide and urine C-peptide/creatinine ratio) good prognostic makers of the complications associated with the 1 diabetes and its treatments? *We exclude the use of these markers in trials of immune modulation therapy to alter the course of type 1 diabetes, as this is not a current therapeutic option and the literature was not reviewed by the committee in this revision.*	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
In adults with type 1 diabetes, what methods can be used to increase the uptake of structured education programmes and to improve their clinical outcomes (particularly achieving and sustaining blood glucose control targets)?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
In adults with newly diagnosed type 1 diabetes, what is the optimal timing and method of delivering structured education in terms of clinical and cost effectiveness?	No new evidence relevant to the research recommendation was found. However, an ongoing trial (DAFNEplus) was identified which is examining the effect of a 5-day training course for healthy eating in adults with type 1 diabetes may be relevant in future. We have added the trial to our event tracker and will assess the impact of the results when they are available.
In adults with type 1 diabetes, what is clinical and cost effectiveness of bolus calculators used in conjunction with self-monitoring blood glucose meters?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
In adults with type 1 diabetes, what is the clinical and cost effectiveness of different types of diet and dietary constituents, particularly in terms of the effect on insulin requirement and blood glucose control?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Research recommendation	Summary of findings
What methods and interventions are effective in increasing the number of adults with type 1 diabetes who achieve the recommended HbA1c targets without risking severe hypoglycaemia or weight gain?	New evidence relating to this research recommendation was identified during surveillance. See section 1.6 above for a summary of findings and impact on guidance.
Can a risk stratification tool be used to aid the setting of individualised HbA1c targets for adults with type 1 diabetes?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
In adults with type 1 diabetes, is HbA1c measurement by laboratory analysis more cost effective compared to site of care HbA1c testing?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
In adults with type 1 diabetes, what is the clinical and cost effectiveness of post-prandial blood glucose monitoring?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
In adults with type 1 diabetes who have chronically poor control of blood glucose levels, what is the clinical and cost effectiveness of continuous glucose monitoring technologies?	New evidence relating to this research recommendation was identified during surveillance. See section 1.6 above for summary of the HypoDE and HypoCOMPaSS trials which examined the effect of CGM on people who took multiple daily injections and had a history of impaired hypoglycaemia awareness or experienced severe hypoglycaemia in the previous year.
In adults with type 1 diabetes, what is the clinical and cost effectiveness of basal insulins with longer action profiles compared to existing regimens, particularly in terms of dose adjustment for flexible lifestyles, such as intermittent exercise or alcohol consumption, and their long-term safety data?	New evidence relating to this research recommendation was identified during surveillance. See section 1.7 above for summary of evidence on comparing different insulin types and dosages.

Research recommendation	Summary of findings
In adults with type 1 diabetes who have recently been diagnosed, what is the clinical and cost effectiveness (particularly in terms of preservation of residual insulin secretion and other long-term outcomes) of different intensities of glycaemic control (for example, inpatient intravenous insulin management versus outpatient multiple daily dose insulin injection therapies)?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
In adults with type 1 diabetes who have recently been diagnosed, what is the clinical and cost effectiveness (particularly in terms of preservation of residual insulin secretion and other long-term outcomes) of using basal-bolus insulin regimens?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
In adults with type 1 diabetes, what modifications of rapid-acting insulin use (including but not limited to timing of administration, and the nature of the insulin) could be employed to improve glycaemic control around different meal compositions?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
In adults with type 1 diabetes and a BMI of ≥25 kg/m^2, what is the clinical and cost effectiveness of metformin as an adjunct to insulin, particularly in terms of glycaemic control and weight loss (or reduction in weight gain)?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
In adults with type 1 diabetes, what is the clinical and cost effectiveness of GLP-1 analogues and other potential pharmacological adjuncts to insulin therapy?	New evidence relating to this research recommendation was identified during surveillance. See section 1.7 above for a summary of the evidence on adjuncts to insulin therapy.

Research recommendation	Summary of findings
In adults with type 1 diabetes, what are the optimum needle length and type for administration of exogenous insulin in terms of clinical and cost effectiveness?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
In adults with type 1 diabetes, what is the optimum injection site and injection site rotation regimen in terms of clinical and cost effectiveness?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
For adults with type 1 diabetes, what are the optimum technologies (such as insulin pump therapy and/or continuous glucose monitoring, partially or fully automated insulin delivery, and behavioural, psychological and educational interventions) and how are they best used, in terms of clinical and cost effectiveness, forpreventing and treating impaired awareness of hypoglycaemia?	New evidence relating to this research recommendation was identified during surveillance. See section 1.7 above for a summary of the new evidence on CSII or insulin pump therapy. See also the new evidence on closed-loop delivery and sensor augmented pump therapy.
In adults with type 1 diabetes, what is the clinical and cost effectiveness (particularly in terms of morbidity, reduction in admission rates, and length of stay) of using blood capillary ketone strips compared to urine ketone strips for the management of DKA?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
In adults with type 1 diabetes, what is the clinical and cost effectiveness (particularly in terms of morbidity, reduction in admission rates, and length of stay) of using blood capillary ketone strips compared to urine ketone strips for the prevention of DKA?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
In adults with type 1 diabetes, what is the clinical and cost effectiveness (particularly in terms of pre-empting admissions) of self-monitoring blood ketones compared to urine ketones?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Research recommendation	Summary of findings
In adults with type 1 diabetes, what is the clinical and cost effectiveness of aspirin and other antiplatelet agents who are at high risk for vascular disease (for example, smokers, those with renal disease, those with other evidence of vascular disease)?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
In adults with type 1 diabetes, what is the clinical and cost effectiveness (particularly in terms of optimal blood glucose control, patient-reported outcomes and experience, length of stay, and short-term complications) of closed-loop insulin delivery systems and automated insulin dose advisors during in-hospital care, and could the development of new systems and technologies improve on current clinical outcomes?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
In adults with type 1 diabetes, clinical and cost effective treatments for diabetic gastroparesis are needed, together with further evidence for the clinical and cost effectiveness of existing treatments such as dopamine antagonists, insulin pump therapy, and gastric electrical stimulation.	New evidence relating to this research recommendation was identified during surveillance. See section 1.15 above for a summary of the new evidence on metoclopramide for the treatment of gastroparesis.
What is the clinical and cost effectiveness of constructing a national database and centralising supervision of the management of adults with type 1 diabetes who have painful neuropathy of rapid glycaemic control?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Editorial amendments

During surveillance of the guideline we identified the following points in the guideline that should be amended:

- 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”.

Data summary tables

Table 1. Education and information

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
Mohn, J.; et al. 2017 (1)	RCT	178	Adults over 30	Guided self-determination by group training	Care as usual	Change in HbA1c	9 months	No significant difference between intervention and comparator
						Diabetes distress scale	9 months	Improved with intervention
Abbreviations: RCT, randomised controlled trial.								

Table 2. Dietary management

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
Hommel, E.; et al. 2017 (2)	RCT	168	Patient with MDIs and HbA1c of 8-11.3%.	Advanced carbohydrate counting with automated basal calculator	Advanced carbohydrate counting with mental calculations	Change in HbA1c	12 months	Improved with intervention
Abbreviations: RCT, randomised controlled trial; MDIs, multiple daily injections.								

Table 3. Blood glucose management

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
Telemedicine								
Flodgren, G.; et al. 2015 (3)	Cochrane	16 (2768 on diabetes)	Adult (age not specified)	Interactive telemedicine	Usual care	Change in HbA1c	9 months	Improved with intervention
Di Bartolo, P.; et al. 2017 (5)	RCT	182	Young adults (average age of 17.7) with poorly controlled T1D and poorly compliant with	Telemedicine	Standard glucose monitoring	Change in HbA1c	6 months	No significant difference between intervention and comparator
						Achievement of compliance with SMBG	6 months	No significant difference between intervention and comparator

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
			self-monitoring of BG			Quality of life	6 months	No significant difference between intervention and comparator
Esmatjes, E.; et al. 2014 (4)	RCT	154	Adults with inadequate metabolic control	Internet-based telematic system (2 face-to-face and 5 internet sessions)	Control (7 face-to-face sessions)	Change in HbA1c	7 sessions	No significant difference between intervention and comparator
						Healthcare professional time	n/a	Significantly less with intervention
Smartphone applications and online platforms								
Zhou, W.; et al. 2016 (6)	RCT	100	Adults with HbA1c >=64 mmol/mol	Smartphone-based application "Welltang"	Usual care	Change in HbA1c	3 months	Improved with intervention
Flash glucose monitoring								
Oskarsson, P.; et al. 2018 IMPACT (8)	RCT	167	Adults with MDIs	Flash glucose monitoring	Self-monitoring of capillary blood glucose	Mean time in hypoglycaemia (<3.9 mmol/L [70 mg/dL])	6 months	Improved with intervention
Bolinder, J.; et al. 2016 IMPACT (7)	RCT	241	Adults with well-controlled T1D	Flash glucose monitoring	Self-monitoring of capillary blood glucose	Mean time in hypoglycaemia (<3.9 mmol/L [70 mg/dL])	6 months	Improved with intervention
Continuous glucose monitoring								
Beck, R. W.; et al. 2017 DIAMOND (9)	RCT	158	Adults with MDIs	Continuous glucose monitoring	Usual care	Change in HbA1c	24 weeks	Improved with intervention
Riddlesworth, Tonya;et al. 2017 DIAMOND (12)	RCT	158	Adults with MDIs	Continuous glucose monitoring	Usual care	Hypoglycaemic events	6 months	Improved with intervention
Polonsky, W. H.; et al. 2017 DIAMOND (11)	RCT	158	Adults with MDIs	Continuous glucose monitoring	Multiple daily injections	Diabetes distress scale	24 weeks	Improved with intervention
Lind, M.; et al. 2017 GOLD (10)	RCT	161	Adults with MDIs	Continuous glucose monitoring	Conventional treatment	Change in HbA1c	26 weeks + 17 week washout	Improved with intervention

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
Heinemann, L.; et al. 2018 HypoDE (13)	RCT	149	Adults with MDIs and a history of impaired hypoglycaemia awareness or severe hypoglycaemia in previous year	Real time CGM (rtCGM) (unmasked)	Self-monitoring of capillary blood glucose (with masked rtCGM)	Mean number of hypoglycaemic events per 28 days (glucose less than 3.0mmol/L for more than 20 minutes)	26 weeks	Improved with intervention
Little, S. A.; et al. 2014 HypoCOMPass (14)	RCT	96	Adults with impaired awareness of hypoglycemia	Real time CGM (rtCGM) (unmasked)	Self-monitoring of blood glucose	Hypoglycaemia awareness	24 weeks	No significant difference between intervention and comparator
Little, S. A.; et al. 2018 HypoCOMPass (15)	RCT	96	Adults with impaired awareness of hypoglycemia	Real time CGM (rtCGM) (unmasked)	Self-monitoring of blood glucose	Hypoglycaemia awareness	2 years	No significant difference between intervention and comparator
Abbreviations: RCT, randomised controlled trial; CGM, continuous glucose monitoring; SMBG, self-monitoing of blood glucose; MDIs, multiple daily injections.								

Table 4. Insulin therapy

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
Insulin analogues compared to human insulins								
Fullerton, B.; et al. 2016 (18)	Cochrane	9 studies (n = 2693)	Adult (age not specified)	Short-acting insulin analogues	Regular human insulins	Change in HbA1c	Mean 37 weeks	Improved with intervention
						Risk of severe hypoglycaemic events	Mean 37 weeks	No significant difference between intervention and comparator
Pedersen-Bjergaard, U.; et al. 2014 HypoAna (19)	RCT	159	Adults prone to recurrent severe hypoglycaemia	Insulin analogue (detemir/aspart)	Human insulin (NPH/regular)	Number of validated episodes of severe hypoglycaemia	2 years	Improved with intervention
Biosimilar insulins								
Heise, T.; et al. 2017 (20)	RCT	57	Adult (age not specified)	Insulin degludec (0.4 U/Kg) Insulin degludec	Insulin glargine (300 U/ml)	Glucose lowing effect - within day variability	12 days	Improved with intervention

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
					Insulin glargine (U100)	Glucose lowing effect - day-to-day variability	12 days	Improved with intervention
Lane, W.; et al. SWITCH-1 (21)	RCT	501	Adult (age not specified)	Insulin degludec (0.4 U/Kg)	Insulin glargine (300 U/ml)	Rate of hypoglycaemic events	32 weeks	Improved with intervention
						Rate of nocturnal hypoglycaemic events	32 weeks	Improved with intervention
						Proportion of patients with severe hypoglycaemia	32 weeks	Improved with intervention
Garg, S. K.; et al. 2017 SORELLA 1 (23)	RCT	507	Adult (age not specified)	Biosimilar of insulin lispro (SAR342434)	Insulin Lispro-Humalog	Change in HbA1c	6 months	Intervention non-inferior
						Hypoglycaemic events	6 months	No significant difference between intervention and comparator
						Adverse events	6 months	No significant difference between intervention and comparator
Davies, M. J.; et al. 2014 (22)	RCT	455	Adult (age not specified)	Insulin degludec	Insulin detemir	Change in HbA1c	26 weeks	Non-inferiority of intervention over comparator
						Rate of confirmed hypoglycaemia	26 weeks	No significant difference between intervention and comparator
Blevins, T. C.; et al. 2015 (24)	RCT	535	Adult (age not specified)	LY296316 insulin glargine	Insulin glargine (lantus)	Change in HbA1c	52 weeks	Intervention non-inferior
Home, Philip D.; et al. 2018 (25)	RCT	508	Adult (age not specified)	MK-1293 Insulin glargine (100U/ml)	Insulin glrgine (Lantus)	Change in HbA1c	52 weeks	Intervention non-inferior
Blevins, T. C.; et al. 2018 (26)	RCT	558	Adult (age not specified)	MYL-1501D (insulin glargine biosimilar)	Reference insulin glargine	Change in HbA1c	52 weeks	Intervention non-inferior
Russell-Jones, D.; et al. 2017 ONSET-1 (27)	RCT	1143	Adult (age not specified) already taking insulin detemir	Fast-acting insulin aspart (double blind mealtime or open label post meal)	Conventional insulin aspart	Change in HbA1c	26 weeks	Intervention non-inferior

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
				Fast-acting insulin aspart (double blind mealtime)	Conventional insulin aspart	Change in HbA1c	26 weeks	Improved with intervention
Buse, John B.; et al. 2018 ONSET-8 (28)	RCT	1024	Adult (age not specified) already taking insulin degludec	Fast-acting insulin aspart (double blind mealtime or open label post meal)	Conventional insulin aspart	Change in HbA1c	26 weeks	Intervention non-inferior
				Fast-acting insulin aspart (double blind mealtime)	Conventional insulin aspart	Change in HbA1c	26 weeks	Improved with intervention
Mathieu, C.; et al. 2018 ONSET-1 (29)	RCT	381	Adult (age not specified) already taking insulin detemir	Fast-acting insulin aspart	Conventional insulin aspart	Change in HbA1c	52 weeks	Improved with intervention
						Hypoglycaemic events	52 weeks	No significant difference between intervention and comparator
Klonoff, David C.; et al. 2018 ONSET-5 (30)	RCT	472	Adult (age not specified)	Fast-acting insulin aspart used in CSII	Conventional insulin aspart used in CSII	Change in HbA1c	16 weeks	Intervention non-inferior
						Change in 1 hour postprandial glucose	16 weeks	Improved with intervention
Dose comparisons								
Matsuhisa, M.; et al. 2016 EDITION JP (31)	RCT	243	Adult (age not specified)	Insulin glargine (300 U/ml)	Insulin glargine (100 U/ml)	Change in HbA1c	6 months	Intervention non-inferior
						Rate of confirmed severe hypoglycaemic events	6 months	Improved with intervention
Home, P. D.; et al. 2015 EDITION 4 (32)	RCT	549	Adult (over 30)	Insulin glargine (300 U/ml)	Insulin glargine (100 U/ml)	Change in HbA1c	6 months	Intervention non-inferior
Adjuncts to insulin								
	RCT	351	Adult (age not specified)	Canagliflozin	Placebo	Change in HbA1c	18 weeks	Improved with intervention

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
Henry, R. R.; et al. 2015 (46)						Percentage of people with no change in body weight	18 weeks	Improved with intervention
Ahren, B.; et al. 2016 ADJUNCT2 (47)	RCT	835	Adult (age not specified)	Liraglutide (1.8, 1.2, 0.6 mg)	Placebo	Change in HbA1c	26 weeks	Improved with intervention
						Body weight	26 weeks	Improved with intervention
Dejgaard, T. F.; et al. 2016 ADJUNCT 1 (49)	RCT	100	Overweight participants with insufficient glycaemic control	Liraglutide (0.6, 1.2, 1.8, mg gradually increasing doses)	Placebo	Change in HbA1c	24 weeks	No significant difference between intervention and comparator
						Change in hypoglycaemic events	24 weeks	Improved with intervention
Abbreviations: RCT, randomised controlled trial; CSII continuous subcutaneous insulin infusion.								

Table 5. Control of cardiovascular risk

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
Hartaigh; et al. 2018 (53)	RCT	4732	Adult (over 30)	Intensive systolic blood pressure target (<120mmHg)	Standard systolic blood pressure target (less than 140mmHg)	Risk of major adverse cardiovascular events	~5 years	Improvement in control group but not intervention group (no between group comparison reported)
ASCEND Study Collaborative; et al. 2018 ASCEND (51)	RCT	15480	Adult (age not specified)	Daily aspirin (100mg)	Placebo	First serious vascular event	mean 7.4 years	Improved with intervention
						First major bleeding event	mean 7.4 years	Worse with intervention
						Incidence of gastrointestinal cancer	mean 7.4 years	No significant difference between intervention and comparator
ASCEND Study Collaborative; et al. 2018 ASCEND (52)	RCT	15480	Adult (age not specified)	Fatty acid supplement-ation	Placebo (olive oil)	First serious vascular event	mean 7.4 years	No significant difference between intervention and comparator
Abbreviations: RCT, randomised controlled trial.								

Table 6. Care of adults with type 1 diabetes in hospital

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
Colunga-Lozano, L. E.; et al. 2018 (54)	Cochrane	5 studies on T1D (n = 667)	Non-critically ill hospitalised adults with diabetes mellitus	Sliding scale insulin	Basal-bolus insulin	Severe hypoglycaemic episodes, defined as blood glucose levels below 40 mg/dL (2.2 mmol/L)	Not reported	Little or no benefit with intervention
						Mean blood glucose level	Not reported	Worse with intervention
Abbreviations: T1D, type 1 diabetes								

Table 7. Managing complications

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
Eye disease								
Martinez-Zapata, M. J. 2014 (62)	Cochrane	1 study (n = 61)	Adult (age not specified)	Bevacizumab with panretinal photocoagulation	Panretinal photocoagulation	Risk of losing 3 or more lines of visual acuity	12 months	Improved with intervention
		5 studies (n = 373)	Adult (age not specified)	Treatment with either bevacizumab, pegaptanib or ranibizumab	No anti-VEGF treatment	Visual acuity	12 months	Improved with intervention
		3 studies (n = 342)	Adult (age not specified)	Any anti-VEGF treatment	No anti-VEGF treatment	Risk of vitreous or pre-retinal haemorrhage	12 months	Improved with intervention
		3 studies (n = 94)	Adult (age not specified)	Bevacizumab plus vitrectomy	Vitrectomy alone	Risk of losing 3 or more lines of visual acuity	12 months	Little or no benefit with intervention
Sivaprasad, S.; et al. 2017 CLARITY (63)	RCT	22 ophthalmic centres (n not reported in the abstract)	Adults with proliferative diabetic retinopathy	Intravitreous injection of aflibercept (2mg/0.05ml)	Photocoagulation	Change in BCVA	1 year	Improved with intervention

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
Jorge, E. C.; et al. 2018 (65)	Cochrane Total includes = 24 studies (4422 eyes)	3703 eyes	Adult (age not specified)	Any type of focal/grid macular laser photocoagulation	No intervention	BCVA	1 year	Improvement with intervention
		29 eyes	Adult (age not specified)	Subthreshold photocoagulation	Standard photocoagulation	Resolution of macular oedema	1 year	No significant difference between intervention and comparator
		385 eyes	Adult (age not specified)	Subthreshold photocoagulation	Standard photocoagulation	Continuous BCVA	1 year	No significant difference between intervention and comparator
		385 eyes	Adult (age not specified)	Subthreshold photocoagulation	Standard photocoagulation	Change in central macular thickness	1 year	No significant difference between intervention and comparator
		773 eyes	Adult (age not specified)	Argon laser	Other type of laser	BCVA	1 year	No significant difference between intervention and comparator
		323 eyes	Adult (age not specified)	Modified ETDRS (mETDRS) grid technique	Mild macular grid technique	BCVA	1 year	Inconclusive
Friedman, S. M.; et al. 2015 (66)	RCT	125	Adult (age not specified)	Nepafenec (0.1%)	Placebo	Mean change in optical coherence tomography retinal volume	12 months	No significant difference between intervention and comparator
Diabetic kidney disease								
Lo, C.; et al. 2018 (67)	Cochrane	7 studies (n = 1092)	Adult (age not specified) with diabetes and chronic kidney disease	SGLT-2 inhibitors	Placebo	Change in HbA1c	Not reported	Improved with intervention
		5 studies (n = 855)	Adult (age not specified) with diabetes and chronic kidney disease	SGLT-2 inhibitors	Placebo	Fasting blood glucose	Not reported	Improved with intervention
		7 studies (n = 1198)	Adult (age not specified) with diabetes and chronic kidney disease	SGLT-2 inhibitors	Placebo	Systolic blood pressure	Not reported	Improved with intervention

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
		7 studies (n = 3086)	Adult (age not specified) with diabetes and chronic kidney disease	SGLT-2 inhibitors	Placebo	Genital infections	Not reported	Worse with intervention
		5 studies (n = 1029)	Adult (age not specified) with diabetes and chronic kidney disease	SGLT-2 inhibitors	Placebo	Weight	Not reported	Improved with intervention
		9 studies (n not reported)	Adult (age not specified) with diabetes and chronic kidney disease	SGLT-2 inhibitors	Placebo	Risk of cardiovascular death	Not reported	No significant difference between intervention and comparator
		9 studies (n not reported)	Adult (age not specified) with diabetes and chronic kidney disease	SGLT-2 inhibitors	Placebo	Hypoglycaemia	Not reported	No significant difference between intervention and comparator
		9 studies (n not reported)	Adult (age not specified) with diabetes and chronic kidney disease	SGLT-2 inhibitors	Placebo	Acute kidney injury	Not reported	No significant difference between intervention and comparator
		7 studies (n = 5897)	Adult (age not specified) with diabetes and chronic kidney disease	DPP-4 inhibitors	Placebo	Change in HbA1c	Not reported	Improved with intervention
		7 studies (n = 5897)	Adult (age not specified) with diabetes and chronic kidney disease	DPP-4 inhibitors	Placebo	Fasting blood glucose	Not reported	Little or no benefit with intervention
		7 studies (n = 5897)	Adult (age not specified) with diabetes and chronic kidney disease	DPP-4 inhibitors	Placebo	Cardiovascular death	Not reported	No significant difference between intervention and comparator
		2 studies (n = 210)	Adult (age not specified) with diabetes and chronic kidney disease	DPP-4 inhibitors	Placebo	Weight	Not reported	No significant difference between intervention and comparator

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
		7 studies (n = 867)	Adult (age not specified) with diabetes and chronic kidney disease	GLP-1 agonists	Placebo	Change in HbA1c	Not reported	Improved with intervention
		2 studies (n = 551)	Adult (age not specified) with diabetes and chronic kidney disease	Sitagliptin	Glipizide	Hypoglycaemia	Not reported	Improved with intervention
DCCT EDIC group 2014 (68)	RCT	1441	Adult (age not specified)	Intensive treatment (target levels of glycaemia as close to non-diabetic range as safely possible)	Conventional treatment (prevention of symptoms of hyperglycaemia and hypoglycaemia)	Incidence of microalbuminuria	18 years	Improved with intervention
Chronic painful neuropathy								
Enomoto, H.; et al. 2018 (69)	RCT	303	Adult (age not specified)	Duloxetine (40-60mg/day)	Pregabalin (300-600 mg/day)	Mean 24hr average pain score	12 weeks	Intervention non-inferior
Mimenza Alvarado, A.; Aguilar Navarro, S. (70)	RCT	270	Adult (age not specified)	Gabapentin plus complex B vitamins	Pregabalin	Pain intensity	12 weeks	No significant difference between intervention and comparator
Mu, Y.; et al. (71)	RCT	620	Adult (age not specified)	Pregabalin (300mg/day)	Placebo	Change in mean pain score	11 weeks	No significant difference between intervention and comparator
Gastroparesis								
Olausson, E. A.; et al. 2014 (73)	RCT	56	Adult (age not specified) with gastroparesis	Small particle sized diet	Control diet	Severity of gastroparetic symptoms	20 weeks	Improved with intervention
Parkman, H. P.; et al. (74)	RCT	89	Adult (age not specified) with gastroparesis	Metoclopramide nasal spray (10 or 20mg)	Oral metoclopramide (10mg)	Total symptom score	6 weeks	Improved with intervention
Psychological problems								
Tovote, K. A.; et al. 2014 (76)	RCT	94	Adult (age not specified) with T1D and	Mindfulness-based CBT	Waitlist control	Severity of depressive symptoms	3 months	Improved with intervention

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
			depressive symptoms	CBT	Waitlist control	Severity of depressive symptoms	3 months	Improved with intervention
Sajatovic, M.; et al. 2017 (77)	RCT	200	Adult (age not specified) with T1D and serious mental illness	Self-management intervention	Usual care	Depressive symptoms	60 weeks	Improved with intervention
Abbreviations: RCT, randomised controlled trial; T1D, type 1 diabetes; CBT, cognitive behavioural therapy; BCVA, best-corrected visual acuity.								

Table 8. Areas not covered in the guideline

Study	Type	n	Population	Intervention	Comparator	Outcome	Follow-up	Result
Closed-loop insulin delivery								
Tauschmann, M.; et al. 2018 (78)	RCT	86	Adults with sub-optimally controlled T1D	Day and night hybrid closed-loop insulin delivery	SAP therapy	Proportion of time that BGC was within target range of 3.9-10 mmol/L	12 weeks	Improved with intervention
						Risk of hypoglycaemia	12 weeks	Improved with intervention
Nimri, R.; et al. (79)	RCT	75	Adults and children	Night time closed-loop control (MD Logic)	SAP therapy	Time spent in hypoglycaemia (glucose concentration below 70mg/dL)	4 nights	Improved with intervention
Sensor-augmented pump therapy								
Rosenlund, S.; et al. 2015 (80)	RCT	60	Adults with a history of albuminuria and were on stable renin-angiotensin system inhibition	SAP therapy	Multiple daily injections	Change in urine albumin creatine ratio	1 year	Improved with intervention
						Change in HbA1c	1 year	Improved with intervention
						Glucose variability	1 year	Improved with intervention
Abbreviations: RCT, randomised controlled trial; BGC, blood glucose control; SAP therapy, sensor-augmented pump therapy								

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