

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 intravitreal 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 A4: Summary of evidence from surveillance

2019 surveillance of [diabetic foot problems: prevention and management](#) (2015) NICE guideline NG19

Contents:

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Evidence considered in surveillance

Search and selection strategy

We searched for new evidence related to specific parts of the guideline. A focused search was undertaken for diabetic foot problems.

We found 46 studies in a search for RCTs and systematic reviews published between 01 August 2014 and 21 February 2019.

We also included:

- 2 relevant studies from a total of 7 identified by topic experts, these were also identified in our search.

From all sources, we considered 46 studies to be relevant to the guideline.

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.
- Pilot studies were excluded
- Systematic reviews (with the exception of Cochrane reviews) were excluded

Ongoing research

We checked for relevant ongoing research; of the ongoing studies identified, 1 study was 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. This study is:

- [Comparing treatments for diabetic foot ulcers](#)

Intelligence gathered during surveillance

Views of topic experts

We sent questionnaires to 20 topic experts and received 7 responses. The topic experts were recruited to the NICE Centre for Guidelines Expert Advisers Panel to represent their specialty.

All 7 topic experts agreed that no update to the guideline is needed at this time. Topic experts highlighted that there have been no substantial changes in this area for any age group and commented that the guideline remains current and relevant in clinical practice.

Other sources of information

We considered all other correspondence received since the guideline was published. Several studies were highlighted on the guideline issue log, and also identified in our search for new evidence. This included topical antimicrobial use and wound healing trials, which were included in the evidence summary, and Granexin gel, for which no new evidence was found.

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/ng19>

1.1 Care within 24 hours of a person with diabetic foot problems being admitted to hospital, or the detection of diabetic foot problems (if the person is already in hospital)

Surveillance proposal

No new information was identified.

This section of the guideline should not be updated.

1.2 Care across all settings

Surveillance proposal

No new information was identified.

This section of the guideline should not be updated.

1.3 Assessing the risk of developing a diabetic foot problem

Surveillance proposal

No new information was identified.

This section of the guideline should not be updated.

1.4 Diabetic foot problems

Surveillance proposal

No new information was identified.

This section of the guideline should not be updated.

1.5 Diabetic foot ulcer

Surveillance proposal

This section of the guideline should not be updated.

2019 surveillance summary

Casts and offloading devices

We identified 4 RCTs(1-4) evaluating casts and/or offloading devices for the treatment of diabetic foot ulcers (see [table 1](#)).

The interventions evaluated in the evidence included:

- Total contact casts
- Lightweight fibreglass casts
- Custom-made knee-high casts
- Removable walking casts

Overall improvements were seen with total contact casts for the outcomes of time to ulcer healing and proportion of ulcers healed, and with removable walking casts for the outcomes of non-severe adverse events and patient acceptance. No improvements were seen with total contact casts for mean healing time or non-severe adverse events, or with fibreglass casts/custom casts for the outcome of proportion of ulcers healed.

Grafting

We identified 2 RCTs(5,6) and 1 Cochrane(7) review assessing grafting for the treatment of diabetic foot ulcers (see [table 2](#)).

Improvements were seen with the human acellular dermal matrix, DermACELL for proportion of completely healed wounds compared to usual care, but not when compared to a second acellular dermal matrix called Graftjacket.

Recurrence rate and appearance of the wound improved at 12 months when split thickness skin grafting (STSG) plus acellular dermal matrix was compared to STSG alone. However, no improvements were seen for rate of complete wound closure or complications at 4 weeks post graft.

Improvements were seen in healing rate and incidence of lower limb amputation when skin grafts or tissue replacements were compared to usual care, with no difference in adverse events seen.

Oxygen therapy and negative pressure

We identified 5 RCTs(8-12) and 3 Cochrane reviews(13-15) assessing casts and/or offloading devices for the treatment of diabetic foot ulcers (see [table 3](#)).

Overall, the evidence indicated that:

- Improvements were seen in wound healing using active continuous oxygen diffusion therapy compared to moist wound therapy (2 studies).
- Negative pressure wound therapy improved the number of wounds healed compared to wound dressings alone.
- Hyperbaric therapy improved the rate of ulcer healing but not health related quality of life (HRQoL).
- Ozone therapy improved ulcer surface area compared to antibiotic treatment; however no improvements were seen when compared to usual care for ulcer surface area, or for either comparator for number of ulcers healed.
- Transdermal continuous oxygen therapy or daily breathing of oxygen at 244 kPa for 90 minutes did not improve wound healing compared with control.

Additional therapies

We identified 2 RCTs(16,17) and 1 Cochrane review(18) assessing additional therapy interventions for the treatment of diabetic foot ulcers (see [table 4](#)).

Shockwave therapy

Focused extracorporeal shockwave therapy (ESWT) plus standard care improved the number of ulcers healed compared to sham therapy plus standard care.

Phototherapy

A Cochrane review found that phototherapy improved complete wound healing compared to no phototherapy or usual care.

Helium-neon laser therapy plus usual care did not improve ulcer surface area compared to infrared laser therapy plus usual care in one small RCT.

Prevention

We identified 1 Cochrane review(19) assessing the prevention of diabetic foot ulcers (see [table 5](#)).

Intensive complex interventions (no further information stated) were found to have improvements over usual care for the outcomes of cost effectiveness (1 study), amputations (2 studies) and foot ulcers (1 study).

Supplements

We identified 7 RCTs(20–26) assessing the use of supplements for the treatment of diabetic foot ulcers (see [table 6](#)).

Improvements in ulcer size and depth were observed in studies examining vitamin D, omega-3 fatty acids from flaxseed oil, probiotics, magnesium oxide, magnesium oxide plus vitamin E and zinc sulphate compared to a placebo.

No improvements were seen for arginine, glutamine and beta-hydroxy-beta-methylbutyrate supplementation for either total wound closure or time to wound healing.

Telemedicine

We identified 2 RCTs(27,28) assessing telemedicine monitoring and follow up care for people with diabetic foot ulcers (see [table 7](#)).

The evidence found for telemedicine was mixed for the outcome of amputations, however no benefits of telemedicine were seen for any other outcome.

Topical treatments

We identified 9 RCTs(29–38) and 3 Cochrane reviews(39–41) assessing topical treatments for diabetic foot ulcers (see [table 8](#)).

The following interventions improved ulcer healing and ulcer size when compared to a placebo or usual care alone:

- Single application acellular dermal matrix (D-ADM),
- Tri-layer porcine small intestine submucosa,
- Autologous platelet-rich plasma (PRP), dehydrated human amnion/chorion membrane allograft,
- LeucoPatch device plus usual care, recombinant human epidermal growth factor (rhEGF)
- 11 different growth factors (from a Cochrane review).

Improvements in complete ulcer closure were seen when the integra dermal regeneration template was compared to sodium chloride gel.

Viable cryopreserved placental membrane improved the number of ulcers healed and average cost per patient when compared to a human fibroblast-derived dermal substitute.

Number of wounds completely healed at 12 weeks was improved with the use of EpiCord (dehydrated human umbilical cord allograft) compared to alginate wound dressings.

The following interventions did not improve outcomes when compared with usual care:

- Clostridial collagenase ointment
- Honey.

Wound dressings

We identified 4 RCTs(42–45) and 1 Cochrane review(46) assessing the use of wound dressings for diabetic foot ulcers (see [table 9](#)).

Improvements in time to wound closure, proportion of ulcers healed and time to ulcer healing was seen for graffix (a human viable wound matrix), Epifix and wound dressing with sucrose octasulfate compared to usual care, a control dressing or Apligraf (Epifix only).

No clear differences were seen when various wound dressings were compared to each other in the Cochrane review.

Intelligence gathering

Initial intelligence gathering highlighted MTG17 [The Debrisoft monofilament debridement pad for use in acute or chronic wounds](#) which recommends the use of the Debrisoft monofilament debridement pad for both acute and chronic wounds, this is linked in the diabetic foot pathway.

MTG42 [UrgoStart for treating leg ulcers and diabetic foot ulcers](#) supports the use of the UrgoStart dressing for diabetic foot ulcer treatment. NG19 does not currently specify what type of wound dressing should be used, however MTG42 is linked within the diabetic foot pathway.

An [NIHR study](#) is being tracked which aims to compare treatments for diabetic foot ulcers. This trial aims to compare 4 different interventions over 5 comparison groups, including usual care, hydrosurgical debridement, decellularized dermal allograft and negative pressure wound therapy.

Impact statement

Casts and offloading devices

Recommendation 1.5.5 currently suggests a non-removable cast should be offered to people with non-ischæmic, uninfected fore or mid foot ulcers, with offloading also being an option for general treatment of diabetic foot ulcers in recommendation 1.5.4. The evidence found at this review suggests patients' acceptability was improved with a removeable device, however this did not correlate with improved ulcer healing. As removable devices did not show an improvement for ulcer healing, the guideline will not be updated in this area until evidence of benefits from this intervention is shown.

Grafting

Recommendation 1.5.11 states to consider the use of dermal or skin substitutes in addition to standard care when healing has not progressed with standard care alone. The evidence found at this review suggests that an acellular dermal matrix offers improvements in wound healing over usual care or a placebo. Different dermal matrix products were used in the 3 studies and all had significant improvements in either wound healing rate or 12-month ulcer recurrence or both. As no specific product was superior in these comparisons, the current recommendation stating to consider dermal substitutes is sufficient.

Oxygen therapy and negative pressure

Recommendation 1.5.9 states to consider negative pressure wound therapy under the advice of a multidisciplinary foot care team. One study found that number of wounds healed was significantly increased with negative pressure therapy compared to wound dressings alone.

This supports recommendation 1.5.9, no further evidence was found to suggest any changes are required to the recommendation at this time.

Recommendation 1.5.12 states that hyperbaric oxygen therapy should not be used outside the context of a clinical trial. The evidence found at this review found both advantages and disadvantages with each oxygen-based therapy. Hyperbaric therapy improved ulcer healing rate but not HRQoL, ozone therapy improved ulcer surface area but not when compared to usual care. No improvements were seen for breathing concentrated oxygen, however wound directed active continuous oxygen diffusion improved number of wounds healed and rate of ulcer closing. The results found at this review span a number of different interventions, with no clear evidence of superiority. This supports the current recommendations and does not suggest any changes are needed at this time.

Additional therapies

Focused shockwave therapy plus usual care improved the number of ulcers healed compared to a sham device plus usual care. There are currently no recommendations on shockwave therapy in NG19, as such further evidence would be required in this area before additions to the recommendations would be suggested.

Phototherapy was found to improve complete wound healing in a Cochrane review, with helium-neon laser therapy showing no improvement over usual care. There are currently no recommendations covering either of these additional therapies. As the evidence is inconclusive no impact is anticipated at this time. In addition, the Cochrane review had a small number of participants included in its meta-analysis and as such further evidence would be required.

Prevention

A Cochrane review found that intensive complex interventions to prevent diabetic foot ulcers led to improvements in cost effectiveness, amputation rates and foot ulcers. As the abstract did not disclose the nature of these interventions, they may or may not already be included in the guideline recommendations. No impact is anticipated at this time.

Supplements

Six supplements were found to improve ulcer size and depth, with one showing no difference over standard care for total wound closure or healing time. There are no recommendations for supplements as a treatment strategy, however recommendation 1.2.4 states that nutritional services should be included in the multidisciplinary foot care team. Further studies are required with comparisons between supplements, as the evidence found at this review involved placebo comparison only. No impact is anticipated at this time.

Telemedicine

The use of telemedicine for monitoring showed no advantage over standard outpatient care, with only amputation rate having an improvement when telemedicine follow up in primary care was used. Telemedicine is not currently included in the recommendations. The evidence found at this review supports this and no impact is anticipated.

Topical treatments

The evidence found at this review suggests that the majority of topical treatments result in a significant improvement in one or more of: ulcer healing, ulcer size, ulcer depth, complete ulcer closure and number of ulcers healed. This included autologous PRP (1 Cochrane review) and growth factors (1 RCT, 1 Cochrane review) and the LeucoPatch device (highlighted by a topic expert). Recommendation 1.5.12 currently states that autologous PRP and growth factors should not be used outside the context of a clinical trial. The review for autologous PRP was a small number of trials from a full Cochrane review, and as such further studies are required where this is the primary intervention method. The studies on growth factors were primarily using platelet derived products, with improvements seen for all of the products used. The authors of the Cochrane review noted a high risk of systemic bias and as such further evidence would be required in this area before a change to the recommendations would be considered.

Wound dressings

A number of wound dressings showed improvements in proportion of ulcers healed, time to wound healing, complete wound closure at 12 weeks and adverse events when compared to usual care or a placebo dressing, however little evidence was found comparing these dressings to each other. Wound dressings are included in recommendations 1.5.4 and 1.5.10, however no specific type of dressing is suggested. The evidence found at this review supports the use of wound dressings as an intervention rather than a specific product. No impact is anticipated at this time.

Overall conclusions

Overall, the evidence found at this surveillance review showed a number of positive improvements with the variety of interventions studied. A large number of these support existing recommendations. Where new treatment options were found, the evidence 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 recommendations. An NIHR study is being tracked which aims to compare treatments for diabetic foot ulcers. This will be evaluated for impact on the guideline once results are available.

New evidence is unlikely to change guideline recommendations.

1.6 Diabetic foot infection

Surveillance proposal

This section of the guideline should not be updated.

2019 surveillance summary

None found.

Intelligence gathering

An antimicrobial prescribing guideline (APG) for diabetic foot infection is currently in development which will impact the recommendations in this section. Systemic antibiotics have not been included in this surveillance review due to this in development guideline. For details on the proposed changes to recommendations 1.6.6 to 1.6.15 please see the [consultation document](#) for the diabetic foot infection APG.

Impact statement

Systemic antibiotics have not been included in this surveillance review due to the in development APG for diabetic foot infection.

New evidence is unlikely to change guideline recommendations.

1.7 Charcot arthropathy

Surveillance proposal

No new information was identified.

This section of the guideline should not be updated.

Research recommendations

Research recommendation	Summary of findings
Does intensive monitoring of people at risk of diabetic foot disease reduce the morbidity associated with developing the disease and is such monitoring cost effective?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Research recommendation	Summary of findings
When and with what criteria should people with diabetes be referred to the foot protection service or the multidisciplinary foot care service?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
What is the role of educational models and psycho-behavioural interventions in prevention of diabetic foot complications?	A Cochrane review was found that included educational components as part of multi-component interventions, however it was difficult to draw conclusions specific to patient education.
What strategies may be useful in the prevention of Charcot arthropathy?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
What is the clinical effectiveness of different dressing types in treating diabetic foot problems?	Evidence was found relating to a number of different wound dressings however no firm conclusions could be reached.
What is the effectiveness of different footwear, insoles and orthoses in the prevention of foot problems?	Evidence was found relating to casts and offloading , however benefits were not seen for ulcer healing for removable devices.
How often should people with diabetic foot problems (foot ulcers, soft tissue infections, osteomyelitis or gangrene) be reviewed?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
What is the clinical effectiveness of negative pressure wound therapy in the treatment of diabetic foot ulcers?	Evidence from 1 study was found relating to negative pressure therapy which supports the current recommendation. Further studies are required in this area.
What is the clinical effectiveness of maggot debridement therapy in the debridement of diabetic foot ulcers?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
Which risk stratification tools can be used to predict the likelihood of Charcot arthropathy?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.
When is it safe to stop contact casting in the treatment of acute Charcot arthropathy?	No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

Research recommendation	Summary of findings
<p>Within the hospital-based MDT, when is it appropriate and effective to refer people with diabetes who have foot problems to specialist services such as investigative or interventional radiology, orthopaedic or vascular services, specialist pain management and specialist orthotics?</p>	<p>No new evidence relevant to the research recommendation was found and no ongoing studies were identified.</p>

Data summary tables

Key to the tables

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

n = number of participants. The number of participants was not always reported in the abstract. For Cochrane reviews the number of studies is entered.

Table 1 – Casts and offloading

Study	Type	n	Intervention	Comparator	Outcome	Result
Lavery, L. A et al (2015)(1)	RCT	73	Total contact casts	Healing sandals	Proportion of ulcers healed	No improvement with intervention
					Time to ulcer healing	Improvement with intervention
			Total contact casts	Shear-reducing footbed boot	Proportion of ulcers healed	Improvement with intervention
					Time to ulcer healing	No improvement with intervention
Jeffcoate, W.; et al. (2017)(2)	RCT	425	Lightweight fibreglass cast plus usual care	Usual care alone	Percentage of ulcers healed in 24 weeks	No improvement with intervention
Bus, S. A.; et al. (2018)(3)	RCT	60	Custom-made knee-high cast [BTCC]	Prefabricated ankle high forefoot-offloading shoe	Proportion of ulcers healed	No improvement with intervention
Piaggese, A.; et al (2016)(4)	RCT	60	Total contact cast	Irremovable walking boot	Mean healing time	No improvement with intervention
					Non-severe adverse events	No improvement with intervention
			Removable walking cast	Total contact cast	Mean healing time	No improvement with intervention
					Non-severe adverse events	Improvement with intervention

Study	Type	n	Intervention	Comparator	Outcome	Result
					Patient acceptance	Improvement with intervention

Table 2- Grafting.

Study	Type	n	Intervention	Comparator	Outcome	Result
Walters, Jodi; et al. (2016)(5)	RCT	168	Human acellular dermal matrix DermACELL	Conventional care	Proportion of completely healed ulcers	Improvement with intervention
				Second acellular dermal matrix, Graftjacket	Proportion of completely healed ulcers	No improvement with intervention
Hu, Z.; et al. (2016)(6)	RCT	52	Split thickness skin grafting (STSG) over acellular dermal matrix	STSG only	Recurrence at 12 months	Improvement with intervention
					Appearance and lower Manchester Scar Scale score	Improvement with intervention
					Rate of complete wound closure	No improvement with intervention
					Complications at 4 weeks post grafting	No improvement with intervention
Santema, T. B.; et al. (2016)(7)	CR	17 studies (n=1655)	Skin grafts or tissue replacement	Usual care	Healing rate	Improvement with intervention
					Adverse events	No improvement with intervention
		2 studies	Skin grafts or tissue replacement	Usual care	Incidence of lower limb amputation	Improvement with intervention

Table 3 -Oxygen therapies and negative pressure.

Study	Type	n	Intervention	Comparator	Outcome	Result
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Driver, V. R.; et al. (2017)(8)	RCT	122	Transdermal continuous oxygen therapy (TCOT) + moist wound therapy	Sham device + moist wound therapy	Proportion of ulcers healed	No effect with intervention
Fedorko, L.; et al. (2016)(9)	RCT	103	Daily, 90 minutes of breathing oxygen at 244 kPa for 30 days (HBOT)	Placebo - daily breathing air at 125 kPa	Criteria for amputation met	No improvement with intervention
					Wounds healed	No improvement with intervention
Niederauer, M. Q.; et al. (2017)(10)	RCT	100	Active continuous oxygen diffusion therapy active CDO device	Placebo device providing moist wound therapy only	Wounds healed	Improvement with intervention
					Ulcer rate of closure	Improvement with intervention
Kranke, P.; et al. (2015)(13)	CR	12 studies, (n=577)	Hyperbaric oxygen therapy	Studies excluding HBOT (with or without sham therapy)	Rate of ulcer healing	Improvement with intervention
Li, G.; et al. (2017)(11)	RCT	103	Hyperbaric oxygen therapy	Sham	Health related quality of life	No improvement with intervention
Liu, J.; et al. (2015)(14)	CR	3 studies, (n=212)	Ozone therapy	Antibiotic treatment	Number of ulcers healed	No improvement with intervention
					Ulcer surface area	Improvement with intervention
				Usual care	Number of ulcers healed	No improvement with intervention
					Ulcer surface area	No improvement with intervention
	RCT	100	Active continuous	Placebo device providing moist	Time to 50% ulcer closure	Improvement with intervention

Niederauer, Mark Q.; et al. (2018)(12)			oxygen diffusion therapy active CDO device	wound therapy only	Proportion of ulcers healed	Improvement with intervention
Liu, Z.; et al. (2018)(15)	CR	5 studies, (n=486)	Negative pressure wound therapy	Wound dressings	Number of wounds healed	Improvement with intervention

Table 4 – additional therapies.

Study	Type	n	Intervention	Comparator	Outcome	Result
Snyder, Robert; et al. (2018)(16)	RCT	336	Focused extracorporeal shockwave therapy (ESWT) and standard care	Sham therapy and standard care	Proportion of ulcers healed	Improvement with intervention
Wang, H. T.; et al. (2017)(18)	CR	8 studies, (n=316)	Phototherapy	No phototherapy/usual care	Meta-analysis of 4 studies (n=116): Complete wound healing	Improvement with intervention
Tantawy, S. A.; et al. (2018)(17)	RCT	65	Helium-neon laser therapy + conventional therapy	Infrared laser therapy + conventional therapy	Ulcer surface area	No improvement with intervention

Table 5 – Prevention.

Study	Type	n	Intervention	Comparator	Outcome	Result
Hoogeveen, R. C.; et al. (2015)(19)	CR	6 studies, (n=5011)	Intensive complex interventions	Usual care	Cost effectiveness	Improvement with intervention
					Amputations	Improvement with intervention
					Amputations and foot ulcers	Improvement with intervention

Table 6 – Supplements.

Study	Type	n	Intervention	Comparator	Outcome	Result
Armstrong, D. G.; et al. (2014)(20)	RCT	270	Arginine, glutamine and beta-hydroxy-beta-methylbutyrate drink for 16 weeks	Control drink	Total wound closure	No improvement with intervention
					Time to wound healing	No improvement with intervention
Razzaghi, R.; et al. (2017)(21)	RCT	60	50,000 IU vitamin D supplements every 2 weeks for 12 weeks	Placebo	Ulcer size and depth	Improvement with intervention
Soleimani, Z.; et al. (2017)(22)	RCT	60	1000 mg omega-3 fatty acids from flaxseed oil BD for 12 weeks	Placebo	Wound size and depth	Improvement with intervention
Mohseni, S.; et al. (2018)(23)	RCT	60	Probiotic	Placebo	Ulcer size and depth	Improvement with intervention
Razzaghi, R.; et al. (2018)(24)	RCT	70	250mg magnesium oxide tablet daily for 12 weeks	Placebo	Ulcer size and depth	Improvement with intervention
Afzali, Hassan; et al. (2019)(25)	RCT	57	250 mg magnesium oxide + 400 IU vitamin E daily for 12 weeks	Placebo	Ulcer size and depth	Improvement with intervention
Momen-Heravi, M.; et al. (2017)(26)	RCT	60	220mg zinc sulphate tablet daily for 12 weeks	Placebo	Ulcer size	Improvement with intervention

Table 7 - Telemedicine.

Study	Type	n	Intervention	Comparator	Outcome	Result
Rasmussen, B. S.; et al. (2015)(27)	RCT	374	Telemedical monitoring	Standard outpatient monitoring	Complete ulcer healing	No improvement with intervention
					Amputation	No improvement with intervention
					Death	No improvement with intervention
Smith-Strøm, H.; et al. (2018)(28)	RCT	182	Telemedicine follow up in primary care in collaboration with specialist health care	Standard outpatient care	Time to ulcer healing	No improvement with intervention
					Proportion of amputations	Improvement with intervention

Table 8 - Topical treatments.

Study	Type	n	Intervention	Comparator	Outcome	Result
Tettelbach, William; et al. (2019)(29)	RCT	155	EpiCord - dehydrated human umbilical cord allograft	Alginate wound dressings	number of wounds healed completely in 12 weeks	Improvement with intervention
Cazzell, S.; et al. (2017)(30)	RCT	168	Single application D-ADM (acellular dermal matrix)	Standard care	Proportion of closed ulcers remaining closed at 4 weeks post-termination	Improvement with intervention
Jimenez, Juan Carlos; et al. (2017)(31)	RCT	215	Clostridial collagenase ointment, 2 mm daily for 12 weeks	Usual care	Ulcer size	No improvement with intervention
Cazzell, Shawn M.; et al. (2015)(32)	RCT	82	Tri-layer porcine small intestine submucosa	Standard care	Proportion of ulcers closed at 12 weeks	Improvement with intervention

Martinez-Zapata, M. J.; et al. (2016)(39)	CR	2 studies, (n=189)	Autologous platelet-rich plasma (PRP)	Usual care	Foot ulcer healing	Improvement with intervention
Ananian, Charles E.; et al. (2018)(33)	RCT	62	Viable cryopreserved placental membrane	Human fibroblast-derived dermal substitute	Proportion of ulcers healed	Improvement with intervention
					Average per patient costs	Improvement with intervention
Tettelbach, William; et al. (2019)(34)	RCT	110	Dehydrated human amnion/chorion membrane allograft	Standard care with alginate dressings	Percentage of ulcers completely healed	Improvement with intervention
					Time to healing	Improvement with intervention
Game, Frances; et al. (2018)(35)	RCT	269	LeucoPatch device + care	Standard care	Proportion of ulcers healed	Improvement with intervention
					Time to ulcer healing	Improvement with intervention
Park, K. H.; et al. (2018)(36)	RCT	167	0.005% recombinant human epidermal growth factor (rhEGF) spray, twice daily until ulcer healing or 12 weeks	Equivalent volume of saline spray	Complete wound healing	Improvement with intervention
					Wound healing speed	Improvement with intervention
					Median time to 50% wound closure	Improvement with intervention
Marti-Carvajal, A. J.; et al. (2015)(40)	CR	28 studies, (n=2365)	11 different growth factors plus standard care	placebo/ no growth factor plus standard care	Increased wound healing with any growth factor	Improvement with intervention
Jull, A. B.; et al. (2015)(41)	CR	2 studies, (n=93)	topical honey	not stated	Healing rate	No improvement with intervention
Driver, V. R.; et al. (2015)(37)	RCT	307	Integra Dermal Regeneration Template (IDRT)	0.9% sodium chloride gel	Complete ulcer closure	Improvement with intervention

Dumville, J. C.; et al. (2017)(38)	CR	945	antimicrobial dressings	non-antimicrobial dressings	number of ulcers healed	Improvement with intervention
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Table 9 Wound dressings.

Study	Type	n	Intervention	Comparator	Outcome	Result
Edmonds, M.; et al. (2018)(42)	RCT	240	Wound dressing with sucrose octasulfate	Wound dressing alone (same dressing)	Proportion of ulcers healed at 20 weeks	Improvement with intervention
Lavery, L. A.; et al. (2014)(43)	RCT	97	Grafix, human viable wound matrix	Usual care	Complete wound closure at 12 weeks	Improvement with intervention
					Time to wound closure	Improvement with intervention
					Adverse events	Improvement with intervention
					Wound related infections	Improvement with intervention
Zelen, C. M.; et al. (2015)(44)	RCT	60	Epifix	Apligraf	Proportion of ulcers healed	Improvement with intervention
					Time to ulcer healing	Improvement with intervention
				Standard care	Proportion of ulcers healed	Improvement with intervention
					Time to ulcer healing	Improvement with intervention
Edmonds, Michael E.; et al. (2018)(45)	RCT	240)	Sucrose octasulfate dressing + standard care	Control dressing (same dressing without sucrose octasulfate) + standard care	Proportion of ulcers healed	Improvement with intervention
Wu, L.; et al. (2015)(46)	CR	30 studies	various wound dressings	alternate dressings	difference in wound healing	Unclear

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