Internal Clinical Guidelines team

Diabetic foot problems

Prevention and management

NICE guideline NG19

Methods, evidence and recommendations

Published August 2015, updated May 2016

Update information

January 2023: NICE's original guidance on diabetic foot problems was published in 2015. It was updated in 2019 and 2023. See the [NICE website for the guideline](#) [recommendations and the evidence reviews for the 2019 and 2023 updates](#). This document preserves evidence reviews and committee discussions for areas of the guideline that were not updated in 2019 or 2023.

May 2016: The glossary has been updated to include a definition of deformity.

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

Contents

1 Overview

1.1 Introduction

Diabetes is 1 of the most common chronic diseases in the UK and its prevalence is increasing. In 2013, there were almost 2.9 million people in the UK diagnosed with diabetes. By 2025, it is estimated that more than 5 million people in the UK will have diabetes. In England, the number of people diagnosed with diabetes has increased by approximately 53% between 2006 and 2013, from 1.9 million to 2.9 million. The life expectancy of people with diabetes is shortened by up to 15 years, and 75% die of macrovascular complications.

The risk of foot problems in people with diabetes is increased, largely because of diabetic neuropathy (nerve damage or degeneration) and / or peripheral arterial disease (poor blood supply due to diseased large- and medium-sized blood vessels in the legs). Peripheral arterial disease affects 1 in 3 people with diabetes over the age of 50 and can also increase the risk of heart attack and stroke. For more information, see the NICE guideline on lower limb peripheral arterial disease.

Foot complications are common in people with diabetes. It is estimated that 10% of people with diabetes will have a diabetic foot ulcer at some point in their lives. A foot ulcer can be defined as a localised injury to the skin and/or underlying tissue, below the ankle, in a person with diabetes.

Diabetes is the most common cause of non-traumatic limb amputation, with diabetic foot ulcers preceding more than 80% of amputations in people with diabetes. After a first amputation, people with diabetes are twice as likely to have a subsequent amputation as people without diabetes. Mortality rates after diabetic foot ulceration and amputation are high, with up to 70% of people dying within 5 years of having an amputation and around 50% dying within 5 years of developing a diabetic foot ulcer. This high mortality rate is believed to be associated with cardiovascular disease and emphasises the importance of good diabetic and cardiovascular risk management. Although people of South Asian, African and African-Caribbean family origin are more at risk of diabetes, there is no evidence that the prevalence of diabetic foot ulceration and amputation is higher in these subgroups than in the general population of people with diabetes in the UK.

1.2 Health and resource burden

Foot problems in people with diabetes have a significant financial impact on the NHS through primary care, community care, outpatient costs, increased bed occupancy and prolonged stays in hospital. A report published in 2012 by NHS Diabetes estimated that around £650 million (or £1 in every £150 the NHS spends) is spent on foot ulcers or amputations each year.

1.3 Reasons for the guideline

Despite the publication of strategies on commissioning specialist services for preventing and managing diabetic foot problems, there is variation in practice across different NHS settings, and amputation rates still vary up to fourfold in the UK.

This variation in practice results from a range of factors including differing levels of organisation of care for people with diabetes and diabetic foot problems. This variability depends on geography, individual trusts, individual specialties (such as the organisation and access of the diabetic foot care services) and availability of healthcare professionals with expertise in the management of diabetic foot problems.

The implementation of foot care screening programmes is still varied across the UK, and there is currently a lack of guidance on foot screening strategies aimed at children and young people with diabetes. There is a need for comprehensive guidance on foot care for people with diabetes that addresses all NHS settings.

1.4 Scope

Diabetic foot problems: prevention and management of foot problems in people with diabetes

1.5 The Remit

This is an update of Management of type 2 diabetes: prevention and management of foot problems (NICE clinical guideline 10, 2004) and a partial update (covering the recommendations on foot care only) of Type 1 diabetes: diagnosis and management of type 1 diabetes in children, young people and adults (NICE clinical guideline 15, 2004) and Diabetic foot problems: inpatient management (NICE clinical guideline 119, 2011). The update will incorporate recommendations 1.1.1 and 1.1.8 - 1.1.10 on inpatient management of diabetic foot problems in adults from Diabetic foot problems: inpatient management (NICE clinical guideline 119, 2011). Recommendations 1.1.37 – 1.1.40 from Diabetic foot problems: inpatient management (NICE clinical guideline 119, 2011) will be stood down as these recommendations have now been updated by Lower limb peripheral arterial disease: Diagnosis and management (NICE clinical guideline 147, 2012). We will also carry out an editorial review of all recommendations to ensure that they comply with NICE's duties under equalities legislation.

1.6 Population

Groups that will be covered

a)   Adults, young people and children with type 1 or type 2 diabetes.

b)   Subgroups that need specific consideration will be considered during development.

Groups that will not be covered

a)   Adults, young people and children without a diagnosis of diabetes.

1.7 Healthcare setting

All settings where NHS healthcare is commissioned or delivered (including a person's home).

1.8 Safeguarding children

Remember that child maltreatment:
- is common
- can present anywhere
- may co-exist with other health problems, including diabetes

See the NICE guideline on child maltreatment for clinical features that may be associated with maltreatment.

1.9 Medicines

The guideline will assume that prescribers will use a medicine's summary of product characteristics to inform decisions made with individual patients.

1.10 Patient-centred care

This guideline offers best practice advice on the care of adults, young people and children with type 1 or type 2 diabetes with, or at risk of developing, diabetic foot problems.

Patients and healthcare professionals have rights and responsibilities as set out in the NHS Constitution for England – all NICE guidance is written to reflect these. Treatment and care should take into account individual needs and preferences. Patients should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. If the patient is under 16, their family or carers should also be given information and support to help the child or young person to make decisions about their treatment. If it is clear that the child or young person fully understands the treatment and does not want their family or carers to be involved, they can give their own consent. Healthcare professionals should follow the Department of Health's advice on consent. If someone does not have capacity to make decisions, healthcare professionals should follow the code of practice that accompanies the Mental Capacity Act and the supplementary code of practice on deprivation of liberty safeguards.

NICE has produced guidance on the components of good patient experience in adult NHS services. All healthcare professionals should follow the recommendations in Patient experience in adult NHS services.

If a young person is moving between paediatric and adult services, care should be planned and managed according to the best practice guidance described in the Department of Health's Transition: getting it right for young people.

Adult and paediatric healthcare teams should work jointly to provide assessment and services to young people. Diagnosis and management should be reviewed throughout the transition process, and there should be clarity about who is the lead clinician to ensure continuity of care.

2 Summary Section

Strength of recommendations

Some recommendations can be made with more certainty than others. The Guideline Committee or Guideline Development Group (GDG) makes a recommendation based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. For some interventions, the GDG is confident that, given the information it has looked at, most patients would choose the intervention. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the strength of the recommendation).

For all recommendations, NICE expects that there is discussion with the patient about the risks and benefits of the interventions, and their values and preferences. This discussion aims to help them to reach a fully informed decision (see also 'Patient-centred care').

Interventions that must (or must not) be used

We usually use 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally we use 'must' (or 'must not') if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Interventions that should (or should not) be used – a 'strong' recommendation

We use 'offer' (and similar words such as 'refer' or 'advise') when we are confident that, for the vast majority of patients, an intervention will do more good than harm, and be cost effective. We use similar forms of words (for example, 'Do not offer…') when we are confident that an intervention will not be of benefit for most patients.

Interventions that could be used

We use 'consider' when we are confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

Recommendation wording in guideline updates

NICE began using this approach to denote the strength of recommendations in guidelines that started development after publication of the 2009 version of 'The guidelines manual' (January 2009). This does not apply to any recommendations shaded in grey and ending [year of original publication] (for example, [2008]) (see 'Update information' box below for details about how recommendations are labelled).

Update information

This guidance is a full update of NICE Clinical Guideline 10 (published [January 2004]), a partial update (covering the recommendations on footcare only) of NICE Clinical Guideline 15 [published [July 2004], and nearly a full update of NICE Clinical Guideline 119 (incorporating 4 recommendations from CG119 only) [published [March 2011]. This new guideline will replace all pieces of previous NICE guidance on diabetic foot problems.

New and updated recommendations in this guideline are marked as [expected year of publication of update] (for example, [2015]) if the evidence has been reviewed but no change

has been made to the recommendation, or [new expected year of publication of update] (for example, [new 2015]) if the evidence has been reviewed and the recommendation has been added or updated.

The original NICE guideline and supporting documents are available here.

2.1 GDG membership, Peer reviewers, ICG technical team

2.1.1 GDG membership

Name	Role applied for	Job title
Damien Longson	Standing Guideline Chair	Consultant Liaison Psychiatrist
Chizo Agwu (from November 2013)	Paediatric Diabetologist	Consultant Paediatrician /Clinical Director. Sandwell & Birmingham NHS Trust/ Honorary. Senior. Clinical Lecturer, University of Birmingham
Susan Benbow	Diabetologist	Consultant Physician in Diabetes and Endocrinology, Aintree University Hospital NHS Foundation Trust
Rachel Berrington	Diabetes Nurse Specialist	Senior Diabetes Specialist Nurse – foot lead University hospitals of Leicester
Issak Bhojani	General Practitioner	General Practitioner, Blackburn
Sue Brown	Patient/ carer member	Patient/ carer member
Sheila Burston	Patient/ carer member	Patient/ carer member
Trevor Cleveland (from October 2013)	Interventional Radiologist (co-opted expert)	Consultant Vascular Radiologist, Sheffield Teaching Hospitals
Nicholas Foster	Microbiologist	Consultant Medical Microbiologist Leeds Teaching Hospitals NHS Trust
Catherine Gooday	Podiatrist	Principal Podiatrist, Norfolk & Norwich University Hospitals NHS Foundation Trust
Stephen Hutchins (from November 2013)	Orthotist (co-opted expert)	Senior Clinical Lecturer in Orthotics - Directorate, Prosthetics and Orthotics, University of Salford, UK.
Rachael Hutchinson	Othopaedic surgeon	Orthapaedic Consultant (Foot and Ankle/ Paediatrics), Norfolk & Norwich University Hospitals NHS Foundation Trust
Laurie King	Podiatrist	Clinical Lead Podiatrist. Diabetic Foot Oxfordshire - Oxford Health NHS Foundation Trust & Seconded to Oxford University Hospitals NHS Trust
Fania Pagnamenta	Nurse Consultant (Tissue Viability); (co-opted expert role)	Nurse Consultant (Tissue Viability), Newcastle upon Tyne Hospitals NHS Foundation Trust
Gerry Rayman	Diabetologist	Consultant Physician & Head of Service

Name	Role applied for	Job title
	15	The Diabetes & Endocrine Centre and Diabetes Foot Clinic & Research Unit, Ipswich
Stella Vig	Vascular Surgeon	Vascular and General Surgical Consultant, Croydon University Hospital

Name	Role applied for	Job title

2.1.2   Technical Team

Stephen Duffield (from April 2014)

Technical Analyst

Susan Ellerby

Clinical Adviser

Nicole Elliott (until June 2014)

Associate Director

Michael Heath (until October 2014)

Programme Manager

Vicky Gillis (from November 2013 to June 2014)

Technical Analyst

Craig Grime (from March 2013 to November 2013)

Technical Analyst

Chris Gibbons

Health Economist

Hugh McGuire (from March 2014)

Technical Adviser

Stephanie Mills

Project Manager

Gabriel Rogers

Technical Adviser

Susan Spiers (from June 2014)

Associate Director

Toni Tan (until March 2014)

Technical Adviser

2.2 Key Priorities for implementation

The following recommendations have been identified as priorities for implementation. The full list of recommendations is in section 2.3.

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)

Each hospital should have a care pathway for people with diabetic foot problems who need inpatient care. **[2011]**

Care across all settings

Commissioners and service providers should ensure that the following are in place:
– A foot protection service for preventing diabetic foot problems, and for treating and managing diabetic foot problems in the community.
– A multidisciplinary foot care service for managing diabetic foot problems in hospital and in the community that cannot be managed by the foot protection service. This may also be known as an interdisciplinary foot care service.
– Robust protocols and clear local pathways for the continued and integrated care of people across all settings, including emergency care and general practice. The protocols should set out the relationship between the foot protection service and the multidisciplinary foot care service.
– Regular reviews of treatment and patient outcomes, in line with the National Diabetes Foot Care Audit.

Assessing the risk of developing a diabetic foot problem

For adults with diabetes, assess their risk of developing a diabetic foot problem at the following times:
- When diabetes is diagnosed, and at least annually thereafter (see recommendation 20).
- If any foot problems arise.
- On any admission to hospital, and if there is any change in their status while they are in hospital.

When examining the feet of a person with diabetes, remove their shoes, socks, bandages and dressings, and examine both feet for evidence of the following risk factors:
– Neuropathy (use a 10 g monofilament as part of a foot sensory examination).
– Limb ischaemia (see the NICE guideline on lower limb peripheral arterial disease).
– Ulceration.
– Callus.
– Infection and/or inflammation.
– Deformity.
– Gangrene.
– Charcot arthropathy.

Assess the person's current risk of developing a diabetic foot problem or needing an amputation using the following risk stratification:

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- Low risk:
  o no risk factors present except callus alone.
- Moderate risk:
  o deformity or
  o neuropathy or
  o non-critical limb ischaemia.
- High risk:
  o previous ulceration or
  o previous amputation or
  o on renal replacement therapy or
  o neuropathy and non-critical limb ischaemia together or
  o neuropathy in combination with callus and/or deformity or
  o non-critical limb ischaemia in combination with callus and/or deformity.
- Active diabetic foot problem:
  o ulceration or
  o spreading infection or
  o critical limb ischaemia or
  o gangrene or
  o suspicion of an acute Charcot arthropathy, or an unexplained hot, red, swollen foot with or without pain.

Diabetic foot problems

If a person has a limb-threatening or life-threatening diabetic foot problem, refer them immediately to acute services and inform the multidisciplinary foot care service (according to local protocols and pathways; also see recommendation 8), so they can be assessed and an individualised treatment plan put in place. Examples of limb-threatening and life-threatening diabetic foot problems include the following:

– Ulceration with fever or any signs of sepsis.
– Ulceration with limb ischaemia (see the NICE guideline on lower limb peripheral arterial disease).
– Clinical concern that there is a deep-seated soft tissue or bone infection (with or without ulceration).
– Gangrene (with or without ulceration).

For all other active diabetic foot problems, refer the person within 1 working day to the multidisciplinary foot care service or foot protection service (according to local protocols and pathways; also see recommendation 8) for triage within 1 further working day.

Diabetic foot infection

All hospital, primary care and community settings should have antibiotic guidelines covering the care pathway for managing diabetic foot infections that take into account local patterns of resistance.

Charcot arthropathy

Suspect acute Charcot arthropathy if there is redness, warmth, swelling or deformity (in particular, when the skin is intact), especially in the presence of peripheral neuropathy or renal failure. Think about acute Charcot arthropathy even when deformity is not present or pain is not reported.

To confirm the diagnosis of acute Charcot arthropathy, refer the person within 1 working day to the multidisciplinary foot care service for triage within 1 further working day. Offer non-weight-bearing treatment until definitive treatment can be started by the multidisciplinary foot care service.

2.3 Recommendations

Unless stated otherwise, the recommendations apply to children, young people and adults with diabetes.

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)**

The recommendations in this section were originally published in the NICE guideline on the inpatient management of diabetic foot problems (NICE guideline CG119), which has been replaced by this guideline.

Each hospital should have a care pathway for people with diabetic foot problems who need inpatient care. (recommendation 1)

A named consultant should be accountable for the overall care of the person, and for ensuring that healthcare professionals provide timely care. (recommendation 2)

Refer the person to the multidisciplinary foot care service within 24 hours of the initial examination of the person's feet. Transfer the responsibility of care to a consultant member of the multidisciplinary foot care service if a diabetic foot problem is the dominant clinical factor for inpatient care. (recommendation 3)

The named consultant and the healthcare professionals from the existing team should remain accountable for the care of the person unless their care is transferred to the multidisciplinary foot care service. (recommendation 4)

2. **Care across all settings**

Commissioners and service providers should ensure that the following are in place:
- A foot protection service for preventing diabetic foot problems, and for treating and managing diabetic foot problems in the community.
- A multidisciplinary foot care service for managing diabetic foot problems in hospital and in the community that cannot be managed by the foot protection service. This may also be known as an interdisciplinary foot care service.
- Robust protocols and clear local pathways for the continued and integrated care of people across all settings, including emergency care and general practice. The protocols should set out the relationship between the foot protection service and the multidisciplinary foot care service.
- Regular reviews of treatment and patient outcomes, in line with the National Diabetes Foot Care Audit. (recommendation 8)

The foot protection service should be led by a podiatrist with specialist training in diabetic foot problems, and should have access to healthcare professionals with skills in the following areas:
- Diabetology.
- Biomechanics and orthoses.
- Wound care. (recommendation 5)

The multidisciplinary foot care service should be led by a named healthcare professional, and consist of specialists with skills in the following areas:

Recommendations from 2011 not updated by an evidence review

- Diabetology.
- Podiatry.
- Diabetes specialist nursing.
- Vascular surgery.
- Microbiology.
- Orthopaedic surgery.
- Biomechanics and orthoses.
- Interventional radiology.
- Casting.
- Wound care. (recommendation 6)

The multidisciplinary foot care service should have access to rehabilitation services, plastic surgery, psychological services and nutritional services. (recommendation 7)

Healthcare professionals may need to discuss, agree and make special arrangements for disabled people and people who are housebound or living in care settings, to ensure equality of access to foot care assessments and treatments for people with diabetes. (recommendation 11)

Take into account any disabilities, including visual impairment, when planning and delivering care for people with diabetes. (recommendation 12)

3. Assessing the risk of developing a diabetic foot problem

3.1. Frequency of assessments

For children with diabetes who are under 12 years, give them, and their family members or carers (as appropriate), basic foot care advice. (recommendation 17)

For young people with diabetes who are 12–17 years, the paediatric care team or the transitional care team should assess the young person's feet as part of their annual assessment, and provide information about foot care. If a diabetic foot problem is found or suspected, the paediatric care team or the transitional care team should refer the young person to an appropriate specialist. (recommendation 18)

For adults with diabetes, assess their risk of developing a diabetic foot problem at the following times:
- When diabetes is diagnosed, and at least annually thereafter (see recommendation 20).
- If any foot problems arise.
- On any admission to hospital, and if there is any change in their status while they are in hospital. (recommendation 19)

3.2. Assessing the risk of developing a diabetic foot problem

When examining the feet of a person with diabetes, remove their shoes, socks, bandages and dressings, and examine both feet for evidence of the following risk factors:
- Neuropathy (use a 10 g monofilament as part of a foot sensory examination)
- Limb ischaemia (see the NICE guideline on lower limb peripheral arterial disease)
- Ulceration.
- Callus.

- Infection and/or inflammation.
- Deformity.
- Gangrene.
- Charcot arthropathy. (recommendation 13)

Use ankle brachial pressure index in line with the NICE guideline on lower limb peripheral arterial disease. Interpret results carefully in people with diabetes because calcified arteries may falsely elevate results. (recommendation 14)

Assess the person's current risk of developing a diabetic foot problem or needing an amputation using the following risk stratification:
- Low risk:
  - o no risk factors present except callus alone.
- Moderate risk:
  - o deformity or
  - o neuropathy or
  - o non-critical limb ischaemia.
- High risk:
  - o previous ulceration or
  - o previous amputation or
  - o on renal replacement therapy or
  - o neuropathy and non-critical limb ischaemia together or
  - o neuropathy in combination with callus and/or deformity or
  - o non-critical limb ischaemia in combination with callus and/or deformity.
- Active diabetic foot problem:
  - o ulceration or
  - o spreading infection or
  - o critical limb ischaemia or
  - o gangrene or
  - o suspicion of an acute Charcot arthropathy, or an unexplained hot, red, swollen foot with or without pain. (recommendation 15)

3.3. Managing the risk of developing a diabetic foot problem

For people who are at low risk of developing a diabetic foot problem, continue to carry out annual foot assessments, emphasise the importance of foot care, and advise them that they could progress to moderate or high risk. (recommendation 16)

Refer people who are at moderate or high risk of developing a diabetic foot problem to the foot protection service (recommendation 9)

The foot protection service should assess newly referred people as follows:
- Within 2–4 weeks for people who are at high risk of developing a diabetic foot problem.
- Within 6–8 weeks for people who are at moderate risk of developing a diabetic foot problem. (recommendation 10)

For people at moderate or high risk of developing a diabetic foot problem, the foot protection service should:
- Assess the feet.
- Give advice about, and provide, skin and nail care of the feet.

- Assess the biomechanical status of the feet, including the need to provide specialist footwear and orthoses.
- Assess the vascular status of the lower limbs.
- Liaise with other healthcare professionals, for example, the person's GP, about the person's diabetes management and risk of cardiovascular disease. (recommendation 21)

Depending on the person's risk of developing a diabetic foot problem, carry out reassessments at the following intervals:

- Annually for people who are at low risk.
- Frequently (for example, every 3–6 months) for people who are at moderate risk.
- More frequently (for example, every 1–2 months) for people who are at high risk, if there is no immediate concern.
- Very frequently (for example, every 1–2 weeks) for people who are at high risk, if there is immediate concern.

Consider more frequent reassessments for people who are at moderate or high risk, and for people who are unable to check their own feet. (recommendation 20)

People in hospital who are at moderate or high risk of developing a diabetic foot problem should be given a pressure redistribution device to offload heel pressure. On discharge they should be referred or notified to the foot protection service. (recommendation 24)

3.4. Patient information about the risk of developing a diabetic foot problem

Provide information and clear explanations to people with diabetes and/or their family members or carers (as appropriate) when diabetes is diagnosed, during assessments, and if problems arise. Information should be oral and written, and include the following:

- Basic foot care advice and the importance of foot care.
- Foot emergencies and who to contact.
- Footwear advice.
- The person's current individual risk of developing a foot problem.
- Information about diabetes and the importance of blood glucose control (also see recommendation 23). (recommendation 22)

For guidance on education programmes and information about diabetes, see the education and information section in 'Type 1 diabetes in adults: diagnosis and management' (NICE guideline NG17), the patient education section in 'Type 2 diabetes in adults: management'[a] and the sections education and information for children and young people with type 1 diabetes and education and information for children and young people with type 2 diabetes in 'Diabetes (type 1 and type 2) in children and young people: diagnosis and management' (NICE guideline NG18). (recommendation 23)

4. Diabetic foot problems

4.1. Referral

If a person has a limb-threatening or life-threatening diabetic foot problem, refer them immediately to acute services and inform the multidisciplinary foot care service (according to local protocols and pathways; also see recommendation 8), so they can be assessed and an

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[a] The link to the education section of the NICE guideline Type 2 diabetes in adults: management will be updated when the guideline is published later in 2015.

individualised treatment plan put in place. Examples of limb-threatening and life-threatening diabetic foot problems include the following:

- Ulceration with fever or any signs of sepsis.
- Ulceration with limb ischaemia (see the NICE guideline on lower limb peripheral arterial disease).
- Clinical concern that there is a deep-seated soft tissue or bone infection (with or without ulceration).
- Gangrene (with or without ulceration). (recommendation 59)

For all other active diabetic foot problems, refer the person within 1 working day to the multidisciplinary foot care service or foot protection service (according to local protocols and pathways; also see recommendation 8) for triage within 1 further working day. (recommendation 60)

4.2. Patient information about diabetic foot problems

Provide information and clear explanations as part of the individualised treatment plan for people with a diabetic foot problem. Information should be oral and written, and include the following:

- A clear explanation of the person's foot problem.
- Pictures of diabetic foot problems.
- Care of the other foot and leg.
- Foot emergencies and who to contact.
- Footwear advice.
- Wound care.
- Information about diabetes and the importance of blood glucose control (also see recommendation 23). (recommendation 35)

If a person presents with a diabetic foot problem, take into account that they may have an undiagnosed, increased risk of cardiovascular disease that may need further investigation and treatment. For guidance on the primary prevention of cardiovascular disease, see the NICE guideline on lipid modification. (recommendation 36)

5. Diabetic foot ulcers

5.1. Investigation

If a person has a diabetic foot ulcer, assess and document the size, depth and position of the ulcer. (recommendation 25)

Use a standardised system to document the severity of the foot ulcer, such as the SINBAD (Site, Ischaemia, Neuropathy, Bacterial Infection, Area and Depth) or the University of Texas classification system. (recommendation 26)

Do not use the Wagner classification system to assess the severity of a diabetic foot ulcer. (recommendation 27)

5.2. Treatment

Offer 1 or more of the following as standard care for treating diabetic foot ulcers:

- Offloading.

- Control of foot infection.
- Control of ischaemia.
- Wound debridement.
- Wound dressings. (recommendation 37)

Offer non-removable casting to offload plantar neuropathic, non-ischaemic, uninfected forefoot and midfoot diabetic ulcers. Offer an alternative offloading device until casting can be provided. (recommendation 38)

In line with the NICE guideline on pressure ulcers, use pressure-redistributing devices and strategies to minimise the risk of pressure ulcers developing. (recommendation 39)

When treating diabetic foot ulcers, debridement in hospital should only be done by healthcare professionals from the multidisciplinary foot care service, using the technique that best matches their specialist expertise and clinical experience, the site of the diabetic foot ulcer and the person's preference. (recommendation 40)

When treating diabetic foot ulcers, debridement in the community should only be done by healthcare professionals with the relevant training and skills, continuing the care described in the person's treatment plan. (recommendation 41)

Consider negative pressure wound therapy after surgical debridement for diabetic foot ulcers, on the advice of the multidisciplinary foot care service. (recommendation 53)

When deciding about wound dressings and offloading when treating diabetic foot ulcers, take into account the clinical assessment of the wound and the person's preference, and use devices and dressings with the lowest acquisition cost appropriate to the clinical circumstances. (recommendation 42)

Consider dermal or skin substitutes as an adjunct to standard care when treating diabetic foot ulcers, only when healing has not progressed and on the advice of the multidisciplinary foot care service. (recommendation 54)

Do not offer the following to treat diabetic foot ulcers, unless as part of a clinical trial:
- Electrical stimulation therapy, autologous platelet-rich plasma gel, regenerative wound matrices and dalteparin.
- Growth factors (granulocyte colony-stimulating factor [G-CSF], platelet-derived growth factor [PDGF], epidermal growth factor [EGF] and transforming growth factor beta [TGF-β]).
- Hyperbaric oxygen therapy. (recommendation 55)

When deciding the frequency of follow-up as part of the treatment plan, take into account the overall health of the person with diabetes, how healing has progressed, and any deterioration. (recommendation 33)

Ensure that the frequency of monitoring set out in the person's individualised treatment plan is maintained whether the person with diabetes is being treated in hospital or in the community. (recommendation 34)

6. Diabetic foot infection

6.1. Investigation

If a diabetic foot infection is suspected and a wound is present, send a soft tissue or bone sample from the base of the debrided wound for microbiological examination. If this cannot

be obtained, take a deep swab because it may provide useful information on the choice of antibiotic treatment. (recommendation 28)

Consider an X-ray of the person's affected foot (or feet) to determine the extent of the diabetic foot problem. (recommendation 29)

Think about osteomyelitis if the person with diabetes has a local infection, a deep foot wound or a chronic foot wound. (recommendation 30)

Be aware that osteomyelitis may be present in a person with diabetes despite normal inflammatory markers, X-rays or probe-to-bone testing. (recommendation 31)

If osteomyelitis is suspected in a person with diabetes but is not confirmed by initial X-ray, consider an MRI to confirm the diagnosis. (recommendation 32)

6.2. Treatment

All hospital, primary care and community settings should have antibiotic guidelines covering the care pathway for managing diabetic foot infections that take into account local patterns of resistance. (recommendation 43)

Do not offer antibiotics to prevent diabetic foot infections. (recommendation 44)

Start antibiotic treatment for suspected diabetic foot infection as soon as possible. Take cultures and samples before, or as close as possible to, the start of antibiotic treatment. (recommendation 45)

Choose the antibiotic treatment based on the severity of the diabetic foot infection, the care setting, and the person's preferences, clinical situation and medical history and, if more than 1 regimen is appropriate, select the regimen with the lowest acquisition cost. (recommendation 46)

Decide the targeted antibiotic regimen for diabetic foot infections based on the clinical response to antibiotics and the results of the microbiological examination. (recommendation 47)

Do not offer tigecycline to treat diabetic foot infections unless other antibiotics are not suitable. (recommendation 48)

For mild diabetic foot infections, initially offer oral antibiotics with activity against gram-positive organisms. (recommendation 49)

Do not use prolonged antibiotic treatment (more than 14 days) for the treatment of mild soft tissue diabetic foot infections. (recommendation 50)

For moderate and severe diabetic foot infections, initially offer antibiotics with activity against gram-positive and gram-negative organisms, including anaerobic bacteria, as follows:

- Moderate infections: base the route of administration on the clinical situation and the choice of antibiotic.
- Severe infections: start with intravenous antibiotics and then reassess, based on the clinical situation. (recommendation 51)

Offer prolonged antibiotic treatment (usually 6 weeks) to people with diabetes and osteomyelitis, according to local protocols. (recommendation 52)

7. Charcot arthropathy

7.1. Investigation

Be aware that if a person with diabetes fractures their foot or ankle, it may progress to Charcot arthropathy. (recommendation 56)

Suspect acute Charcot arthropathy if there is redness, warmth, swelling or deformity (in particular, when the skin is intact), especially in the presence of peripheral neuropathy or renal failure. Think about acute Charcot arthropathy even when deformity is not present or pain is not reported. (recommendation 57)

To confirm the diagnosis of acute Charcot arthropathy, refer the person within 1 working day to the multidisciplinary foot care service for triage within 1 further working day. Offer non-weight-bearing treatment until definitive treatment can be started by the multidisciplinary foot care service. (recommendation 58)

If acute Charcot arthropathy is suspected, arrange a weight-bearing X-ray of the affected foot and ankle. Consider an MRI if the X-ray is normal but Charcot arthropathy is still suspected. (recommendation 61)

7.2. Treatment

If the multidisciplinary foot care service suspects acute Charcot arthropathy, offer treatment with a non-removable offloading device. If a non-removable device is not advisable because of the clinical, or the person's, circumstances, consider treatment with a removable offloading device. (recommendation 63)

Do not offer bisphosphonates to treat acute Charcot arthropathy, unless as part of a clinical trial. (recommendation 64)

Monitor the treatment of acute Charcot arthropathy using clinical assessment. This should include measuring foot–skin temperature difference and taking serial X-rays until the acute Charcot arthropathy resolves. Acute Charcot arthropathy is likely to resolve when there is a sustained temperature difference of less than 2 degrees between both feet and when X-ray changes show no further progression. (recommendation 62)

People who have a foot deformity that may be the result of a previous Charcot arthropathy are at high risk of ulceration and should be cared for by the foot protection service. (recommendation 65)

2.4 Research recommendations

The Guideline Development Group (GDG) has made the following recommendations for research, based on its review of evidence, to improve NICE guidance and patient care in the future:

When and with what criteria should people with diabetes be referred to the foot protection service or the multidisciplinary foot care service?

Why this is important

The evidence surrounding different referral criteria for those at risk of, or who have developed diabetic foot problems was limited. It is proposed that a prospective cohort study is undertaken to explore this question. The proposed study would monitor and evaluate the rates (and recurrent rates) of foot ulceration, infection and gangrene resulting from diabetes, resource use and costs (including referral rates), rates of hospital admission for foot problems resulting from diabetes, length of hospital stay, and the health-related quality of life as a result of different referral criteria to these teams.

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?

Why this is important

The evidence surrounding different monitoring frequencies for those at risk of diabetic foot problems was limited. It is proposed that a randomised controlled trial or cohort study is undertaken to explore this question. The proposed study would monitor and evaluate the rates of foot ulcer or infection resulting from diabetes, rates and extent of amputation (major or minor), health-related quality of life, adverse events and hospital admission rates and length of stay as a result of different monitoring frequencies.

What is the role of educational models and psycho-behavioural interventions in prevention of diabetic foot complications?

Why this is important

The evidence surrounding the role of educational measures for those at risk of diabetic foot problems was limited and inconclusive. It is proposed that new interventions are developed that target psychological and behavioural factors. The proposed study would monitor and evaluate the rates (and recurrent rates) of foot ulceration, infection and gangrene resulting from diabetes, rates and extent of amputation, rates of hospital admission for foot problems resulting from diabetes, length of hospital stay, and resource use and cost as a result of applying these interventions.

What is the effectiveness of different footwear, insoles and orthoses in the prevention of foot problems?

Why this is important

The evidence surrounding the role of different kinds of footwear, insoles and orthoses for those at risk of diabetic foot problems was limited. It is proposed that a randomised control trial is undertaken to explore these questions. The proposed study would monitor and evaluate the rates (and recurrent rates) of foot ulceration, infection and gangrene resulting from diabetes, rates and extent of amputation, rates of emergency and hospital admission for foot problems resulting from diabetes and resource use and cost as a result of applying the above preventative therapies to these patients.

How often should people with diabetic foot problems (foot ulcers, soft tissue infections, osteomyelitis or gangrene) be reviewed?

Why this is important

The evidence surrounding different monitoring frequencies for those who have developed diabetic foot problems was limited. It is proposed that a randomised controlled trial is undertaken to explore this question. The proposed study would monitor and evaluate the cure rates of foot ulcer or infection resulting from diabetes, rates of re-ulceration, time to further ulceration, rates and extent of amputation (major or minor), and hospital and emergency admission rates and mortality as a result of different monitoring frequencies.

What is the clinical effectiveness of different dressing types in treating diabetic foot problems?

Why this is important

The evidence surrounding different dressing types for diabetic foot ulcer was often limited or inconclusive. It is proposed that more randomised controlled trials are undertaken to explore this question, but alternative methodologies may also be considered in the case of treating a complex wound. The proposed study would monitor and evaluate the cure rates of foot ulcer resulting from diabetes, rates and extent of amputation (major or minor), health-related quality of life, adverse events and hospital admission rates and length of stay.

What is the clinical effectiveness of negative pressure wound therapy in the treatment of diabetic foot ulcers?

Why this is important

The evidence reviewed for negative pressure wound therapy was limited and of low quality. It would be useful to have more evidence for this commonly used treatment. It is proposed that a randomised controlled trial is undertaken to explore this question. The proposed study would monitor and evaluate the cure rates of foot ulcer resulting from diabetes, rates and extent of amputation (major or minor), health-related quality of life, adverse events and hospital admission rates and length of stay.

What is the clinical effectiveness of maggot debridement therapy in the debridement of diabetic foot ulcers?

Why this is important

The evidence surrounding maggot debridement therapy was limited. It would be useful to have more evidence for this commonly used treatment. It is proposed that a randomised controlled trial is undertaken to explore this question. The proposed study would monitor and evaluate the cure rates of foot ulcer resulting from diabetes, rates and extent of amputation (major or minor), health-related quality of life, adverse events and hospital admission rates and length of stay.

Which risk stratification tools can be used to predict the likelihood of Charcot arthrophathy?

Why this is important

The evidence surrounding Charcot arthropathy was limited and of low quality. It is proposed that a test and treat randomised control trial, or cohort study is undertaken to explore this question. The proposed study would monitor and evaluate the rates of Charcot arthropathy resulting from diabetes, rates of amputation (major and minor), rates of defomity resulting from Charcot foot and resource use and costs as a result of the use of a Charcot arthropathy risk stratification tool.

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?

Why this is important

The evidence surrounding different referral criteria for those who have developed diabetic foot problems within the multidisciplinary foot care service to other specialist services was limited. It is proposed that a cohort study is undertaken to explore this question. The proposed study would monitor and evaluate the rates (and recurrent rates) of foot ulceration, infection and gangrene resulting from diabetes, resource use and costs, rates and extent of amputation, rates of hospital admission for foot problems resulting from diabetes, length of hospital stay, and the health-related quality of life as a result of different referral criteria to these teams.

When is it safe to stop contact casting in the treatment of acute Charcot arthropathy?

Why this is important

The evidence surrounding Charcot arthropathy was limited and of low quality. It is proposed that a test and treat randomised control trial, cross-sectional study or case control study is undertaken to explore this question. The proposed study would monitor and evaluate the test validity, test reliability, sensitivity, specificity, positive predictive value, negative predictive value, diagnostic odds ratios and likelihood ratios as a result of different tests for acute Charcot arthropathy remission. Alternatively the study could examine the rates of Charcot recurrence, deformity, amputation and ulceration following the stopping of contact casting in the treatment of acute Charcot arthropathy.

What strategies may be useful in the prevention of Charcot arthropathy?

Why this is important

The evidence surrounding Charcot arthropathy was limited and of low quality. It is proposed that a prospective cohort study is undertaken to explore this question. The proposed study would monitor and evaluate the rates of Charcot arthropathy resulting from diabetes, rates and extent of amputation (major or minor), rates and extent of deformity, health-related quality of life, and hospital admission rates following strategies for the prevention of Charcot arthropathy or its sequelae.

2.5 Related NICE guidance

2.5.1 Published guidance

2.5.1.1 NICE guidance to be updated

This guideline will update and replace the following NICE guidance.

- Type 1 diabetes (recommendations on foot care only). NICE clinical guideline 15 (2004).
- Management of type 2 diabetes: foot care. NICE clinical guideline 10 (2004).
- Diabetic foot problems: inpatient management. NICE clinical guideline 119 (2011).

2.5.1.2 NICE guidance to be incorporated

This guideline will incorporate the following NICE guidance.

- Diabetic foot problems: inpatient management. NICE clinical guideline 119 (2011). Recommendations 1.1.1 and 1.1.8 - 1.1.10 from this guideline will be incorporated.

2.5.1.3 Other related NICE guidance

- Antimicrobial stewardship. NICE guideline NG15. (2015)
- Type 1 diabetes in adults: diagnosis and management. NICE guideline NG17. (2015)
- Diabetes (type 1 and type 2) in children and young people: diagnosis and management. NICE guideline NG18. (2015)
- Maintaining a healthy weight and preventing excess weight gain among adults and children. NICE guideline NG7. (2015)
- Diabetes in pregnancy. NICE clinical guideline NG3. (2015)
- Obesity: identification, assessment and management of overweight and obesity in children, young people and adults. NICE guideline CG189 (2014)
- Exercise referral schemes. NICE public health guidance 54 (2014).
- Lipid modification (update). NICE clinical guideline 181 (2014).
- Pressure ulcers (update). NICE clinical guideline 179 (2014).
- VibraTip for testing vibration perception to detect diabetic peripheral neuropathy. NICE medical technology guidance 22 (2014)
- Neuropathic pain – pharmacological management (update). NICE clinical guideline 173. (2013).
- Tobacco: harm reduction approaches to smoking. NICE guideline PH45 (2013)
- Physical activity: brief advice for adults in primary care. NICE public health guidance 44 (2013).
- Lower limb peripheral arterial disease. NICE clinical guideline 147 (2012).
- Walking and cycling. NICE public health guidance 41 (2012).
- Preventing type 2 diabetes: risk identification and interventions for individuals at high risk. NICE public health guidance 38 (2012).
- Preventing type 2 diabetes: population and community interventions. NICE public health guidance 35 (2011).
- Hypertension. NICE clinical guideline 127 (2011).
- Venous thromboembolism: reducing the risk. NICE clinical guideline 92 (2010).
- Depression with a chronic physical health problem. NICE clinical guideline 91 (2009).
- Depression in adults. NICE guideline CG90 (2009)

- Obesity: guidance on the prevention of overweight and obesity in adults and children. NICE guideline CG43 (2006)
- Smoking cessation services. NICE public health guidance 10 (2008).
- Brief interventions and referral for smoking cessation. NICE public health guidance 1 (2006).
- Guidance on the use of patient-education models for diabetes. NICE technology appraisal guidance 60 (2003).

2.5.1.4 Guidance under development

NICE is currently developing the following related guidance (details available from the NICE website).

- Type 2 diabetes in adults: management. NICE clinical guideline. Publication expected October 2015.
- Sepsis: the recognition, diagnosis and management of severe sepsis. NICE clinical guideline. Publication expected July 2016.

This guideline update [2015] was developed in accordance with the process and methods outlined in 'The guidelines manual (2012)'. Sections 3.2 - 3.16 have been updated in 2015 and systematic reviews for each clinical question followed the review protocols (see appendix C) agreed by the Guideline Development Group (GDG). GRADE methodology was used and/or adapted for appraising the quality of the evidence, and the Linking Evidence to Recommendations (LETR) framework was adopted to transparently document the GDG's decision making process. In instances where the guidelines manual does not provide advice, additional methods were used and are described in detail below.

3 Methods

3.1.1 Outcomes

The outcomes prioritised in the review questions reflect the treatment objectives in the prevention, recognition, diagnosis, treatment and management of diabetic foot problems such as rates of ulceration, infection, complications and amputation rates. Unless otherwise stated, the minimal important difference (MID) for dichotomous outcomes was defined as a relative risk reduction or an increase of 25% or more to beconsidered clinically important. If required, the minimum important difference for continuous outcomes could be decided by looking at appropriate published evidence or under agreement with the GDG following discussion within committee meetings.

3.1.2 Process

Data were extracted by 1 reviewer. A second reviewer checked a random 10% of sifted out titles and abstracts, and all excluded studies with the reason for exclusion, and all data extracted for the included studies.

3.1.3 Evidence synthesis and meta-analyses

Where possible, meta-analyses were conducted to combine the results of studies for each outcome. For continuous outcomes, where change from baseline data were reported in the trials and were accompanied by a measure of spread (for example standard deviation), these were extracted and used in the meta-analysis. Where measures of spread for change from baseline values were not reported, the corresponding values at study end were used and were combined with change from baseline values to produce summary estimates of effect. These studies were assessed to ensure that baseline values were balanced across the treatment groups; if there were significant differences at baseline these studies were not included in any meta-analysis and were reported separately.

3.1.4 Quality assessment

GRADE was used to assess the quality of evidence for the selected outcomes as specified in 'The guidelines manual (2012)'.Where RCTs are possible, these are initially rated as high quality and the quality of the evidence for each outcome was downgraded or not from this initial point. If non-RCT evidence was included for intervention-type systematic reviews then these are initially rated a low quality and the quality of the evidence for each outcome was downgraded or not form this point.

3.1.4.1 GRADE for pairwise meta-analyses for interventional evidence

The quality of the evidence for each outcome was downgraded where appropriate for the reasons outlined in Table 1

Table 1: Rationale for downgrading quality of evidence for intervention studies

GRADE criteria	Example reasons for downgrading quality
Risk of bias	The quality of the evidence was downgraded if there were concerns about the design or execution of the study, including concealment of allocation, blinding, loss to follow up using intervention checklists in the NICE guidelines manual (2012)
Inconsistency	The quality of the evidence was downgraded if there were concerns about inconsistency of effects across studies: occurring when there is variability in the treatment effect demonstrated across studies (heterogeneity). This was assessed using the statistic, I^2 where ; $I^2 < 30$ was categorised as no

GRADE criteria	Example reasons for downgrading quality
	inconsistency, I^2 between 30% and 60% was categorised as serious inconsistency and $I^2 > 60\%$ was categorised as very serious inconsistency
Indirectness	The quality of the evidence was downgraded if there were concerns about the population, intervention and outcome in the included studies and how directly these variables could address the specific review question.
Imprecision	The quality of the evidence was downgraded if is uncertainty around the estimate of effect, for example when the confidence intervals are wide and cross the 'imaginary' lines of clinically significant effect that is a minimal important difference. This reflects the confidence in the estimate of effect.
Other considerations	The quality of the evidence was downgraded if there is a large magnitude of effect, evidence of a dose-response relationship, or confounding variables likely to have reduced the magnitude of an effect; these can increase the quality ratings in observational studies, provided no downgrading for other features has occurred

3.1.4.2 Modified GRADE for prognostic evidence

GRADE has not been developed for use with prognostic studies; therefore a modified approach was applied using the GRADE framework with prognostic studies.

The same criteria (risk of bias, inconsistency, imprecision and indirectness) were used to downgrade the quality of evidence as outlined in Table 2.

Table 2: Rationale for downgrading quality of evidence for prognostic questions

GRADE criteria	Example reasons for downgrading quality
Risk of bias	The quality of the evidence was downgraded if there were concerns about the design or execution of the study, including selection of participants, adjustment for confounding variables,
Inconsistency	The quality of the evidence was downgraded if there were concerns about Inconsistency of effects across studies: This was assessed using the statistic, I^2 where ; $I^2 < 30$ was categorised as no inconsistency, I^2 between 30% and 60% was categorised as serious inconsistency and $I^2 > 60$ was categorised as very serious inconsistency (this can reduce the quality rating)
Indirectness	The quality of the evidence was downgraded if there were concerns about the population, intervention and outcome in the included studies and how directly these variables could address the specific review question.
Imprecision	The quality of the evidence was downgraded if is uncertainty around the estimate of effect, for example when the confidence intervals are wide and cross the 'imaginary' lines of clinically significant effect that is minimal important difference. This reflects the confidence in the estimate of effect.
Other considerations	Large magnitude of effect, evidence of a dose-response relationship, or confounding variables likely to have reduced the magnitude of an effect; these can increase the quality ratings in observational studies, provided no downgrading for other features has occurred

3.1.4.3 Modified GRADE for diagnostic evidence

GRADE has not been developed for use with diagnostic studies; therefore a modified approach was applied using the GRADE framework.

Cohort studies within the non-modified GRADE approach start at the low quality level due to accepted inherent study design limitations. Within a modified approach it is acceptable to initially indicate a high quality level to this study type and to assess the quality of evidence

from this point. The same criteria (risk of bias, inconsistency, imprecision and indirectness) were used to downgrade the quality of evidence as detailed in Table 3 below.

Table 3: Rationale for downgrading quality of evidence for diagnostic questions

GRADE criteria	Example reasons for downgrading quality
Risk of bias	This includes limitations in the design or execution of the study, including concealment of allocation, blinding, loss to follow up (these can reduce the quality rating)
Inconsistency	The quality of the evidence was downgraded if there were concerns about Inconsistency of effects across studies: This was assessed using the statistic, I^2 where ; I^2 < 30 was categorised as no inconsistency, I^2 between 30% and 60% was categorised as serious inconsistency and I^2 > 60% was categorised as very serious inconsistency (this can reduce the quality rating)
Indirectness	The quality of the evidence was downgraded if there were concerns about the population, intervention and outcome in the included studies and how directly these variables could address the specific review question.
Imprecision	The quality of the evidence was downgraded if there is uncertainty around the estimate of effect, for example when the confidence intervals are wide and cross the 'imaginary' lines of clinically significant effect that is minimal important difference. This reflects the confidence in the estimate of effect.
Other considerations	The quality of the evidence was downgraded if there is a large magnitude of effect, confounding variables likely to have reduced the magnitude of an effect; these can increase the quality ratings in observational studies, provided no downgrading for other features has occurred

4 Evidence reviews and recommendations

4.1 Key components and organisations of hospital care

4.1.1 Review question

What are the key components and organisations of hospital care to ensure optimal management of people with diabetic foot problems?

4.1.2 Evidence review

The systematic search retrieved 9817 studies. Of these, 282 were retrieved in full-text formal. Five studies were included for this review question (for the review protocol and inclusion/exclusion criteria, please see appendix C). The remaining 277 studies were excluded (please see Excluded studies list in Appendix E).

4.1.3 Description of included studies

This section from 2011 has not been updated by an evidence review

Table 4: Characteristics of included studies

Study	Key components (specific organised/multidisciplinary care)	Outcome of interest
Crane et al. (1999)	Critical pathway approach to diabetic foot infections compared with non-pathway standard care. The pathway was initiated in the Emergency Department utilising committee-approved standing physician's orders and clinical progress records to facilitate transitions between departments.	Length of stay Major amputations Readmission
Dargis et al. (1999)	Multidisciplinary approach compared with standard care. The multidisciplinary team was staffed by a diabetologist, a rehabilitation physician, a podiatrist, orthopaedic surgeons and shoemakers.	Ulcer recurrence Amputations
Larsson et al. (1995)	Multidisciplinary foot care team approach compared with standard care. The team consisted of a diabetologist and an orthopaedic surgeon assisted by a diabetes nurse, a podiatrist and an orthotist, working in close cooperation with the Department of Vascular Surgery and the Department of Infectious Diseases. A programme for patient and staff education was also started.	Amputations
Canavan et al. (2008)	Organised diabetes foot care compared with standard care.	Lower extremity amputations
Driver et al. (2005)	Multidisciplinary foot care (limb preservation service model) compared with standard care. Services included prevention and education, wound care, infection management, surgical and hospital management, research and grant development, community and regional education, and the creation of orthoses, prosthetics and shoes.	Lower extremity amputations

Table 5: Summary GRADE profile – key components of care (specific organised/ multidisciplinary care)

No. of studies	Design	Intervention	Control	Summary of results	GRADE quality
Outcome : Amputation					
1 [Cr]	Cohort	60	25	Percentage of major amputation: Intervention = 7%, control = 29%, p = 0.02	Very low
1 [D]	Cohort	56	89	Percentage of amputation (major and minor): Intervention = 7%, control = 13.7%	Very low
1 [L]	Cohort	294	NK[1]	The incidence of major amputations decreased by 78% from 16.1 to 3.6/100 000 (p < 0.001).	Very low
1 [Ca]	Cohort	223	NK[2]	LEA rates decreased from 564.3/100,000 persons in the first year to 176.0/100,000 persons in the fifth year.	Very low
1 [Dr]	Cohort	223	NK[2]	LEA rates decreased from 9.9/1000 persons in the first year to 1.8/1000 persons in the fifth year.	Very low
Outcome: Hospital length of stay					
1 [Cr]	Cohort	60	25	Mean hospital length of stay (days): [year 1995]: Intervention = 5.4, control = 7.8, p < 0.05 [year 1996]: Intervention = 3.6, control = 8.7, p < 0.05	Very low
Outcome: Hospital admission					
1 [Cr]	Cohort	60	25	Percentage of hospital readmission: [year 1995]: Intervention = 7%, control = 18% [year 1996]: Intervention = 15%, control = 15%	Very low
Outcome: ulcer recurrence					
1 [D]	Cohort	56	89	Percentage of ulcer recurrence: Intervention = 30.4%, control = 58.4%	Very low

[Ca] = Canavan et al. (2008)

[Cr] = Crane et al. (1999)

[D] = Dargis et al. (1999)

[Dr] = Driver et al. (2005)

[L] = Larsson et al. (1995)

LEA = lower extremity amputation; NK = not known

This section from 2011 has not been updated by an evidence review

1 Actual number unknown, only reported participants treated prior to 1983.

2 Actual number unknown, not reported.

4.1.4   Evidence statements

Five observational studies suggested that organised care or multidisciplinary care improved outcomes of patients with diabetic foot problems compared with standard care. However, there was inconclusive evidence on the specific elements and composition of both the organised and multidisciplinary care. (Very low quality)

4.1.5   Evidence to recommendations

Table 6: Linking evidence to recommendations

Quality of the evidence	The GDG agreed that there was very limited evidence and the evidence was of very low quality. Nevertheless, this limited, very low quality evidence suggested that some form of organised care or multidisciplinary care improved outcomes of patients with diabetic foot problems. However, evidence on the specific elements and composition of organised or multidisciplinary care was inconclusive. The GDG also noted the existence of skills and competency frameworks, such as the National Minimum Skills Framework for the Commissioning of Foot Care Services for People with Diabetes (www.diabetes.org.uk/Professionals/Education_and_skills/Competencies_-_Feet/).
Other considerations	As the limited evidence showed that organised care or multidisciplinary care improved patients outcomes, the GDG further discussed this particular component of care. Based on the GDG's expertise, knowledge, experience, and the Diabetes UK document 'Putting feet first' (2009), the GDG reached consensus on the following:
	• There should be a care pathway, managed by a multidisciplinary foot care team, for inpatients with diabetic foot problems.
	• The overall care pathway should consist of providing care within 24 hours of admission or detection of a foot problem, and further investigation and management of specific diabetic foot problems.
	• The multidisciplinary foot care team should consist of healthcare professionals who:
	☐ have the resources and specialist skills
	☐ are competent to deliver the key components of inpatient care.
	• The multidisciplinary foot care team should normally include a diabetologist, a surgeon with the relevant expertise in managing diabetic foot problems,, a diabetes nurse specialist, a podiatrist and a tissue viability nurse, together with access to other specialist services required.
	• A named consultant should be accountable for the overall care of the patient and referral to the multidisciplinary foot care team within 24 hours.
	• The responsibility of care should be transferred to a consultant member of the multidisciplinary foot care team if a diabetic foot problem is the dominant clinical factor for inpatient care.
	• Relevant information and clear explanations that support informed decision making, and a named contact person as a coordinator, should be offered to patients.

4.1.6 Recommendations

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)

1. **Each hospital should have a care pathway for people with diabetic foot problems who need inpatient care.**

2. **A named consultant should be accountable for the overall care of the person, and for ensuring that healthcare professionals provide timely care.**

3. **Refer the person to the multidisciplinary foot care service within 24 hours of the initial examination of the person's feet. Transfer the responsibility of care to a consultant member of the multidisciplinary foot care service if a diabetic foot problem is the dominant clinical factor for inpatient care.**

4. **The named consultant and the healthcare professionals from the existing team should remain accountable for the care of the person unless their care is transferred to the multidisciplinary foot care service.**

This section from 2011 has not been updated by an evidence review

4.2 Composition of foot protection services and multidisciplinary foot care services

4.2.1 Review question

In UK current practice, are there existing definitions and compositional models (including skills and specialism) for the foot protection service and the multidisciplinary foot care service?

4.2.2 Evidence Review

Stakeholder feedback during the scoping consultation for the guideline indicated that foot care for people with diabetes was mainly provided by 2 types of services: foot protection services providing care for people at risk of foot problems and multidisciplinary foot care service providing care for people with diabetic foot problems. This narrative review was undertaken to establish current practice in the UK regarding the types and composition of teams providing diabetic foot care services. The protocol for this review question can be found in Appendix C (see review question 2).

For this review question, papers were identified from a number of different databases:
a) Medline
b) Embase
c) Medline in Process
d) Cochrane Database of Systematic Reviews
e) Database of Abstracts of Reviews of Effects
f) Central
g) HTA database

A broad search strategy was used to identify papers relating to the provision and composition of services providing care for the diabetic foot (Appendix D). Papers were excluded if they were non-UK based, published prior to the year 2000 or focussed on criteria for referral. The year 2000 was chosen as a cut-off point by the guideline development group (GDG) because provision and delivery of diabetic foot care services has changed markedly since this time and literature published before then would not be applicable to their decision-making. A full list of excluded studies and reasons for exclusion can be found in Appendix E.

The original and rerun searches identified 5501 papers. Of these, 5463 were excluded on title or abstract. Thirty-nine full papers were requested (including 1 identified from references). Of these 39 papers, 31 were excluded upon examination of the full text as they did not give a tangible description of the composition of foot care teams or they only included descriptions of best practice. A total of 8 papers were examined by the GDG. (Williams,D.T. (2012), Sampson,M.J. (2007), El,Sakka K. (2006), Winocour,P.H. (2002), Jude,E.B. (2003), Housley,A, (2006), National Diabetes Inpatient Audit, Diabetes UK (2013), Gooday, C. (2013)). Evidence tables for the included studies can be found in Appendix F.

Table 7: Summary of included studies

Study	Results			
NHS IC (2013) UK wide clinical audit of inpatient services for diabetes	Composition of multidisciplinary foot teams, England 2012:			
		Percentage of sites		
		Member	Accessible	No access
	Vascular surgeon	56.6	40.9	2.5

Study	Results			
	Diabetologist	81.3	18.2	0.5
	Specialist podiatrist	82.2	11.7	6.1
	Diabetes specialist nurse	59.6	36.9	3.5
	Interventional radiologist	9.7	75.9	14.4
	Orthopaedic surgeon	25.4	69.0	5.6
	Tissue viability nurse	26.2	69.7	4.1
	Microbiologist	24.9	74.1	1.0
	Orthotist	36.3	57.0	6.7
	Composition of multidisciplinary foot teams, Wales 2012:			
		Percentage of sites		
		Member	Accessible	No access
	Vascular surgeon	35.3	64.7	0.0
	Diabetologist	64.7	35.3	0.0
	Specialist podiatrist	76.5	23.5	0.0
	Diabetes specialist nurse	56.3	43.8	0.0
	Interventional radiologist	0.0	68.8	31.3
	Orthopaedic surgeon	18.8	75.0	6.3
	Tissue viability nurse	31.3	68.8	0.0
	Microbiologist	12.5	75.0	12.5
	Orthotist	23.5	64.7	11.8
Williams (2012) Observational study of a diabetes service in the UK	Multidisciplinary foot service (established by a vascular unit in a UK general hospital) consisted of: • Consultant vascular surgeon (lead) • Vascular nurse specialist • Podiatrist with an interest in diabetic foot disease • Nurse with an interest in lower limb wound care • Orthotist.			
Sampson (2007) Survey of UK acute hospitals	Sixty hospitals (25.1%) had no guidelines for the immediate management of the diabetic foot and also did not refer these patients to the diabetes team on admission. Of 228 responding hospital teams, 96 (42.2%) of 227 hospital teams reported that they had access to a podiatrist for in-patients with diabetes.			
Housley (2006) Clinical audit of podiatry and specialist services in Chorley and South Ribble.	Foot care service in the community provided by • 16 podiatrists • 1 diabetes specialist podiatrist • 1 foot care assistant work • 1 community tissue viability nurse			

Study	Results
	• district nurses. The hospital specialist foot clinic is led by the consultant diabetologist with a special interest in feet working closely with: • community diabetes specialist podiatrist • clinic nurses • diabetes specialist nurses • orthotist • plaster technician • vascular surgeons • radiologists • microbiologists. In addition, community podiatrists attend this clinic in rotation mainly for training to ensure continued high quality diabetes care.
El Sakka (2006) Cohort study in an MDT	Multidisciplinary team consisted of: • consultant vascular surgeon • vascular registrar • diabetes consultant • consultant podiatrist • radiology procedure coordinator.
Jude (2003) Survey of consultant diabetologists in secondary care	67.1% of respondents had a designated foot clinic. Availability of vascular surgery was reported by 91.1%. Availability of podiatry services was reported by 92.4%. Availability of orthotist services was reported by 77.2%.
Winocour (2002) Survey of UK acute NHS Trusts	97% of diabetes services had a state registered chiropodist attached. In 75% of responses care was provided by a designated chiropodist, whereas a 'pool' of chiropodists provided care in 20% of responses. 44% reported chiropodists present in all diabetic clinics. 49% had a separate diabetic foot clinic. >90% recorded access to plaster technician. 66.5% reported access to orthotists (majority at stated times). 46% reported a dedicated foot surgeon in hospital.
Gooday (2013) An analysis of impact of loss of 50% of non-operative podiatrists from a tertiary specialist foot clinic in Norfolk.	Acute diabetic foot complications were triaged by the clinic and team of podiatrists. There was a 50% reduction in specialist podiatry staff members in 2010. Resource use and cost The increase in hospital admissions and length of stay during the staff shortage equated to 327 extra bed days compared to the 12 months prior to service disruption. The increased expenditure for this year equated to £89,925 Rates of hospital admission and mean length of hospital admission Staff experienced an increase in the number of admissions during the year in which there was a 50% reduction in the number of specialised podiatric staff.

4.2.3   Health Economic Evidence

A literature search was conducted for the question using standard health economics filters applied to the clinical search strategies. No relevant cost-utility analyses were found. Health economic modelling was not prioritised for this review question.

4.2.4   Evidence Statements

Six studies reported the make-up of a hospital based multidisciplinary team. Of these studies one study reported the make-up of a community based foot care service.

One study reported the prevalence of hospitals that did not refer patients on to a diabetic foot care team immediately after admission. This study also reported the prevalence of hospitals with access to a podiatrist.

One study reported the negative impact on patient and cost outcomes after the loss of 50% of non-operative podiatrists from a tertiary specialist foot clinic.

4.2.5   Evidence to Recommendations

Table 8: Linking evidence to recommendations

Relative value of different outcomes	The guideline development group (GDG) agreed that reducing ulceration and re-ulceration rates was the critical outcome for this question and the guideline. The GDG argued that if these could be prevented then the subsequent likelihood of other outcomes such as infection, gangrene, amputation and death would be diminished.
Trade off between clinical benefits and harms	Establishing the appropriate composition of the foot protection service or multidisciplinary foot service will produce the following desired outcomes: a person will be provided with a service covering all of their treatment and prevention needs under one team, resulting in a more streamlined service with less delay and better communication between healthcare professionals. Such outcomes will result in faster treatment, fewer mistakes and a better informed and satisfied person. The person would receive the best available care at the earliest stage possible, and this could help manage risk and prevent complications such as ulceration. For those who had developed active disease, such improved care could prevent ulceration from developing into further complications such as infection, gangrene, amputation and death.
	On the other hand, a poorly composed foot protection service or multidisciplinary foot care service could result in the service not being able to provide all of the persons treatment and/or prevention needs. This may increase the frequency of costly referrals, ineffective communication, and wasted time for the person along with general dissatisfaction with the service. Poor levels of patient satisfaction may reduce future engagement with the service and potentially could increase the incidence of diabetic foot problems such as ulceration leading to increased levels of infection, gangrene and amputation.
	The GDG agreed that the benefits of a foot protection service and a multidisciplinary foot care service for patients include regular monitoring of their risk of ulceration, timely management of newly occurring foot problems and referral to more specialist services when appropriate. The benefit to the NHS is the implementation of clear local pathways and clear lines of communication across services and between service members.

Trade-off between net health benefits and resource use	The GDG considered the substantial resource implications inherent in setting up multidisciplinary services, but found that the evidence of long-term benefit (see section 4.3) suggests that they would be future cost savings in return for any initial outlay. All evidence reviewed suggested that in terms of cost effectiveness, a foot protection service and multidisciplinary foot care service was a good investment in resources. The GDG was mindful of the competing pressures on the NHS budget but considered that commissioners and managers would recognise the opportunity to configure services to the benefit of patients and to their services when they considered the potential net savings from reduced complication and hospitalisation rates.
Quality of evidence	The papers describing the definitions and composition of existing foot protection services and multidisciplinary foot care services were largely reports from clinical audits, service evaluation or surveys. These papers were not subject to critical appraisal, as there were no commonly used methodological checklists for this kind of evidence and most of the evidence presented was non-comparative. However, the group felt that the papers reflected their experience of the variety in provision of services. Across the UK there is a lack of standardised approaches to providing support for people with diabetic foot problems. For example, there were found to be clear differences between the specialties available for those in the England and Wales areas of the United Kingdom. The UK-wide audit also showed varying proportions of specialty service availability depending on whether the subject was a core member of the team, available to the multidisciplinary team or not at all available.
Other considerations	The GDG noted evidence demonstrating that the presence of trained specialist podiatrists from a tertiary specialist foot clinic in Norfolk was found to have a positive impact in reducing the rate of hospital admissions in the area. Further evidence presented for sections 4.3 and 4.14 also showed that the presence of multidisciplinary care with a well-defined team may improve rates of amputation, hospital admission and length of hospital stay. The GDG discussed the current variation in practice across the UK and felt that standardisation of the provision of services would result in more consistent care for people with diabetic foot problems. The UK-wide audit of services demonstrated that the majority of trusts were resourced to provide, at a minimum, access to healthcare professional with the skills needed to provide care to people at risk of, or with, diabetic foot problems. The GDG considered that either the foot protection service or the multidisciplinary foot care service may be restricted by currently available services but that a set standard should be aspirational for all trusts. The GDG discussed the need for a podiatrist to be the lead for the foot protection service. This was decided on consensus, based on the fact that a specialist podiatrist would be the healthcare professional best placed to triage across all services applicable to diabetic foot patients. Furthermore, the group felt that the multidisciplinary foot care service and foot protection service should consist of a core membership with access to other relevant specialities within the service if clinically required. In their expert opinion it would not be an appropriate use of resources to recommend all service members be present in person to support every person referred to the multidisciplinary team. The group agreed that a distinction between the 2 types of services does not preclude overlapping of team members across services. This can enable shared learning and facilitate the provision of an integrated service.

> The GDG discussed whether there is a need to stipulate actual healthcare professionals in the recommendations to ensure that the core members of the foot protection service and the multidisciplinary foot care service contain only regulated health care professionals with accountable practice. The GDG opted, instead, to recommend the mandatory core skills that only certified health professionals should be able to perform and that each team should have access to. The 1 exception to this was that a podiatrist with specialist training in diabetic foot problems was named specifically to lead the foot protection service. In the GDG's experience, the podiatrist would be best placed to lead this service and therefore this is the only certified speciality named in the recommendations focussing on foot care.

4.2.6 Recommendations

Across all healthcare settings

5. **The foot protection service should be led by a podiatrist with specialist training in diabetic foot problems, and should have access to healthcare professionals with skills in the following areas:**
   - Diabetology.
   - Biomechanics and orthoses.
   - Wound care.

6. **The multidisciplinary foot care service should be led by a named healthcare professional, and consist of specialists with skills in the following areas:**
   - Diabetology.
   - Podiatry.
   - Diabetes specialist nursing.
   - Vascular surgery.
   - Microbiology.
   - Orthopaedic surgery.
   - Biomechanics and orthoses.
   - Interventional radiology.
   - Casting.
   - Wound care.

7. **The multidisciplinary foot care service should have access to rehabilitation services, plastic surgery, psychological services and nutritional services.**

4.2.7 Research recommendations

No research recommendations were drafted for this review question

4.3 Criteria for referral to the foot protection service or multidisciplinary foot care service

4.3.1 Review Question

When and with what criteria should people with diabetes be referred to the foot protection service or the multidisciplinary foot care service?

4.3.2 Evidence Review

The aim of this review was to establish the situations when it is appropriate and effective to refer people with diabetes to foot protection services or multidisciplinary foot care service. The protocol for this review can be found in Appendix C (see review question 3).

The original and rerun searches identified 9,738 citations. Five relevant papers found while sifting for review question 13 were also identified. From this, 57 citations were identified as potentially relevant to this question and were requested for full text. Following the examination of full text papers 11 observational studies were found to be relevant to the review question and were included in the final review. The full list of excluded studies and reasons for exclusion can be found in Appendix E.

The papers were extracted for useful information which was used to fill the evidence tables and the GRADE profiles. The evidence tables are shown in Appendix F. The GRADE profiles for the included studies can be found in Appendix I.

Table 9 outlines the PICO framework used for this review question.

Table 9: PICO framework

Population	Children, young people and adults with type 1 or type 2 diabetes
Intervention	Varying criteria for referral of people with diabetes to foot protection and multidisciplinary foot care service
Comparator	Not applicable
Outcomes	Rates (and recurrent rates) of foot ulceration, infection and gangrene resulting from diabetes
	Resource use and costs (including referral rates)
	Rates of hospital admission for foot problems resulting from diabetes.
	Length of hospital stay
	Health-related quality of life
Include	Systematic review
	Prospective or retrospective cohort study
Exclude	Configuration of foot protection service or multidisciplinary foot care service providing care for children and young people with diabetes admitted to hospital who have foot problems
	Examination of service arrangements and composition of foot protection service and multidisciplinary foot care service in the UK

Summary of quality and methodological issues

The GDG discussed the purpose of this question and which types of studies they would be interested in. As we were unable to find studies discussing whether referral to a foot protection service at a certain point in time, or a certain stage in disease process, had better outcomes than those who were referred at different stages or time points the decision was

made to extract data from studies which compared multidisciplinary foot protection care to non-multidisciplinary foot protection care (or foot protection services to lack of foot protection services) and use the populations, protocols and services described in these studies to guide discussion and recommendations.

After the review was conducted 11 observational studies were found. (Gooday, C. (2013), Patout, C. A. (2000), Rith-Najarian, S. (1998), Birke, J. A. (2002), Armstrong, D. G. (1998), Schraer, C. D. (2004), Lavery, L. A. (2005), Dargis (1999), Driver, V. R. (2010), Carrington, A. L. (2001), Nason, G. J. (2013))

Details of the skills, tasks or professionals involved in the multi-disciplinary teams are outlined in Table 10.

Since there was substantial overlap between section 4.3 and section 4.14, and as both questions had similar methodological issues and required similar types of evidence, both reviews were presented together.

Table 10: Included studies and skills, tasks or professionals involved in multi-disciplinary teams

Study	Skills, tasks or professionals involved in multi-disciplinary teams
Armstrong 1998	A multidisciplinary diabetic foot care team, which included aggressive foot care and consistent treatment-based risk classification. Available specialties include general internal medicine, podiatry, endocrinology, opthalmology, diabetes nurse education and nutritional and social services with an active vascular consultancy.
Birke 2003	Diabetes foot Program providing regional referral care for high-risk foot problems. The program provides treatment for foot ulcerations or Charcot fractures within 24 hours of referral and a detailed treatment algorithm. The diabetes foot programme uses staff including a physician, nurse practitioner, physical therapists, registered nurse, pedorthist, cast technicians and other support staff.
Gooday 2013	Acute diabetic foot complications were triaged by the clinic and team of podiatrists. Replacement of podiatry footcare team members with non-specialist community non-operative podiatrists for some of this time
Lavery 2005	Lower extremity disease management program consisting of screening and treatment protocols diabetic members in a managed care organisation. Patients were stratified into high and low risk groups and implemented preventive or acute care protocols. Utilisation was tracked for 28 months and compared to 12 months of historic data prior to implementation of the disease management program. Staff included pedorthist and podiatrist care.
Patout 2000	Comprehensive diabetes lower-extremity amputation prevention programme. Assessment of risk and management
Rith-Najarian 1998	A two year staged diabetes management period during which comprehensive guidelines for diabetic foot management were adapted by primary care clinicians to their practice and were systematically implemented. A foot care team was formed consisting of a family physician, two clinic nurses, a home care nurse, a nutritionist and a registrar.
Schraer 2004	The programme provided training for a physiotherapist to become a pedorthist who established long-term maintenance by conducting diabetic foot clinics routinely at a referral centre. A system was established in a common database management program to track the patient's foot conditions. A risk category system was found useful in planning follow up for diabetic foot care. This person also worked in consultation with Orthopaedics, Vascular Surgery and the Diabetes Clinic to provide conventional wound care management and offloading as indicated.
Dargis 1999	A multidisciplinary foot clinic staffed by a diabetologist, rehabilitation

Study	Skills, tasks or professionals involved in multi-disciplinary teams
	physician, orthopaedic surgeon, podiatrist, and shoe makers.
Driver 2010	Limb protection team: employing: podiatric and vascular surgery, a orthotist, a wound care nurse and a research unit.
Carrington 2001	Focused foot care program. Peripheral vascular and nerve assessment, education and podiatry were provided for each patient.
Nason 2013	A dedicated bi-weekly consultant led multidisciplinary foot protection clinic employing vascular surgery, endocrinology, orthopaedic surgery, podiatry, orthotics, tissue viability established in a university hospital as part of an integrated foot protection service.

A modified GRADE approach was used to quality assess the evidence. (see Appendix I)

The included studies did not report the outcome of health-related quality of life

Statements of the evidence findings for rates and recurrent rates of foot ulceration, resource use and costs, rates of hospital admission, length of hospital stay and rates of amputation can be found below.

4.3.3   Health Economic Evidence

A literature search was conducted for the question using standard health economics filters applied to the clinical search strategies. No relevant cost-utility analyses were found. Health economic modelling was not prioritised for this review question.

4.3.4   Evidence Statements

Rates (and recurrent rates) of foot ulceration, infections and gangrene.

Evidence from 4 observational studies including 1025 participants found that the screening for high risk patients, the presence of a complete multidisciplinary foot protection service and the application of a treatment pathway/guideline resulted in improved rates of ulceration outcomes for the population under study. The quality of the evidence was very low.

Resource use and costs

Evidence from 1 observational study including 4058 participants found an increased estimated hospital expenditure following the loss of 50% of specialist podiatrist staff and the subsequent disruption of the multidisciplinary foot protection service. The quality of the evidence was very low.

Rates of hospital admissions for foot problems relating to diabetes

Evidence from 2 observational studies including 2,883 participants and 2 studies reporting per person years found that the screening for high risk patients, the presence of a complete multidisciplinary foot protection service and the application of a treatment pathway/guideline resulted in improved rates of hospital admission for the population under study. The quality of the evidence was very low.

Evidence from 1 observational study including 4058 participants found increased hospital admissions following the loss of 50% of specialist podiatrist staff and the subsequent disruption of the multidisciplinary foot protection service. The quality of the evidence was very low.

Length of hospital stay

Evidence from 2 observational studies including 2,989 patients and 1 study reporting in person years, found that the screening for high risk patients, the presence of a complete multidisciplinary foot protection service and the application of a treatment pathway/guideline resulted in shortened length of hospital stay for the population under study. The quality of the evidence was very low.

Evidence from 1 observational study including 4058 participants found increased hospital length of stay following the loss of 50% of specialist podiatrist staff and the subsequent disruption of the multidisciplinary foot protection service. The quality of the evidence was very low.

Rates and extent of amputation

Evidence from 5 observational studies including 4,257 participants and 3 studies that reported per person year, found that the screening for high risk patients, the presence of a complete multidisciplinary foot protection service and the application of a treatment pathway/guideline resulted in improved rates of amputation for the population under study. The quality of the evidence was very low.

Evidence from 1 observational study including 485 participants found that the screening for high risk patients, the presence of a complete multidisciplinary foot protection service and the application of a treatment pathway/guideline resulted in increased rates of minor amputation (with improved survival and ulceration rates) for the population under study. The quality of the evidence was very low.

Evidence from 1 observational study including 291 participants showed no significant effect from the establishment of a specialist foot clinic for unilateral lower limb amputees. The quality of evidence was very low.

Health-related quality of life

No included studies reported outcomes for health-related quality of life

4.3.5 Evidence to Recommendations

Table 11: Linking evidence to recommendations table

Relative value of different outcomes	The importance of reducing ulceration and re-ulceration rates was, again, of critical importance.
	In this review some of the persons included would have already developed diabetic foot problems and the primary aim would be to cure active foot ulceration and reduce the rate of reulceration. This would have long term impact in diminishing the likelihood of further complications from developing such as infection, gangrene, amputation and a reduced health-related quality of life. Reducing the incidence of these complications would also result in reduced rates of hospital admission, resource use and costs.
Trade-off between benefits and harms	The benefits of appropriate referral to the foot protection service or the multidisciplinary foot care service at the optimum time include the following desired outcomes: the person would be identified at an early stage, their risk of developing a foot problem would be determined at an early stage, both of which

would result in better control of the person's risk factors and a reduced likelihood of foot ulcers or other foot problems developing. Appropriate referral to the multidisciplinary foot care service for those with active disease would result in the best available care at the earliest stage possible, which could prevent complications such as ulceration from developing into further complications such as infection or gangrene, and subsequent amputation or death.

On the other hand, inappropriate referral to either the foot protection service or to the multidisciplinary foot care service could result in wastage of NHS resources, wasted time for the referred person and dissatisfaction with the service. This could result in the person presenting late or not presenting at all next time they develop a problem, which could cause an increase in the incidence of severe diabetic foot problems such as ulceration, leading to an increase in the rates of infection, gangrene and amputation outcomes.

Trade-off between net health benefits and resource use	The GDG considered the substantial resource implications inherent in setting up multidisciplinary services, but found that the evidence of long-term benefit suggests that there would be future cost-savings in return for any initial outlay. All evidence reviewed suggested that in terms of cost effectiveness, the multidisciplinary foot protection service was a good investment in resources. The GDG was mindful of the competing pressures on the NHS budget but considered that commissioners and managers would recognise the opportunity to configure services to the benefit of patients and of their services when they considered the potential net savings from reduced complication and hospitalisation rates.
Quality of evidence	Since no prognostic evidence as initially requested by the GDG was identified, the post-hoc decision to review descriptive observational evidence was made. This approach could only indirectly answer the question of who would benefit from referral to a foot protection service. The initial purpose of the evidence review was to identify those individuals with diabetes who would benefit from referral to either the foot protection service or multidisciplinary foot care service. Instead, the evidence reviewed identified the wider benefit of implementation of pathways, protocols and interdisciplinary care across different healthcare settings. Since all studies were of the observational type with a high risk of bias, all presented evidence was rated as very low quality. The GDG discussed the difficulty in finding the source of the beneficial effect within a study showing the effect of establishing multidisciplinary care. For example, it is impossible to prove that a particular referral pathway within each study was the effective component, as the studies can only show the benefit of the implementation of a protocol within the service as whole. The included studies could give an idea of the benefit of the foot protection service in terms of reduced rates and recurrent rates of foot ulceration, infection and gangrene, resource use and cost, hospital admission rates, length of hospital stay and rates and extent of amputation. While this would not directly answer the question of who should be referred for foot protection care,

	we were able to look at the types of populations included in these studies and consider the stages at which it would be effective for patients to receive foot protection and multidisciplinary care.
Other considerations	The GDG considered the value of an integrated model of management/care pathway (incorporating a foot protection service and a multidisciplinary foot care service) for people with diabetic foot starting at the point of diagnosis of diabetes and continuing indefinitely. It includes a risk assessment (see section 4.4) and should be responsive to changing needs of the patient if problems or increased risk develop during the course of the disease progression.
	The evidence seemed to show that having a foot protection service or multidisciplinary foot care service was not only beneficial in terms of patient outcomes such as rates and recurrent rates of foot ulceration, infection and gangrene, hospital admission rates, length of hospital stay and rates and extent of amputation but also that such a strategy could be significantly more cost saving in the long term across all study settings. One study showed the associated increase in cost and hospital bed days and admissions after the disruption of their multidisciplinary foot clinic following the loss of 50% of their podiatric specialist staff.
	One study, however, did not find a significant improvement in rates of bilateral amputations amongst unilateral amputated persons after the implementation of a multidisciplinary focused foot protection programme. Even if this very-low-quality evidence was more reliable, it would be hard to discount all the other evidence that multidisciplinary care is beneficial for all other patient groups. It also would not make sense to offer such high-risk persons inferior care. It is likely, rather, that this population need an even more enhanced level of care due to their extremely high risk.
	As a result of the largely consistent evidence about the benefits of multidisciplinary care, the GDG decided that a recommendation should be made to support a foot protection service for the prevention of diabetic foot problems and the treatment and management of simple diabetic foot problems.
	Evidence showed the benefit of clear protocols and pathways spanning the care of people with diabetes who have a low risk of developing diabetic foot complications to those people who have developed active complications. The GDG wanted to make recommendations that foot protection services should not stand alone but rather should have integrated care pathways shared between the hospital and the community. Implementation of such protocols should be based upon the recognised risk assessment of the patient and the severity of any current disease (this approach was seen in the evidence presented). Such assessments should be standardised across inpatient multidisciplinary foot care services and foot protection services (also see section 4.4).
	Such complex treatment initiatives would require constant and regular review. For this reason the GDG decided to make a

consensus recommendation that patient and treatment outcomes should be regularly audited in line with the National Diabetes Foot Care Audit.

Considering the types of treatments received by the patients, for whom a detailed protocol was given, the GDG was able to extrapolate the types of services that they would want to provide such treatments and protective management for patients at different risk levels. Using the SIGN risk classification criteria defined in a later review question, the GDG decided that those at moderate and high risk of developing diabetic foot problems should be referred to the foot protection service as consistent with the evidence reviewed and their own experience in clinical practice.

The majority of the studies describing what the GDG considered to be a foot protection service included patients at lower to higher risk of ulceration or with more simple diabetic foot problems whereas the studies with multidisciplinary foot care-style services included people with more active or complex diabetic foot problems requiring more frequent follow-up and specialist care.

Risk stratification was reviewed in section 4.4. The GDG therefore stated that the foot protection service should provide protection (see section 4.6) for those at high and medium risk of developing diabetic foot complications.

The GDG also referred to the studies in this review when deliberating on the timeframes by which patients should be referred from primary care to either of the teams. By considering the risk assessment (section 4.4), the GDG discussed the frequency of monitoring that each risk category would necessitate and how soon newly referred people with diabetes should be seen by the service. The GDG were careful to define a reasonable standard for care providers to achieve.

The GDG debated the proportion of patients with diabetes who would be referred to the foot protection service (20 to 40%) and, after considering the workload that this would lead to, agreed that for newly referred medium risk patients, assessment at between 6 and 8 weeks would be appropriate. This would not be too onerous for either the patient or the foot protection service but would allow for timely management of newly diagnosed diabetic foot problems and referral to the multidisciplinary foot care service if appropriate.

When considering the frequency of monitoring for those assessed as high risk, as defined in section 4.4, the GDG was mindful of the need for prompt care in these situations and agreed that those newly referred at high risk should be assessed at between 2 and 4 week intervals.

The GDG agreed that the multidisciplinary foot care service should treat and manage diabetic foot care problems that the diabetic foot protection service is unable to manage. The GDG allowed for the fact that some foot protection services may be more sophisticated and better equipped to treat diabetic foot problems than others and that therefore the flexibility of the

recommendations should reflect this.

Having some of the same team members in both services would help facilitate the rapid referral between services, but the GDG was mindful that having clear protocols/pathways would also be of benefit. The GDG agreed that clear communication between the services was also essential for integrated care to be effective.

The GDG was eager that no patients should "fall out of the system." The main area of concern was for those patients who bypass the foot protection service and present in emergency care. There was potential for such patients to have treatment delayed if it was felt that the care of diabetic foot was not the responsibility of the healthcare provider to which the patient presents. For this reason both in emergency care and general practice it was recommended that each trust should have available a shared protocol for the treatment of a diabetic foot complications. This protocol should be integrated across the multidisciplinary foot care service, the foot protection service, accident and emergency services and general practice services.

Lastly, while considering the best service structure for the populations described, the GDG agreed that special arrangements would be needed for disabled people and people who are housebound or living in care or nursing homes, to ensure equality of access to foot care assessments and treatments. This recommendation was made on consensus.

There was substantial overlap between section 4.3 and section 4.14 and, as both questions had similar methodological issues and required similar types of evidence, both reviews were presented together. The GDG drafted recommendations for both services under these 2 sections. Section 4.14 refers to indications for referral to specialist services, and since the multidisciplinary foot care service consists of many different specialists the decision was made to write the recommendations specific to the multidisciplinary foot care service within that section.

4.3.6   Recommendations

Care across all settings

8. **Commissioners and service providers should ensure that the following are in place:**
   – A foot protection service for preventing diabetic foot problems, and for treating and managing diabetic foot problems in the community.
   – A multidisciplinary foot care service for managing diabetic foot problems in hospital and in the community that cannot be managed by the foot protection service. This may also be known as an interdisciplinary foot care service.
   – Robust protocols and clear local pathways for the continued and integrated care of people across all settings, including emergency care and general practice. The protocols should set out the relationship between the foot protection service and the multidisciplinary foot care service.

– Regular reviews of treatment and patient outcomes, in line with the National Diabetes Foot Care Audit.

9. **Refer people who are at moderate or high risk of developing a diabetic foot problem to the foot protection service**

10. **The foot protection service should assess newly referred people as follows:**

    – Within 2–4 weeks for people who are at high risk of developing a diabetic foot problem.

    – Within 6–8 weeks for people who are at moderate risk of developing a diabetic foot problem.

11. **Healthcare professionals may need to discuss, agree and make special arrangements for disabled people and people who are housebound or living in care settings, to ensure equality of access to foot care assessments and treatments for people with diabetes.**

12. **Take into account any disabilities, including visual impairment, when planning and delivering care for people with diabetes.**

4.3.7   Research recommendations

When and with what criteria should people with diabetes be referred to the foot protection service or the multidisciplinary foot care service?

Why this is important

The evidence surrounding different referral criteria for those at risk of, or who have developed diabetic foot problems was limited. It is proposed that a prospective cohort study is undertaken to explore this question. The proposed study would monitor and evaluate the rates (and recurrent rates) of foot ulceration, infection and gangrene resulting from diabetes, resource use and costs (including referral rates), rates of hospital admission for foot problems resulting from diabetes, length of hospital stay, and the health-related quality of life as a result of different referral criteria to these teams.

4.4 Classifying and stratifying risk of foot problems

4.4.1 Review Question

What are the clinical utilities of assessment and risk stratification tools for examining the feet of people with diabetes and classifying risk of foot problems?

4.4.2 Evidence Review

This review question focused on the use of tools and techniques to examine the feet of people with diabetes and stratify their risk of developing foot problems. Papers were identified from a number of different databases (Medline, Embase, Medline in Process, the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials and the Centre for Reviews and Dissemination) using a broad search strategy, pulling in all papers relating to diabetic foot problems. The protocol for this review can be found in Appendix C (see review question 4).

For development purposes this review was treated as two questions:

- What are the clinical utilities of stratification systems for classifying the risk of foot problems for people with diabetes?
- What are the clinical utilities of assessment tests for examining the feet of people with diabetes?

4.4.2.1 Risk stratification systems

In assessing risk stratification systems, papers were considered for inclusion if they reported systematic review, test and treat RCT, cohort studies or case control studies. Papers reporting cross-sectional studies or case series were excluded. The original and rerun searches identified 9,738 abstracts, 37 full-text articles were examined. 32 papers were excluded: 5 papers describing 4 primary studies met the inclusion criteria for the review of stratification systems. (Leese,G.P. (2006), Monteiro-Soares,M. (2012), Monteiro-Soares,M. (2011), Monteiro-Soares,M. (2010), Peters,E.J. (2001). The protocol for this review question can be found in Appendix C (see review question 4). The evidence tables for the included studies can be found in Appendix F. The list of excluded studies can be found in Appendix E.

1 paper was a systematic review (Monteiro-Soares, 2011) examining three of the identified primary studies and therefore has not been included in the summary tables or GRADE profiles. GRADE profiles for the included studies can be found in Appendix I.

Table 12 outlines the PICO framework used for this review question. Table 13 summarises the stratification systems identified and Table 14 lists the details of the included studies.

Table 12: PICO framework

Population	All people with diabetes
Intervention	Risk stratification system
Comparator	Clinical judgement / other stratification system
Outcome	Foot ulcer incidence Rates of gangrene Amputation rates Rates of ED / hospital use Resource use and costs
Inclusion	Systematic review, test and treat RCT, cohort or case-control studies Papers reporting validation of risk stratification systems
Exclusion	Cross sectional studies or case series

Papers reporting derivation of risk stratification systems

Table 13: Summary of risk stratification systems

Model	Summary	
IWGDF	Four categories: 0 No Diabetic neuropathy 1 Diabetic neuropathy 2 Diabetic neuropathy and (foot deformity or peripheral vascular disease) 3 History of foot ulcer or peripheral vascular disease	Modified version: 0 No Diabetic neuropathy or peripheral vascular disease 1 Diabetic neuropathy, no peripheral vascular disease or foot deformity 2a Diabetic neuropathy and foot deformity, no peripheral vascular disease 2b peripheral vascular disease 3a History of foot ulcer 3b peripheral vascular disease
SIGN	Three categories: Low – No risks factors - no loss of sensation, no signs of peripheral vascular disease and no other risk factors. Moderate – One risk factor - loss of sensation or signs of peripheral vascular disease without callus or deformity High – Previous ulceration or amputation or more than one risk factor present e.g. loss of sensation or signs of peripheral vascular disease with callus or deformity.	
Seattle risk score	Score according to presence of: Neuropathy Previous ulcer Previous amputation Visual impairment HbA1c Tinea pedis Onychomycosis Four score-based risk categories: Lowest risk Next to lowest risk Next to highest risk Highest risk	
ADA	Four categories: 0 No Diabetic neuropathy 1 Diabetic neuropathy and/or foot deformity 2 Diabetic neuropathy and/or peripheral vascular disease 3 History of foot ulcer and lower extremity amputation	
UT	Four categories: 0 No Diabetic neuropathy 1 Diabetic neuropathy 2 Diabetic neuropathy and foot deformity 3 Diabetic neuropathy, foot deformity and history of lower extremity amputation	

Abbreviations: IWGDF, International Working Group on Diabetic Foot; SIGN, Scottish Intercollegiate Guidelines Network; ADA, American Diabetes Association; UT, University of Texas.

1

2 **Table 14: Summary of included studies on risk stratification systems**

Study	Population	System	Follow up	Authors conclusions
Monteiro-Soares (2012) Retrospective cohort study Portugal	364 patients with diabetes attending a podiatry section Jan 2008 to Dec 2010 Mean age 64 (19 to 94 years) 49% male 99.7% type II diabetes 42% used insulin Mean diabetes duration 17 years (range 1 to 52 years)	Modified IWGDF SIGN Seattle risk score ADA UT	Median follow up 12 months (range 1 to 12)	Authors conclude that all systems are equally and highly accurate. Trend observed for increased diabetic foot ulcer occurrence in higher risk groups. All systems presented <30% positive predictive values – of those classified as at risk more than 70% will not develop a diabetic foot ulcer. For highest risk group (or highest combined with medium risk) there are excellent negative predictive values. Almost all patients developing a foot ulcer are predicted by the systems.
Monteiro-Soares (2010) Retrospective cohort study Portugal	360 patients attending the podiatry section of a diabetic foot clinic from 2002 to 2008. Median age 65 years 98% Type II diabetes 45% male	Boyko stratification model (Seattle Risk Score)	Median follow-up of 25 months Range 3 to 86 months. Follow up ended on first ulcer occurrence.	Authors conclude that the Boyko system is an excellent discriminating instrument for foot ulcer prediction in patients with diabetes. Inclusion of footwear variable may improve the model.
Leese (2006) Prospective cohort study UK	3526 patients attending for routine diabetes care in hospital and community. Mean age 64.7 years (range 15-101) 91% Type 2 Mean diabetes duration 8.8 years	SIGN system	Mean follow up 1.7 years (+/- 0.9)	Authors conclude that the main value of the tool is in identifying patients at low risk of ulceration. Low risk patients had a 99.6% chance of remaining free from ulceration.
Peters (2001) Prospective case control study USA	236 patients Female 53.5% Type 2 diabetes 93.8% Mean age 52.6 (+/- 10.4 SD) Mean diabetes duration 11 years (+/- 9.3 SD)	IWGDF system	Mean follow up 30 months	Authors conclude that the system is effective in predicting groups that are more likely to develop foot complications.

3 *Abbreviations: IWGDF, International Working Group on Diabetic Foot; SIGN, Scottish Intercollegiate Guidelines*
4 *Network; ADA, American Diabetes Association; UT, University of Texas.*

5

4.4.2.2 Assessment tests

In evaluating tests for examining the feet of people with diabetes, papers were considered for inclusion if they reported systematic review, test and treat RCT or prospective cohort studies. Papers reporting case-control, cross-sectional studies or case series were excluded. The original and rerun searches identified 8195 and 1543 abstracts, 107 full-text articles were examined and 95 studies were subsequently excluded. 12 papers describing 12 primary studies met the inclusion criteria for the review of examination tools. (Nather, A. (2008), Boyko, E. J. (2006), Abbott, C. A. (2002), Carrington, A. L. (2002), Kastenbauer, T. (2001), Pham, H.. (2000), Adler, A. I. (1999), Boyko, E. J. (1999), Litzelman, D. K. (1997), Young, M. J. (1994), Rith-Najarian, S. J. (1992), Leese, G. P. (2013))

Table 15 outlines the PICO framework used for this review question. Table 16 lists the details of the included studies.

Papers were included only if they evaluated clinical tests or tools for examining the foot used to predict the occurrence of foot problems. Data was not extracted on the predictive accuracy of patient characteristics or clinical history. Papers on tests for the diagnosis of peripheral vascular disease were also excluded as the diagnosis of peripheral vascular disease in people with diabetes is addressed by NICE clinical guideline 147.

Table 15: PICO framework

Population	All people with diabetes
Intervention	Assessment tests
Comparator	Clinical judgement / other tests
Outcome	Foot ulcer incidence Rates of gangrene Amputation rates Rates of ED / hospital use Resources use and costs
Inclusion	Systematic review, test and treat RCT or cohort studies Papers reporting validation of risk stratification systems
Exclusion	Case control, cross sectional studies or case series Papers reported derivation of examination tools Papers not reporting prognostic accuracy Studies of tests for PVD

Table 16: Summary of included studies on assessment tests

Study	Population	Test	Follow up	Authors conclusions
Nather (2008) Prospective cohort Singapore	202 patients treated in outpatient multi-disciplinary hospital setting for foot problems Jan 2005 to May 2006	5.07 Semmes-Weinstein monofilament	Not stated	Authors conclude that sensory neuropathy by monofilament is a univariate predictive factor for limb loss. However, monofilament sensitivity not significant in step-wise logistical regression.
Boyko (2006) Prospective cohort USA	1285 patients. Recruited from general internal medicine clinic at a Veterans Affairs Medical Center. 210 died 277 lost to follow up	5.07 Semmes-Weinstein monofilament	Mean follow up 3.38 years	Authors conclude that a risk prediction model (combining clinical characteristics) is more accurate than monofilament testing
Abbott (2002) Prospective cohort UK	9710 patients receiving community healthcare in 6 districts. 6613 responding to follow-up 2300 non-responders	NSS NDS Pain sensation (Neurotip) Vibration score (128Hz tuning fork) Temperature score (warm and cool rods) 10g monofilament Foot deformity score Achilles tendon reflex (hammer)	2 year (+/- 6 weeks)	Authors conclude that NDS and/or 10g monofilament plus foot palpation can identify high risk patients and predict foot ulcer occurrence.
Carrington (2002) Prospective cohort UK	169 patients consecutively attending routine clinic at a diabetes centre. 22 people without diabetes recruited from staff members, friends and relatives) Recruited 1994 and 1995.	Motor Nerve Conduction Velocity PPT (dorsum) PPT (plantar) VPT	Median time: First ulcer / study end 67.9 months (range 0.6 to 79.9) Amputation / study end 69.7 months (range 7.3-79.9) Death / study end 69.5 months	Authors conclude that MNCV is the best predictor new foot ulceration. PPT was the test with best predictive of amputation. MNCV was the test with best predictive of mortality.

Study	Population	Test	Follow up	Authors conclusions
Kastenbauer (2001) Prospective cohort	187 patients recruited from a diabetes centre	VPT by biothesiometer 10g monofilament Plantar pressure (Novel SF device)	Mean follow-up 3.6 years	Authors conclude that elevated VPT is strongest independent predictor of ulceration.
Pham (2000) Prospective cohort USA	248 patients consecutively enrolled from 3 foot care centres Exclusions: none stated	NSS NDS Biothesiometer Monofilament F-scan mat (plantar foot pressure) Goniometer (joint mobility)	Mean follow up 30 months (range 1-60 months)	Authors conclude that NDS obtained in clinical examination and 10g monofilament provide best sensitivity in identifying patients at risk of ulceration.
Adler (1999) Prospective cohort USA	776 veterans in a general medicine clinic at a Veterans Affairs Medical Center	10g monofilament	Median 3.3 years (0.5-8)	Authors conclude that peripheral neuropathy as measured by 10g monofilament is an independent predictor of lower extremity amputation.
Boyko (1999) Prospective cohort USA	749 patients recruited from general internal medicine clinic at a Veterans Affairs Medical Center.	5.07 monofilament 128-Hz tuning fork Achilles tendon reflex	Mean follow-up 3.7 years	Authors conclude that foot sensory neuropathy as measured by 5.07 monofilament emerged as the test most predictive of foot ulcer risk.
Litzelman (1997) Prospective cohort USA	352 patients with NIDDM receiving primary care from a university affiliated general medicine practice. 395 originally enrolled, 43 did not complete the study.	10g monofilament Thermal sensitivity (Sensortek)	12 month	Authors conclude that monofilament insensitivity is an important predictor of wounds, even when minor injuries included in the definition. Thermal insensitivity was also a strong univariate predictor but did not enter the multivariate model for wound score >=1.3.
Young (1994) Prospective cohort	469 patients consecutively recruited between 1988 and 1989 in a diabetic or diabetic foot clinic	VPT by biothesiometry	4 years	Authors conclude that VPT can predict those patients at increased risk of foot ulceration and that a VPT >25V carries a seven fold risk of ulceration compared to <15V

Study	Population	Test	Follow up	Authors conclusions
Rith-Najarian (1992) Prospective cohort USA	358 examined in primary care setting 19 died 2 lost to follow up	5.07 Semmes-Weinstein monofilament	32 month follow up period	Authors conclude that presence of deformity and history of lower extremity event can identify high risk patients. However, ulceration and amputation still occurred in people sensate to monofilament testing.
Leese (2013) cohort UK	15, 938 were identified between 2004 and 2006 Over 3 years follow up 670 people developed new foot ulcers	10g monofilament	3 year follow up period	Authors concluded risk factors for foot ulceration were age, previous ulcer, absent foot pulses, absent sensation to monofilaments, insulin use, duration of diabetes, previous retinal laser treatment and social deprivation.

4.4.3 Health Economic Evidence

A literature search was conducted for the question using standard health economics filters appplied to the clinical search strategies. No relevant cost-utility analyses were found. Health economic modelling was prioritised for this review question

4.4.4 Evidence Statements

Limited evidence from 4 cohort studies of mixed quality shows that 5 stratification systems (SIGN, Seattle risk score, UT, ADA and IWGDF) can predict ulcer occurrence, lower limb amputation or death. The systems were found to have similar predictive ability.

Limited evidence from 13 low to very low quality cohort studies showed that tests for loss of sensation in the feet of people with diabetes can predict foot ulcer occurrence, lower limb amputation and death.

4.4.5 Evidence to Recommendations

Table 17: Linking evidence to recommendations table

Relative value of different outcomes	The GDG considered the predictive accuracy of the different scores and tools. The group agreed that they would be prepared to accept lower specificity in exchange for higher sensitivity in order to ensure all patients at risk are included in the correct risk categories. The group felt that false positives were preferable to false negatives given the impact that foot ulcer can have on a person's life. The importance of reducing ulceration and re-ulceration rates was again paramount in this question as in previous questions.
Trade-off between benefits and harms	Regarding accuracy the GDG considered that, in instances of a true positive, referral to appropriate services and appropriate care resulted in decreased risk of ulceration, infection, both minor and major amputation and death (see Section 4.3 and 4.14 for protocols and diabetic foot protection services and multidisciplinary foot care services). In instances of true negatives then reassurance and ongoing monitoring by appropriate healthcare professionals in the appropriate setting or service would be considered appropriate (see Section 4.3 and 4.14 for protocols and diabetic foot protection services and multidisciplinary foot care services). The consequences of a false negative include increased possibility of ulceration, infection, both minor and major amputation, and death, whereas the consequences of a false positive include increased assessment and discharge from one service to another (see Section 4.3 and 4.14 for protocols and diabetic foot protection service and multidisciplinary foot care service). Because of the potential consequences for both the patient and the services, the GDG agreed that all patients, and not just those at high risk, should be categorised correctly by stratification systems.
Economic considerations	At the outset of guideline development, the GDG had been keen to review original economic evidence on stratification tools for classifying risk of foot problems. However, having explored the available evidence, it was concluded that it was not possible to provide a robust analysis that directly answered this question. This

was predominantly because none of the evidence identified for this question provided any indication of the relative effectiveness of different risk stratification tools, in terms of reduced incidence of ulcers, amputations, or other clinically relevant outcomes.

However, the GDG was aware that some indirect evidence was available in the original analysis undertaken for prevention strategies for people at risk of developing foot problems (section 4.6). Because that analysis modelled strategies in which the intervention was offered depending on each individual's risk of developing ulcers, it provided evidence that dividing the population into low-, medium- and high-risk strata was a theoretically sensible thing to do, and could also result in the effective targeting of resources so that total costs could be managed (or even reduced) compared with strategies in which everyone or no one received preventative care. Therefore, although the original analysis in section 4.6 concentrated on a single intervention (the provision of orthotic footwear), it could also be seen as providing economic support for the notion of risk stratification more broadly.

The GDG was mindful of the resource implication required once any risk stratification models are used if patients are to be appropriately triaged and appropriately cared for. Assessment tests likewise carry a resource cost and this was kept in mind in the discussions surrounding the use of assessment tools such as the monofilament touch test.

Quality of evidence	The group downgraded those studies that only examined patients who were more likely to develop foot ulcer. For example, some studies were conducted in tertiary referral services and not the community. The review question focussed on stratification and assessment tests for all people with diabetes, and the group felt it important that evidence be generalisable to patients in community settings as the risk assessment in the NHS would be carried out in general practice.
Other considerations	Based on the recommendations concerning the frequency of monitoring for those at risk of developing foot complications in section 4.5, the GDG also felt it was important to stipulate when, and under which circumstances, this risk assessment should be performed. The GDG were especially keen that all people with diabetes should have their feet examined and a thorough risk assessment performed both at the diagnosis of diabetes and at any subsequent admission to hospital whatever the cause. The GDG reached this consensus by acknowledging that a person with diabetes and risk factors for foot ulceration who is admitted is at particularly high risk for developing heel ulcers, therefore the purpose of screening as they come into hospital is to first stratify the risk and then reduce the risk of heel ulceration using the strategies outlined in this guidance.

The group discussed the limited evidence available on the ability of the various tests of sensation loss to predict foot ulceration. There was also limited evidence available from multivariate analysis on the ability of tests to predict foot ulcer occurrence. More evidence was available for use of the 10g monofilament in testing for lack of sensation to predict diabetic foot problems than any other test. Coupled with its general acceptability in clinical practice, and relative cheap cost, the group recommended its use as a measure of loss of sensation. The evidence reviewed showed the usefulness of the monofilament test for predicting diabetic foot problems, however since we had not performed a diagnostic review of the investigations |

for neuropathy the GDG could not rule out other forms of testing for neuropathy. Instead it was decided to recommend monofilament testing as part of a foot sensory examination.

The GDG highlighted that the risks of developing foot ulcer can change throughout a person's life and that it was important to reclassify a person's risk category at regular intervals.

The GDG discussed other aspects of clinical utility of stratification tests, specifically acceptability in the UK and current practice. The group felt that the most widely used risk stratification system was the SIGN system and the evidence did not support changing this practice. The group also felt it important to recommend a specific type of risk assessment system in order to encourage uniformity of practice across the NHS.

The group discussed the other tests used in examining the feet of people with diabetes. The group wanted to cross-reference to the PAD guideline for recommendations on the correct tests to assess for peripheral arterial disease. The group however felt it was important that caution be recommended when interpreting results as people with diabetes can often have falsely elevated ABPI levels because of calcified arteries.

The GDG produced a risk stratification system almost identical to the SIGN risk stratification criteria with the addition that those on renal replacement therapy should be also treated as high risk. This modification was done by consensus.

4.4.6 Recommendations

13. When examining the feet of a person with diabetes, remove their shoes, socks, bandages and dressings, and examine both feet for evidence of the following risk factors:

- Neuropathy (use a 10 g monofilament as part of a foot sensory examination).
- Limb ischaemia (see the NICE guideline on lower limb peripheral arterial disease).
- Ulceration.
- Callus.
- Infection and/or inflammation.
- Deformity.
- Gangrene.
- Charcot arthropathy.

14. Use ankle brachial pressure index in line with the NICE guideline on lower limb peripheral arterial disease. Interpret results carefully in people with diabetes because calcified arteries may falsely elevate results.

15. Assess the person's current risk of developing a diabetic foot problem or needing an amputation using the following risk stratification:

- Low risk:

- o no risk factors present except callus alone.
- Moderate risk:
  - o deformity or
  - o neuropathy or
  - o non-critical limb ischaemia.
- High risk:
  - o previous ulceration or
  - o previous amputation or
  - o on renal replacement therapy or
  - o neuropathy and non-critical limb ischaemia together or
  - o neuropathy in combination with callus and/or deformity or
  - o non-critical limb ischaemia in combination with callus and/or deformity.
- Active diabetic foot problem:
  - o ulceration or
  - o spreading infection or
  - o critical limb ischaemia or
  - o gangrene or
  - o suspicion of an acute Charcot arthropathy, or an unexplained hot, red, swollen foot with or without pain.

16. **For people who are at low risk of developing a diabetic foot problem, continue to carry out annual foot assessments, emphasise the importance of foot care, and advise them that they could progress to moderate or high risk.**

4.4.7 Research recommendations

No research recommendations were drafted for this review question

4.5 Monitoring those at risk of foot problems

4.5.1 Review Question

How often should people with diabetes who are at risk of developing foot problems be reviewed?

4.5.2 Evidence Review

The aim of this review question was to determine the appropriate review frequency for people with diabetes who are at risk of developing foot problems. This question was previously considered in Clinical Guideline 10 however, no appropriate evidence was identified at that time. The protocol for this review can be found in Appendix C (see review question 5).

The original and rerun searches identified 9738 abstracts, 10 papers were identified. These 10 papers were subsequently excluded because they did not fit the inclusion criteria (see Appendix E for a full list of excluded studies).

Table 18 outlines the PICO framework used for this review question.

Table 18: PICO Framework

Population	Children, young people and adults with type 1 or type 2 diabetes
Intervention	Review schedules of varying frequency
Comparator	Standard care based on risk category
Outcomes	Rates of foot ulceration/ infection
	Rates of gangrene resulting from diabetes
	Rates of amputation (major and minor)
	Rates of foot ulceration, infection and gangrene resulting from diabetes
	Rates of A & E/ hospital admission for foot problems resulting from diabetes
	Resource use and costs
Include	Systematic reviews and randomised controlled trials. If insufficient evidence is available progress to non-randomised controlled trials and cohort studies
Exclude	Studies of children, young people and adults with diabetes and foot problems who are admitted to hospital

4.5.3 Health Economic Evidence

A literature search was conducted for the question using standard health economics filters appplied to the clinical search strategies. No relevant cost-utility analyses were found. Health economic modelling not prioritised for this review question.

4.5.4 Evidence Statements

No evidence was identified for this review.

4.5.5 Evidence to Recommendations

Table 19: Linking evidence to recommendation table

Relative value of different outcomes	This review assessed effects of different frequencies of monitoring on the rates of ulceration, admission, infection, gangrene, minor and major amputation.

	The GDG felt this was reflective of concerns in practice, that the primary outcome that clinicians seek to avoid is the occurrence of ulcer; amputation and death, and that these are preventable secondary outcomes of having an ulcer.
Trade-off between benefits and harms	The GDG considered that benefit from increased frequencies of monitoring was found in those at moderate or high risk of developing diabetic foot problems (see Section 4.3 and 4.14 on protocols). It was also agreed that increasing the frequency of monitoring should increase with each level of risk.
	For the patient, the benefits from increased frequencies of monitoring include more contact with appropriately skilled health care professionals and the increased probability that problems will be prevented and, if problems do occur, that timely, appropriate care will be available.
	For the NHS, the prevention and early treatment of developing foot problems can help avoid unnecessary hospitalisation and the need for longer term management of complications such as infection, gangrene and amputations.
	The harms associated with increased frequency of monitoring include inconvenience to the patient, which may result in dissatisfaction and missed appointments with resulting increases in complications and possible hospitalisation. For the NHS, the resource implications needed to support an increased number of appointments and treatment would need to be considered.
Trade-off between net health benefits and resource use	At the outset of guideline development, the GDG had been keen to review the original economic evidence on the frequency of follow-up. However, having explored the available evidence, they concluded that it was not possible to provide a robust analysis on this question. The difficulties largely related to the problem of defining the natural history of occult foot problems which, by definition, cannot be found in evidence. Furthermore, the absence of any evidence from the clinical review regarding the relative effectiveness of different approaches meant it was not possible to quantify what the benefits and harms of more or less frequent follow-up would be. For these reasons, no original quantitative analysis was presented to the GDG.
	Nevertheless, the GDG was aware of the need to balance resource use and the potential for effective prevention in writing its recommendations. For the NHS, the prevention and early treatment of developing foot problems can help avoid unnecessary hospitalisation and longer term management of complication such as infection, gangrene and amputations. This will also help avoid unnecessary resource use.
	The harms associated with increased frequency of monitoring include inconvenience to the patient, which may result in dissatisfaction and missed appointments with resulting increases in complications and possible hospitalisation. For the NHS, the resource implications needed to support an increased number of appointments and treatment were considered.
	Therefore a careful choice in monitoring frequency was clearly required to achieve the necessary balance.

Quality of evidence	The GDG discussed the only previously included study by Plank et al. This was deemed not to fit the inclusion criteria of the review question since it did not truly compare the value of 2 different frequencies of review, rather comparing monthly chiropodist appointments to no intervention at all. The control group was also permitted to see the chiropodist should they wish to pay for their own therapy. No details were given about the quality of chiropodist care or the care of the control group. As such the paper was excluded and no relevant studies were found for this review question.
Other considerations	Despite the lack of evidence the GDG wanted to make recommendations based on the identified risk of the patient (see section 4.4). These recommendations were made to provide a structure for foot review frequency in patients with diabetes. It was important to give guidance here for the reasons outlined above and so that high risk patients could be reviewed most frequently and low risk patients reviewed least frequently. No evidence was identified for children and young people and a subsequent consensus recommendation was made for this population. The GDG felt it was very important to stipulate that the care of a young person's foot should be done by the appropriate specialist and this specialist should also be the one to perform the yearly assessment. Children under the age of 12 with diabetes were also discussed; it was felt that the risk of foot problems in this group was so low that basic foot care advice would suffice unless a diabetic foot problem were to develop.

4.5.6 Recommendations

17. For children with diabetes who are under 12 years, give them, and their family members or carers (as appropriate), basic foot care advice.

18. For young people with diabetes who are 12–17 years, the paediatric care team or the transitional care team should assess the young person's feet as part of their annual assessment, and provide information about foot care. If a diabetic foot problem is found or suspected, the paediatric care team or the transitional care team should refer the young person to an appropriate specialist.

19. For adults with diabetes, assess their risk of developing a diabetic foot problem at the following times:
- When diabetes is diagnosed, and at least annually thereafter (see recommendation 20).
- If any foot problems arise.
- On any admission to hospital, and if there is any change in their status while they are in hospital.

20. Depending on the person's risk of developing a diabetic foot problem, carry out reassessments at the following intervals:
- Annually for people who are at low risk.

- Frequently (for example, every 3–6 months) for people who are at moderate risk.
- More frequently (for example, every 1–2 months) for people who are at high risk, if there is no immediate concern.
- Very frequently (for example, every 1–2 weeks) for people who are at high risk, if there is immediate concern.

Consider more frequent reassessments for people who are at moderate or high risk, and for people who are unable to check their own feet.

4.5.7 Research recommendations

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?

Why this is important

The evidence surrounding different monitoring frequencies for those at risk of diabetic foot problems was limited. It is proposed that a randomised controlled trial or cohort study is undertaken to explore this question. The proposed study would monitor and evaluate the rates of foot ulcer or infection resulting from diabetes, rates and extent of amputation (major or minor), health-related quality of life, adverse events and hospital admission rates and length of stay as a result of different monitoring frequencies.

4.6 Prevention strategies for those at risk of diabetic foot problems

4.6.1 Review Question

What is the effectiveness of different prevention strategies for people with diabetes at risk of developing foot problems?

4.6.2 Evidence Review

The aim of this review was to determine the effectiveness of strategies to prevent foot problems in people with diabetes.

This includes

• Information, advice and education about self-monitoring and preventing foot problems

• Appropriate footwear, provision of foot orthoses

• Skin and nail care.

The original and rerun searches identified 9738 abstracts 117 were potentially relevant to review question 6 and the full text articles were requested. Following examination of full text papers 23 papers from 22 original randomised controlled trials were found to relevant to the review question and were included in the final review. (Lavery, Lawrence A. (2007), Armstrong, D. G. (2007). Lavery, L. A. (2004), Annersten Gershater, M. (2011), McMurray, S. D. (2002), Bloomgarden, Z. T. (1987), Lincoln, N. B. (2008), Malone, James M. (1989), Litzelman, D. K. (1993), Armstrong, D. G. (2005), LeMaster, J. W. (2008) Cisneros, L. L. (2010), Reiber, G. E. (2002), Lavery, L. A. (2012), Uccioli, L. (1995), Rizzo, L. (2012), Scire, V. (2009), Rönnemaa, T. (1997), Hämäläinen, H. (1998), McCabe, C. J. (1998), Plank, J. (2003), Ulbrecht, J. S. (2014), Bus, S. A. (2013)). The protocol for this review question can be found in Appendix C (see review question 6)

The remaining 94 studies and the reasons for their exclusions are provided in Appendix E.

These papers were extracted for relevant information and were used to fill both the evidence tables and the GRADE profiles. The evidence tables are shown in Appendix F. The GRADE profiles for the included studies can be found in Appendix I.

Table 20 outlines the PICO framework used for this review question.

Table 20: PICO Framework

Population	Children, young people and adults with type 1 or type 2 diabetes.
Intervention	Information, advice and education on self-monitoring Skin and nail care Information, advice and education about foot wear Provision of foot orthoses Provision of skin and nail care treatment Other preventive and management strategies Education for healthcare professionals
Comparator	Standard care
Outcomes	Rates of foot ulceration/ infection Rates of gangrene resulting from diabetes. Rates of amputation (major and minor) Rates of A&E / hospital admission for foot problems resulting from diabetes

	Resource use and costs
Include	Systematic review
	Randomised controlled trials
	If insufficient evidence is available progress to:
	Non-randomised controlled trials
	Cohort study
Exclude	Strategies for management of current foot problems in people with diabetes.
	Strategies for prevention of foot problems in people without diabetes.

Summary of quality and methodological issues

Although many of the interventions listed in this question could be grouped together under terms such as education, the actual method of intervention may vary significantly between papers. The definition of what constitutes the comparator of standard care also potentially varied greatly between studies. For this reason the decision was made not to pool data together to produce a point estimate for most interventions considered. Forest plots, however, were produced to aid discussion and to make the presentation of data clearer during the GDG meeting. The two exceptions to this decision were three papers discussing the use of self-temperature monitoring and two papers comparing the use of pressure customised orthoses to shape customised orthoses. These meta-analyses can be found in appendix H.

None of the included studies reported the outcome of rates of gangrene

Statements of the evidence findings for the outcomes of rates of foot ulceration, infection, amputation, hospital admission and resource use and costs is presented below and the full GRADE profiles in appendix I.

Table 21: Summary table of included studies for prevention strategies for those at risk of developing diabetic foot problems

Author (year)	Study type	Participants	Comparisons	Outcomes of interest	Length of follow up	Study Location
Structured foot examination or temperature monitoring vs standard of care						
Lavery 2007	RCT	Randomised= 173 Standardised therapy group= 58 Structured foot exam group= 56 Enhanced therapy group= 59 Inclusion: Aged 18-80 years History of foot ulceration Diagnosis of diabetes Ability to provide informed consent Ankle brachial index ≥0.70	Standard therapy as below and training to conduct a structured foot inspection twice a day using a mirror and recording findings in a log book with a checklist of elements to be included in self-examination. Or Standard therapy as below and training to use a digital infrared thermometer to measure and record temperatures on each foot. Foot temperature taken over 6 sites and recorded in a logbook. Subjects with amputation were given alternative sites. If the skin temperatures were elevated by >4°F (2.2°C) compared with the corresponding site on the opposite foot for two consecutive days subjects were instructed to contact the research nurse and decrease activity until temperatures normalised. Versus Lower extremity examination by a physician every 8 weeks, regularly scheduled podiatry assessments to see if footwear required replacing or repairing, video education and pedometer provided.	Rates of foot ulceration/infection	15 months	USA

Author (year)	Study type	Participants	Comparisons	Outcomes of interest	Length of follow up	Study Location
Temperature monitoring versus standard care						
Armstrong 2007	RCT	Randomised= 225 Standardised therapy group= 115 Thermometry monitoring group= 106 Inclusion: Aged 18-80 years Southern Arizona VA Health Care System Category 2 or 3 of the International Diabetic Foot Risk Classification System	Participants used an infrared skin thermometer to measure 6 sites on the foot twice a day. Temperature differences greater than 2.2°C between left and right corresponding sites triggered patients to contact the study coordinator and reduce activity until their temperatures normalised. Versus General diabetic foot care was standardised for all participants and included therapeutic footwear, diabetic foot education and regular foot care. All subjects were instructed to perform a structured foot inspection daily and record their findings in a logbook.	Rates of foot ulceration/infection	18 months	USA
Temperature monitoring versus standard care						
Lavery 2004	RCT	Randomised= 85 Standardised therapy group= 41 Thermometry monitoring group= 44 Inclusion: Aged 18-80 years Diagnosis of diabetes Category 2 or 3 of the International Diabetic Foot Risk Classification	Participants used an infrared skin thermometer to measure 6 sites on the foot twice a day. Temperature differences greater than 2.2°C between left and right corresponding sites triggered patients to contact the study coordinator and reduce activity until their temperatures normalised. Versus General diabetic foot care was	Rates of foot ulceration/infection Rates of amputation Rates of A&E/ Hospital admission for foot problems resulting from diabetes	6 months	USA

Author (year)	Study type	Participants	Comparisons	Outcomes of interest	Length of follow up	Study Location
		System	standardised for all participants and included Therapeutic footwear, diabetic foot education and foot evaluation by a podiatrist every 10-12 weeks			
Self-inspection with antifungal nail lacquer versus standard care						
Armstrong 2005	RCT	Randomised= 70 Education group= 34 Standard therapy group= 36 Inclusion: International Diabetes Foot Classification risk category 2 or 3	Preventive foot care program using daily self-inspection with the possible use of antifungal nail lacquer (ciclopirox 8%). All participants received standard therapy. Self-inspection instruction: n=85 Versus Patients were followed every 3 months for 12 months or until ulceration in a multidisciplinary high-risk diabetic foot clinic. Patients were also given contact information for a foot hotline that was staffed 24 hours a day by a clinician familiar with the care and status of these patients. Clinicians could appoint patients into pre-assigned emergency visit slots in each daily clinic schedule..	Rates of foot ulceration/infection	12 months	USA
Education programme versus standard care						
Gershater 2011	RCT	Randomised= 131 Intervention group= 40 Standard therapy group= 58 Inclusion: Previously known	Diabetes specialist nurse lead sessions for 60 minutes in which participants actively participated in discussions. Each participant took part in one of the group sessions. All participants received standard care. Versus	Rates of foot ulceration/infection	6 months	Sweden

Author (year)	Study type	Participants	Comparisons	Outcomes of interest	Length of follow up	Study Location
		diabetes mellitus Signs of sensory neuropathy Aged 35-79 years Healed index ulcer (Wagner grade 1 or more) below the ankle	General diabetic foot care was standardised for all participants and included adjusted shoes and individually fitted insoles for indoor use, and recommended regular chiropody. All patients received standard information provided by a registered nurse working at the foot clinic.			
Education programme vs standard care						
McMurray 2002	RCT	Randomised= 126 Intervention group= 45 Standard therapy group= 38 Inclusion: End stage renal failure requiring renal replacement therapy with either haemodialysis or peritoneal dialysis Diagnosis of type 1 or type 2 diabetes	An education programme followed up by a care manager who provided self-management education, diabetes self-care monitoring/management, motivational coaching and foot checks. Participants also received nutrition counselling with a dietician and follow up reminders from the diabetes case manager. Versus After baseline assessments were completed, the control group had no further contact with the diabetes care manager until end of study evaluations were initiated. They received standard diabetes care from the dialysis facility as directed by the physician. This included monitoring random blood glucose and quarterly HbA1c levels	Rates of amputation Rates of A&E/ Hospital admission for foot problems resulting from diabetes	12 months	USA
Education sessions vs standard care						
Bloomgarden 1987	RCT	Randomised= 749 Education group= 165 Standard therapy	9 education sessions were offered to each patient in the education group. 82 participants in the education group attended at least 7 of these	Rates of foot ulceration/infection	Length of follow up also varied between groups 1.5 ± 0.3 years	USA

Author (year)	Study type	Participants	Comparisons	Outcomes of interest	Length of follow up	Study Location
		group= 180 Inclusion: Insulin treated patients Mount Sinai Medical Center Diabetes Clinic	educational sessions. All participants received standard therapy. Versus Patients had a contact at each visit with their physician and a nurse who reviewed medications and specific problems. Patients in the education group attended 5.7 ± 2.7 clinic visits, those in the control group attended 5.2 ± 2.7 clinic visits during follow up period.		in the control group and 1.6 ± 0.3 years in the in the education group	
Education programme versus standard care						
Lincoln 2008	RCT	Randomised= 172 Education group= 87 Standard therapy group= 85 Inclusion: Patients attending specialist foot clinics in Nottingham and Derby Diabetes mellitus Recently healed ulcers of the foot (on or below the malleoli) Remained ulcer free for 28 days	Footcare education programme with one to one targeted education. A single 1 hour session within 4 weeks of randomisation. All participants received standard therapy. Versus No structured education, many patients were discharged to the care of their general practitioner, with or without input from a community podiatrist. Any education regarding prevention of ulcer recurrence was unstructured and opportunistic. Participants were provided with regular podiatry and suitable orthoses when appropriate. Their overall medical care followed UK guidelines.	Rates of foot ulceration/infection Rates of amputation	12 months	UK
Education programme versus standard care						
Malone 1989	RCT	Randomised= 203 Education group= 90	Foot care education programme including a review of slides of	Rates of foot ulceration/infection	Length of follow up varied	USA

Author (year)	Study type	Participants	Comparisons	Outcomes of interest	Length of follow up	Study Location
		Standard therapy group= 92 Inclusion: Patients referred to either the vascular surgery or podiatry clinic Diabetic Stable patients with uninfected foot ulcers or prior amputation Excluded participants below who had received definitive surgical treatment	infected/amputated limbs and a simple set of instructions for foot care: 1 hour educational session per patient. Standard care. Versus Routine diabetic teaching with respect to diet, weight, exercise and medication. Standard care otherwise unclear.	Rates of amputation	between participants: for Group 1 the range of follow up was 1-26 months, mean 13.2 months; for group 2 the range of follow up was 1-26 months, mean 9.2 months. The study states that overall there was no statistically significant difference in follow up between groups	
Foot care education and practice guidelines versus standard care						
Litzelman 1993	RCT	Randomised= 396 Intervention group= 191 Standard therapy group= 205 Inclusion: Type 2 diabetes Seen at least 2 times in the preceding year by the same provider Aged >40 years Diagnosis of diabetes after 30 years of age Diagnosis of diabetes	The intervention was multifaceted: Patients received foot-care education and entered into a behavioural contract for desired self-foot care, which was reinforced through telephone and postcard reminders. Health care providers were given practice guidelines and informational flow sheets on foot related risk factors for amputation in people with diabetes. In addition, the folders for intervention patients had special identifiers that prompted health care providers to 1) ask that patients remove their foot wear, 2) perform foot examinations and 3) provide foot-care education	Rates of amputation	12 months	USA

Author (year)	Study type	Participants	Comparisons	Outcomes of interest	Length of follow up	Study Location
		based on National Diabetes Data Group criteria Disease requiring medication for the control of hyperglycaemia Intention to obtain care at the general medical practice for the next 2 years Body weight either ideal or heavier than ideal	Versus Unclear definition of usual care			
Education programme and therapeutic footwear vs standard care						
Cisneros 2010	RCT	Randomised= 53 Education group= 30 Standard therapy group= 23 Inclusion: Diabetes mellitus and peripheral neuropathy	Intervention involved therapeutic education with weekly group meetings (4 meetings of 90 minutes in groups of up to 8 participants) and provision of two pairs of special protective shoes. The participants could choose their colour and model. Versus All participants maintained the routine care assistance offered by the unit where the study was conducted. Both groups were monitored by the researcher through foot inspection to survey the incidence and recurrence of neuropathic injury. The control group received instructions on foot care and use of footwear when requested during individual consultations with the researcher. Participants who had	Rates of foot ulceration/infection	24 months	Brazil

Author (year)	Study type	Participants	Comparisons	Outcomes of interest	Length of follow up	Study Location
			neuropathic injuries during the study received medical and nursing care and instructions on how to reduce loads on the affected limb.			
Weight bearing activity programme versus standard of care						
Lemaster 2008	RCT	Randomised= 70 Education group= 34 Standard therapy group= 36 Inclusion: Aged 50 years and over Received diabetes or foot care at primary care, endocrinology, or podiatry practices in central Missouri Inactive (did not engage in moderately intense activity more than twice per week for more than 20 minutes per session Diagnosed type 1 or 2 diabetes mellitus Absent sensation 5.07 Semmes-Weinstein monofilament sensation on at least one of 10 points on the foot and loss of vibratory sensation.	Intervention involved leg strengthening and balance exercises; a graduated, self-monitored walking program followed by motivational telephone calls every 2 weeks apart. Versus Both groups received diabetic foot care education, regular foot care and 8 sessions with a physical therapist. Participants received usual medical care from their own providers. Project staff referred all participants to local orthotists or podiatrists to obtain therapeutic footwear at enrolment	Rates of foot ulceration/infection Rates of amputation Rates of A&E/ Hospital admission for foot problems resulting from diabetes	12 months	USA
Therapeutic shoes and cork inserts or polyurethane inserts versus standard of care						
Reiber 2002	RCT	Randomised= 400 Therapeutic shoes and custom cork inserts=	Participants were randomly assigned to receive 3 pairs of therapeutic shoes and 3 pairs of customised medium-	Rates of foot ulceration/infection Resource use and costs	24 months	USA

Author (year)	Study type	Participants	Comparisons	Outcomes of interest	Length of follow up	Study Location
		121 Therapeutic shoes and prefabricated polyurethane inserts= 119 Usual footwear group=160 Inclusion: Diabetes mellitus Aged 45-84 years Men from either Veterans Affairs Puget Sound health Care System or Group Health Cooperative Women from Group Health Cooperative (there were few female veterans meeting eligibility) History of full thickness foot lesion or foot infection requiring antibiotic treatment Ability to walk 1 block and climb 1 flight of stairs per day Shoe size 8-12.5 for men, 7-10.5 for women Willingness to consent to randomisation and study footwear provisions	density cork inserts with a neoprene closed cell cover. All shoes and inserts in the two treatment groups were fitted by the same study pedorthist who manufactured the custom inserts, performed shoe-fitting adjustments and replaced footwear based on wear patterns. Or Participants were randomly assigned to receive 3 pairs of therapeutic shoes and 3 pairs of prefabricated, tapered polyurethane inserts with a brushed nylon cover. All shoes and inserts in the two treatment groups were fitted by the same study pedorthist who manufactured the custom inserts, performed shoe-fitting adjustments and replaced footwear based on wear patterns. Versus All participants maintained the routine care assistance offered by the health care system they were under. As well as this; four visits occurred within 1 month of enrolment to ensure proper footwear fit in the in the intervention groups. Thereafter, visits were scheduled every 17 weeks to collect information. To prevent contamination of the footwear interventions by patient education or clinical care, no			

Author (year)	Study type	Participants	Comparisons	Outcomes of interest	Length of follow up	Study Location
			participants received such education or care at the study site			
Shear reducing insole versus standard care						
Lavery 2012	RCT	Randomised= 299 Shear reducing insole= 149 Standard therapy group= 150 Inclusion: Diabetes mellitus 18-80 years of age Informed consent History of foot ulceration and/or presence of sensory neuropathy with loss of protective sensation and foot deformity	Standard therapy and shear reducing insole with elastic binders and two thin Teflon sheets. Versus Standard therapy consisted of foot and lower extremity evaluation by a physician every 10-12 weeks, an education program that focused on foot complications and self-care practices, and therapeutic shoes and insoles. If study patients identified an area of concern on their feet they were instructed to contact the study nurse. All patients were provided with the same brand of therapeutic shoes. Insoles were replaced every 4 months and shoes once a year.	Rates of foot ulceration/infection	18 months	USA
Therapeutic shoes with custom mold insoles versus standard therapy						
Uccioli 1995	RCT	Randomised= 69 Therapeutic shoes with custom mold insoles= 33 Standard therapy group= 36 Inclusion: Previous foot ulceration and those considered to be at high risk of foot ulceration	Therapeutic shoes with custom mold insoles Versus Standard therapy consisted of the same educational guidelines on foot care and general information on the importance of appropriate footwear (i.e. proper size, durability, and sole)	Rates of foot ulceration/infection	12 months	Italy

Author (year)	Study type	Participants	Comparisons	Outcomes of interest	Length of follow up	Study Location
Therapeutic shoes and custom made orthosis versus standard care						
Rizzo 2012	RCT	Randomised= 334 Custom made orthesis and shoes = 148 Standard therapy group= 150 Inclusion: Patients with peripheral vascular disease or deformities associated with sensory neuropathy or if previous diabetic foot ulcers or amputations. (International Consensus on Diabetic Foot risk category 2 and 3.)	Custom made orthesis and shoes and standard therapy Versus Standard therapy consisted of in-depth education on how to prevent ulceration and advice to use comfortable shoes with non-traumatizing characteristics. A list of suitable shoes was delivered to patients and their features were discussed to be sure that patients would understand properly. In case of new diabetic foot ulcer, patients of both groups were requested to refer to our clinic for an urgent consultation within 24 hours, otherwise patients were seen quarterly for 12 months for assessment of feet and footwear condition.	Rates of foot ulceration/infection Resource use and costs	Length of follow up was 12 months, 3 years and 5 years	Italy
Silicone padding offloading versus standard therapy						
Scire 2009	RCT	Randomised= 167 Digital offloading silicone padding = 89 Standard therapy group= 78 Inclusion: Aged older than 18 years Diagnosis with diabetes mellitus for at least 5 years Peripheral neuropathy	Digital offloading silicone padding and standard therapy Versus Standard therapy consisted of clinical examination to find and treat areas of hyperkeratosis using mechanical keratolysis. Patients were then prescribed an accommodating soft insole and extra deep shoe. The study states participants in this group were not fitted with orthotic protection but it	Rates of foot ulceration/infection	3 months	Italy

Author (year)	Study type	Participants	Comparisons	Outcomes of interest	Length of follow up	Study Location
		and deformity or preulcerative conditions of the forefoot	is presumed that they did receive the accommodating soft insole and extra deep shoe.			
Plantar Pressure-based In-Shoe Orthoses compared to Shape-based In-Shoe Orthoses						
Ulbrecht 2014	RCT	Randomised= 130 Pressure customised footwear= 66 Shape customised footwear= 64 Inclusion: Men and women ≥18 years of age Diabetes and loss of protective sensation (inability to feel the 10-g monofilament at one or more sites) At least one recently healed foot ulcer (>1 week but < 4 months) Plantar MTH-related foot ulcer Peak barefoot plantar pressure in the area of this previous ulcer >450 kPa Community ambulatory No current ulcer below the malleoli Partial foot amputation of no greater than two MTHs or rays per foot Ability to comply with protocol	Orthoses initially designed to be similar to shape only insole and then modified using a computer-aided design process according to defined algorithms based on the peak barefoot plantar pressure distribution contours. In all cases subjects received three pairs of identical orthoses to be rotated while using the primary study footwear according to a written rotation protocol. Patients received education and motivation to encourage adherence Versus Foot shape obtained using foam boxes and sent to the manufacturer of the control insoles, no plantar pressure based adjustments made. In all cases subjects received three pairs of identical orthoses to be rotated while using the primary study footwear according to a written rotation protocol. Patients received education and motivation to encourage adherence.	Ulceration	15 months	USA

Author (year)	Study type	Participants	Comparisons	Outcomes of interest	Length of follow up	Study Location
Plantar Pressure-based In-Shoe Orthoses compared to Shape-based In-Shoe Orthoses						
Bus 2013	RCT	Randomised= 171 Pressure customised footwear= 85 Shape customised footwear= 86 Inclusion: ≥18 years of age Confirmed type 1 or type 2 diabetes Loss of protective foot sensation as a result of peripheral neuropathy A healed plantar foot ulcer (in the 18 months preceding randomisation A new prescription of custom-made footwear	Custom-made footwear of which the offloading properties were improved and subsequently preserved based on inshoe plantar pressure measurement and analysis Versus Custom-made footwear that did not undergo improvement based on in-shoe pressure measurement i.e usual care	Ulceration	18 months	Netherlands
Education and primary prevention measures under podiatric care versus standard care						
Ronnemaa 1997	RCT	Randomised= 530 Referral to podiatrist = 267 Written instructions= 263 Inclusion: Type 1 and type 2 diabetes	Standard therapy otherwise unclear. Podiatric care group: education and primary prevention measures. Patients were visited by a podiatrist during the 12 month period after the baseline examination as many times as judged appropriate by the podiatrist. Education was given individually to every patient, taking into account each patient's age, occupation, earlier foot care habits. The first visit lasted 45 minutes and focused mainly on education including proper use of footwear, hygiene, toenail cutting, emollient cream, foot exercises and	Rates of foot ulceration/infection Rates of amputation	7 years	Finland

Author (year)	Study type	Participants	Comparisons	Outcomes of interest	Length of follow up	Study Location
			avoidance of high risk situations. In addition certain preventive measures were available, including preparation of individual insoles, treatment for ingrown toenails and gentle trimming of callosities provided free of charge. Versus Standard therapy otherwise unclear			
Monthly Chiropody vs standard care						
Plank 2003	RCT	Total number of participants: Out of 93 eligible participants, 91 adult patients receiving routine outpatient care at a diabetic foot clinic were randomised (after their foot ulcer had healed) to receive either routine chiropodist care at least once a month or to a control group where chiropodist care was not specifically recommended. 47 patients were randomised to the intervention group; 44 patients were randomised to the control group. Inclusion criteria: All patients had type 1	Patients in the intervention group were asked to see a chiropodist at least once a month. The cost was remuneration free. Versus Patients in the control group were not specifically recommended to see a chiropodist, although, they could choose to visit a chiropodist if they wished to and they were required to pay for their attendance.	Ulceration Amputation Death	12 months	Austria

Author (year)	Study type	Participants	Comparisons	Outcomes of interest	Length of follow up	Study Location
		or type 2 diabetes and neuropathy.				
Primary and secondary screening programme followed by foot protection programme versus no special care						
McCabe 2009	RCT	Randomised= 2001 Screening and foot protection programme = 1001 Control group= 1000 Inclusion: Diabetic patients at a diabetic specialist clinic	Standard therapy as below if not high risk patient. All in the intervention group received primary foot screening examination using Semmes-Weinstein monofilaments, biothesiometer and palpation of pedal pulses. Patients found to have a significant deficit in any of these areas were given an appointment for a second examination which repeated the above tests and also calculated ankle brachial pressure index, subcutaneous oxygen levels, foot pressure and x-rays were taken. Patients with foot deformities, or a history of foot ulceration or an ankle brachial pressure index of ≤0.75 were judged to be high risk of ulceration and were entered into the foot protection programme. The foot protection programme provided chiropody, hygiene maintenance, support hosiery, and protective shoes for patients in the high risk category. Clinic was weekly and patients received advice and were allowed to contact the clinic whenever they felt necessary. Versus The control group consisted of 1000 patients who were silently tagged and	Rates of foot ulceration/infection Rates of amputation Resource use and costs	2 years	UK

Author (year)	Study type	Participants	Comparisons	Outcomes of interest	Length of follow up	Study Location
			continued to attend the general out-patients clinic but received no special care.			

4.6.3 Health Economic Evidence

4.6.3.1 Systematic review of published cost–utililty analyses

A literature search was conducted to find any existing cost-utility analyses (CUAs) of prevention of diabetic foot problems. (see appendix D for details of the search strategies). Three studies were found; one from Sweden, one based on a Dutch cohort and the other from Austria. Ragnarson-Tenvall (2001) used Swedish diabetic registry data to simulate a cohort of 10,000 patients with diabetes mellitus. The interventions considered were the provision of orthotic footwear, podiatry, and patient education. Ortegon (2004) modelled a cohort of Dutch patients and the impact of optimal foot care described in national clinical guidelines as incorporating professional protective foot care, education of patients and staff, regular inspection of the feet, identification of the high-risk patient, treatment of nonulcerative lesions, and a multidisciplinary approach to established foot ulcers. In addition to, and separately from, these interventions the impact of improving patients' glycaemic control was evaluated. A CUA by Rauner (2005) used the same model as described by Ragnarson-Tenvall (2001) using costs specific to the Austrian population. All of these CUA studies used the International Working Group on the Diabetic Foot classification to describe a patient's risk of ulceration, and used Markov modelling approaches.

There are commonalities in the limitations of these studies, including a lack of precise information on the parameterisation of the effectiveness of interventions, and instead using an exploratory approach instead which examined the threshold of effectiveness (in terms of ulcers and amputations avoided, and associated QALY's saved) at which these interventions become cost effective. These analyses were also single foot models, which terminated after the first occurrence of a major amputation. Given these limitations, the GDG felt it was difficut to translate their findings into an NHS setting and that a de-novo economic model should be built to address this evidence gap.

These studies are summarised in the evidence tables in appendix F

4.6.3.2 Original health economic analysis– methods

This question, along with review questions (RQ) 4 & 5, was prioritised by the GDG for de-novo health economic analysis. However, owing to the lack of suitable clinical studies from which to parameterise a model only RQ 6 could be addressed directly. By incorporating risk stratification into the model, the analysis does indirectly address the utility of risk assessment (RQ 4) as a means of effectively targeting interventions. Of the prevention strategies identified in the review protocol, only evidence that showed the effectiveness of bespoke orthoses and insoles (and education on using them) was found and considered suitable for parameterising the model. This economic evaluation therefore aimed to assess the cost effectiveness of providing custom orthotic footwear (shoes and inserts, and education on the importance of using them) to patients at low, moderate and high risk of developing foot ulcers.

A full description of the model is given in Appendix J, a summary is presented here. The model was developed in line with the NICE reference case (National Institute for Health and Care Excellence 2013). A Markov model was developed that runs on a monthly cycle length for the remaining life expectancy of a cohort of patients with a mean age of 60 years. A life expectancy time horizon was chosen because the patients receiving orthotic shoes and inserts will require a new set each year for the rest of their lifetime, and will therefore accrue costs and benefits for that time. A monthly cycle was considered appropriately short to capture the important pathological changes in diabetic feet whilst remaining computationally manageable, and was selected following consultation with the GDG. Costs associated with the provision of orthotic shoes and inserts are attached to the intervention arms as per the four scenarios considered. Quality of life decrements and costs are associated with

ulceration and amputation states. These costs were sourced from standard NHS tarrifs, the PSSRU and from relevant literature where standard sources were not suitable. Both costs and benefits are discounted at 3.5% per year as per the NICE reference case. A schematic representation of the model is given in Figure 1.
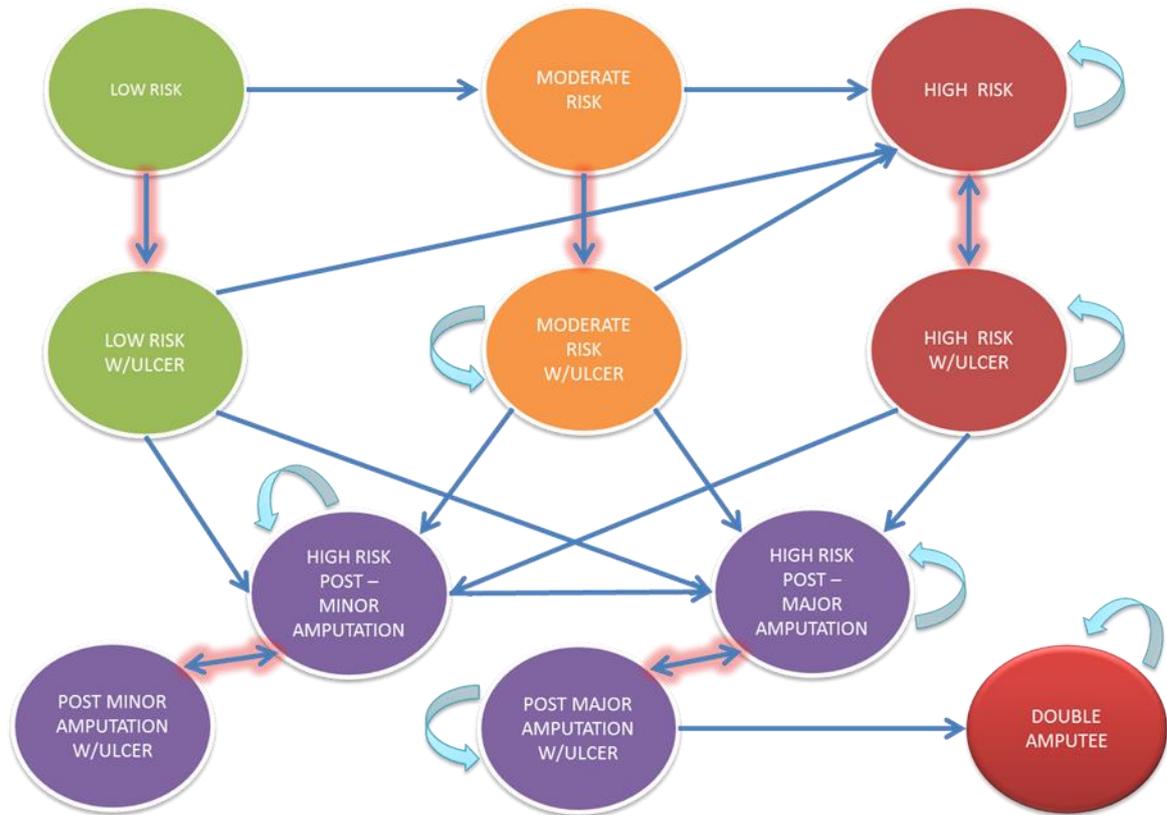
Figure 1 Simplified diagram of the de-novo Markov model- highlighted arrows indicate transitions affected by the intervention

Where possible, model parameters were sourced from the included clinical studies. We used the point estimates of effects taken from the Rizzo (2012) and Uccioli (1995) studies to parameterise the effectiveness of bepoke orthoses, insoles and education. We also modelled another scenario where less effective "off-the-shelf" orthoses and inserts with education were considered, using the pooled effects estimate that included the Rieber (2002) and Cisernos (2010) analyses.

There are few EQ-5D-based utility values for diabetic foot, but one paper by Redekop et al (2010) provided utility values for each of the disease states used in our model.

The health economic model has a number of limitations that should be considered. The model assumes that all patients receive a risk assessment, whereas in practice some patients will not receive any screening and will present with an active foot problem. The model also uses an average cost of ulceration for patients at different risk levels. Ulcers are complex events which will have wide ranging costs associated with them, but in the absence of more detailed data a micro-costing is not possible. We also assume that risk elevation occurs because patients develop symptoms which are only a small subset of those characteristics outlined by Leese (2006) which constitute a given risk level. A more complex analysis would require an individual patient model approach and currently data limitations preclude this.

4.6.3.3 Original health economic analysis – results

In the base case, providing bespoke footwear and inserts (and education on the importance of using them) to high-risk patients is cost saving. The scenario in which the intervention is given to moderate- and high-risk patients generates additional QALYs at additional cost, leading to an ICER of £13,818 per QALY. The model suggests that the provision of such footwear to all patients, including those at low risk of ulceration, generates a small average incremental QALY gain; however, this comes at substantial cost, producing an ICER of over £150,000 per QALY.

Table 22 Cost-effectiveness results for the provision of bespoke shoes, orthotic inserts and education on their use

Treatment	Absolute		Incremental			Net monetary benefit	
	Costs (£)	Effects (QALYs)	Costs (£)	Effects (QALYs)	ICER (£/QALY)	£20K/QALY	£30K/QALY
High risk only	£4055.23	9.77				£191,304	£289,044
No bespoke orthoses	£4677.53	9.72	£622.30	-0.05	dominated	£189,632	£286,922
Moderate and high risk	£5486.33	9.87	£1431.10	0.10	£13,818.75	£191,944	£290,613
Low, moderate and high risk	£8543.73	9.89	£3057.40	0.02	£151,823.78	£189,290	£288,156

In the scenario analysis in which the effects of providing 'off-the-shelf' footwear and inserts (and education on the importance of using them) were explored, results were less favourable. The ICER for the scenario in which the intervention is given to high-risk patients is just below the WTP threshold of £20,000 per QALY, and the ICER for high- & moderate-risk patients is slightly greater than £20,000 per QALY (moderate- and high-risk ICER = £20,740). This uncertainty is reflected in the sensitivity analysis, with bespoke orthoses having an 75% probability of being cost effective when QALYs are assumed to be worth £20,000 each, compared with 40% for the off-the-shelf alternatives. If the threshold is raised to £30,000 per QALY, off-the-shelf orthoses have a 65% chance of being cost effective. Deterministic sensitivity analysis suggests that these findings are driven primarily by the cost and effects of the interventions themselves (that is, the cost of the footwear and its relative effectiveness in reducing ulcers, compared with standard care alone).

Table 23 Cost-effectiveness results for the provision of "off-the-shelf" shoes, orthotic inserts and education on their use

Treatment	Absolute		Incremental			Net monetary benefit	
	Costs (£)	Effects (QALYs)	Costs (£)	Effects (QALYs)	ICER (£/QALY)	£20K/QALY	£30K/QALY
No orthoses	£4677.53	9.72				£189,632	£286,922
High risk only	£5411.49	9.75	£733.96	0.04	£19,371.63	£189,655	£287,088
Moderate and high risk	£7008.19	9.83	£1596.70	0.08	£20,740.53	£189,598	£288,007
Low, moderate and high risk	£10060.93	9.85	£3052.74	0.02	£200,176.66	£186,851	£285,552

4.6.4 Evidence Statements

Ulceration

This review found a significant benefit in terms of ulceration rate for the following interventions when compared to standard care:

- infrared temperature monitoring at home (moderate quality evidence from 2 studies including 398 participants)
- pressure customised footwear for patients with previous ulceration and neuropathy (low quality evidence from 1 study including 130 participants)
- therapeutic shoes with a custom mould insert (very low quality evidence from 1 study including 69 participants)
- custom made orthoses and therapeutic shoes (low quality evidence from 1 study including 334 participants).
- orthotic silicone padding (low quality evidence from 1 study including 167 participants).

This review found no significant difference in ulceration rate for the following interventions when compared to standard care

- education (very low to low quality evidence from 3 studies including 1052 participants)
- augmented foot examination (very low quality evidence from 2 studies including 184 participants).
- weight bearing activity (low quality evidence from 1 study including 70 participants)
- education combined with protective footwear (very low quality evidence from 1 study including 53 participants)
- footwear and a customised cork insert (very low quality evidence from 1 study including 400 participants)
- pressure customised footwear for patients with previous ulceration and neuropathy. (very low quality evidence from 1 study including 171 participants)
- footwear and customised cork insert or footwear and polyurethane insert (Low quality evidence from 1 study including 400 participants)
- shear reducing insole (low quality evidence from 1 study including 299 participants)

Very low quality evidence from 1 study and low quality evidence from 1 study including 91 participants found no significant difference between those participants who received free of charge monthly chiropody care and those who did not for the outcomes of ulceration and amputation.

Amputation

This review found very low quality evidence from 1 study including 2001 participants which found a significant difference between those who received orthotic silicone padding compared to those who received standard care for the outcome of amputation.

This review found conflicting evidence from 3 studies including 501 participants found in terms of amputation rate for those who received education compared to those who received standard care when compared to standard care: The quality of the evidence was low.

This review found no significant difference in amputation rate for the following interventions when compared to standard care

- Infrared temperature monitoring at home (very low quality evidence from 1 study including 85 participants)
- physician and participant education (very low quality evidence from 1 study including 396 participants)

- weight bearing activity (low quality evidence from 1 study including 70 participants)

Infection

Very low quality evidence from 1 study including 203 participants found no significant difference in infection rates between those who received education compared to those who received standard care for the outcome of infection per limb.

Hospitalisation

Low quality evidence from 1 study including 126 participants found a significant difference in hospitalisation rates between those who received education compared to those who received standard care.

Low quality evidence from 1 study including 70 participants found no significant difference in hospitalisation rates between those who received weight bearing activity compared to those who received standard care.

Health economics

2 CUA studies with potentially serious limitations (Ragnarson-Tenvall, 2001 and Rauner, 2005) suggest that prevention programs consisting of education, orthoses provision and access to podiatry and foot care are cost effective and potentially cost saving when they reduce ulceration and LEA rates by at least 25% in higher risk patient groups. This study suggests that these interventions are not cost effective for patients at low risk of ulceration and/or LEA. One CUA study with potentially serious limitations suggests that similar interventions are cost-effective, and the addition of improved glycaemic control is cost-effective when ulceration and LEA rates are reduced by 10% or more, although the exact relationship between rates of ulceration and rates of LEA (which is extrapolated in this study) is uncertain.

A directly applicable health economic model with minor limitations suggests that providing patients who are at moderate & high risk of ulceration with bespoke orthotic footwear is cost effective. Providing high risk patients with this intervention is cost saving. In the base case analysis, off-the-shelf orthoses were not cost effective at a threshold of £20,000 per QALY. The model was shown to be sensitive to the effect estimates and the cost of the intervention, with high cost orthoses only considered cost effective for use in high risk patients.

4.6.5 Evidence to Recommendations

Table 24: Linking evidence to recommendations table

Relative value of different outcomes	This review assessed the effects of different prevention strategies on the rates of ulceration, admission, infection, gangrene, minor and major amputation.
	The GDG felt this was reflective of concerns in practice, that the primary outcome that clinicians seek to avoid is the occurrence of ulcer; amputation and death which are preventable secondary outcomes of having developed an ulcer.
	It was noted that the majority of studies reported the outcomes of ulceration, whereas rates of hospital admissions, infections, gangrene and the use of resources were less widely reported. Rates of amputation were reported in some studies but the extent of amputation was not always reported.
Trade-off between benefits and harms	The GDG felt that there are 3 aims of a good, preventative treatment strategy. Firstly, preventative treatment should stop

diabetic foot problems developing. The most important problem to prevent is ulceration, because preventing the development of a foot ulcer also prevents the development of further, more severe complications, such as infection, gangrene and amputation. Secondly, any strategy should be safe and do no harm. Thirdly, it should be easy and simple to implement into everyday clinical practice.

Potential harm as a result of offering preventative therapy could be a direct adverse effect that develops as a result of using the preventative strategy. There may be a negative impact if NHS resources are used inappropriately to offer preventive therapy to patients at low risk of developing foot problems. Giving preventative treatment to low risk patients may make them feel that they are being treated unnecessarily, which in turn could lead them to becoming disenfranchised with the foot protection services, resulting in poor motivation and adherence in general. A poorly motivated patient may allow their disease to go unmanaged or poorly controlled, which could lead to an increased likelihood of the development of diabetic foot complications such as ulceration. This may, in turn, lead to increased rates of infection, gangrene, amputation, hospital admission with resulting high resource use and costs.

Economic considerations	The GDG remarked that it was difficult to translate the health economic literature evidence presented for this question into the NHS context, and that therefore an original health economic analysis was appropriate.
	The only aspect of preventative care for which sufficient evidence was available for original modelling was the provision of orthotic footwear. The GDG was convinced by the finding that providing bespoke orthotic footwear to people at highest risk of ulceration is very likely to be cost effective and may even result in net cost savings.
	The GDG noted that the effectiveness of orthotics was modelled as the capacity to reduce ulceration rates, and further recognised that this estimate was quantified using RCTs that had been performed in relatively high-risk population (this was clear from the high frequency of ulcers in the control arms of the trials). The absolute probability of ulceration in people at lower risk would be much lower, and the model reflected this. However, it is also possible that the relative effectiveness of orthotic footwear in lower-risk populations would also be diminished, because the risk factors that bespoke footwear can directly mitigate (especially deformity) will be less prevalent. If this were true, then the model would somewhat overestimate the value of providing the intervention to people at low and medium risk of ulceration.
	For this reason, the GDG was convinced by the finding that providing bespoke orthotic footwear to people who have a high risk of ulceration is likely to be cost-saving, but was hesitant about recommending that everyone at medium risk should also receive the intervention. Instead, the GDG chose to emphasise that all people at medium and high risk should receive biomechanical assessment with a view to providing orthotic footwear if appropriate. The group thought that, especially when it comes to people at medium risk of ulceration, this

	recommendation would result in the intervention being targeted at people who have the greatest capacity to benefit (for example, those with deformity). The GDG remarked that the costs presented in the model were appropriate, but commented that the evidence included for "off-the-shelf" orthotic footwear potentially included materials that are not commonly used in NHS practice on effectiveness grounds, such as cork insoles.
Quality of evidence	Regarding foot wear, the GDG made the point that there are good insoles and poor insoles. The study by Reiber et al was noted to have been heavily criticised due to the inadequacy of the insoles provided for its participants and the study was downgraded in quality due to the limited information provided. Regarding the 2 papers on podiatry and chiropody care; there were quality issues with both of the evidence papers. Notably 1 of the studies only included participants that would normally not require podiatry care. This resulted in extremely low event rates in both the intervention and control groups, making it difficult to draw any conclusions from the evidence provided. The other study also allowed its control group to access chiropodist care if they were willing to pay.
Other considerations	The GDG reviewed the evidence for education as a preventive strategy. The point was made that, in many of these studies, the standard of care and the standard of education used in the control group was better than would often be seen in normal practice. As such, the offering of an educational programme on top of what was already good care meant that the true benefit of education that the GDG would expect to see (from their experience in clinical practice) was not made clear. The GDG also considered that the RCT may have an element of self-selection in that those who are motivated to enter a research study may also be motivated to adhere to instructions received, even if they were in the control group. This may also explain the lack of benefit demonstrated in these studies. The GDG wanted to stress that good education for patients is universally regarded as a key component of diabetes care in general, and were concerned that the evidence statement presented may be misleading in this regard. They were eager that the evidence statements should reflect the good standard of education that is expected for all patients. For the above reasons, 2 recommendations were made to emphasise the importance of education in this patient group. Since no evidence was presented for the specific prevention strategies in young people and children, a consensus recommendation was made for this population group to encourage education of not only the patient but also any responsible carers. In examining evidence for the provision of footwear, insoles, and orthoses, the GDG felt that 'footwear' was too broad a term to use and that the important aspect of treatment is how well customised the orthosis was to the patients feet. With insoles the GDG made the point that insoles vary in quality and that the evidence summaries should not therefore be too simplified. It was noted that the use of orthotic treatment proved effective in the studies that included high risk participants therefore the

recommendations should reflect the population's risk.

While temperature foot monitoring was found to be the only effective form of augmented self-examination, the intervention tool was felt to be quite difficult to use and required a strongly motivated population to actually perform consistently and fill out the required log books.

The 2 studies that examined the provision of free-of-charge podiatry care found no significant differences between comparison groups. The point was made that many of the other studies actually included treatment that would normally be carried out by a podiatrist as part of their standard of care anyway. Also in 1 of the studies, patients in the control group could access podiatry care if they were willing to pay for it. Having examined the papers closely the GDG felt that the lack of effect reflected a scarcity of evidence and not evidence of lack of effect.

Based on the clear differences between higher and lower risk diabetic foot populations the GDG split the recommendations by risk category using the SIGN criteria agreed on in a previous review for this guideline (see section 4.4). The type of preventive management and treatment recommended was dependent upon their risk of developing complications.

The GDG discussed the evidence from 2 studies that looked at the use of 2 different kinds of bespoke footwear. One group customised its shoes based on shape and the other used more complex pressure-based algorithms to design the shoe. The papers were so similar that data was pooled and a non-significant finding was the result. The GDG discussed how this was likely due to both the shape and pressure customised groups receiving a high standard of care (both bespoke). The positive finding in one of the papers may have been due to the smaller number of participants.

GDG believed that the evidence shows the provision of footwear should be based on the risk of the patient and that footwear and inlays should be properly customised (bespoke). For this reason patients should be triaged through the foot protection service, which can both assess risk and provide referral to orthotic teams to provide a high quality preventative treatment where appropriate.

4.6.6   Recommendations

21. **For people at moderate or high risk of developing a diabetic foot problem, the foot protection service should:**

   - Assess the feet.
   - Give advice about, and provide, skin and nail care of the feet.
   - Assess the biomechanical status of the feet, including the need to provide specialist footwear and orthoses.
   - Assess the vascular status of the lower limbs.

- Liaise with other healthcare professionals, for example, the person's GP, about the person's diabetes management and risk of cardiovascular disease.

22. **Provide information and clear explanations to people with diabetes and/or their family members or carers (as appropriate) when diabetes is diagnosed, during assessments, and if problems arise. Information should be oral and written, and include the following:**

   - Basic foot care advice and the importance of foot care.
   - Foot emergencies and who to contact.
   - Footwear advice.
   - The person's current individual risk of developing a foot problem.
   - Information about diabetes and the importance of blood glucose control (also see recommendation 23).

23. **For guidance on education programmes and information about diabetes, see the education and information section in 'Type 1 diabetes in adults: diagnosis and management' (NICE guideline NG17), the patient education section in 'Type 2 diabetes in adults: management'[b] and the sections education and information for children and young people with type 1 diabetes and education and information for children and young people with type 2 diabetes in 'Diabetes (type 1 and type 2) in children and young people: diagnosis and management' (NICE guideline NG18).**

24. **People in hospital who are at moderate or high risk of developing a diabetic foot problem should be given a pressure redistribution device to offload heel pressure. On discharge they should be referred or notified to the foot protection service.**

4.6.7 Research recommendations

What is the role of educational models and psycho-behavioural interventions in prevention of diabetic foot complications?

Why this is important

The evidence surrounding the role of educational measures for those at risk of diabetic foot problems was limited and inconclusive. It is proposed that new interventions are developed that target psychological and behavioural factors. The proposed study would monitor and evaluate the rates (and recurrent rates) of foot ulceration, infection and gangrene resulting from diabetes, rates and extent of amputation, rates of hospital admission for foot problems resulting from diabetes, length of hospital stay, and resource use and cost as a result of applying these interventions.

What is the effectiveness of different footwear, insoles and orthoses in the prevention of further foot problems?

Why this is important

The evidence surrounding the role of different kinds of footwear, insoles and orthoses for those at risk of diabetic foot problems was limited. It is proposed that a randomised control trial is undertaken to explore these questions. The proposed study would monitor and evaluate the rates (and recurrent rates) of foot ulceration, infection and gangrene resulting

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[b] The link to the education section of the NICE guideline Type 2 diabetes in adults: management will be updated when the guideline is published later in 2015.

from diabetes, rates and extent of amputation, rates of emergency and hospital admission for foot problems resulting from diabetes, , and resource use and cost as a result of applying the above preventative therapies to these patients.

4.7 Tools for assessing and diagnosing foot problems

4.7.1 Review Question

What are the clinical utilities and accuracy of tools for assessing and diagnosing:

- foot ulcers (including severity)
- soft tissue infections
- osteomyelitis
- gangrene?

4.7.2 Evidence Review

The aim of this review was to assess the different systems for classifying the severity of diabetic foot ulcers and tests to diagnose co-existing soft tissue infections, osteomyelitis and gangrene. The protocol for this review can be found in Appendix C (see review question 7).

Elements of this question were previously addressed by NICE clinical guideline 119 (CG119) which focussed on the diagnosis of soft tissue infection, osteomyelitis and gangrene in people admitted to hospital with diabetic foot ulcer. These areas were updated in this review. This review question also extends the focus to include tools to classify the severity of ulcers according to risk of complications (including amputation) in any setting.

The original and rerun searches identified 9738 abstracts sifted on title and preliminarily identified 244 papers. Included and excluded lists in the appendices for CG119 were cross checked to make sure that nothing had been missed, as a result one study which was conducted in primary care settings was subsequently included. Following examination of abstracts, 91 papers were read in full and 57 new papers were included; 15 on classification systems and 42 on diagnostic tests for soft tissue infection, osteomyelitis and gangrene. (Abbas,Z.G. (2008), Alvaro-Afonso,F.J. (2013), Armstrong, DG, (1998), Asli,I.N. (2011), Beckert,S. (2009), Beckert,S. (2006), Bernard,L. (2011), Elamurugan,T.P. (2011), Erdman,W.A. (2012), Garcia,Morales E. (2011), Gul,A. (2006), Heiba,S.I. (2010), Ince, P. (2008), Kagna,O. (2012), Lavery,L.A. (2007), Lavery,L.A. (2007), Meyr,A.J. (2011), Morales,Lozano R. (2010), Mutluoglu,M. (2012), Mutluoglu,M. (2012), Nawaz,A. (2010), Oyibo,S.O. (2001), Parisi,M.C. (2008), Saeed,S. (2013), Treece,K.A. (2004), Michail, M. (2013), Wang, A. (2014), Won, S. H. (2014), Tsai, C. Y. (2013), Wukich, D. K. (2013) Al-Khawari HA, (2005), Beltran J, (1990), Croll SD, (1996), Devillers A, (1998), Ertugrul BM, (2009), Ertugrul MB, (2006), Grayson ML, (1995), Harwood SJ, (1999), Harvey, J (1997), Kaleta JL, (2001) ,Keenan AM, (1989) ,Larcos G, (1991), Levine SE, (1994), Malabu UH, (2007), Morrison WB, (1995) ,Newman LG, (1991) ,Newman LG, (1992) ,Palestro CJ, (2003) ,Poirier JY, (2002) ,Remedios D, (1998) ,Rozzanigo U, (2009) ,Rubello D, (2004) ,Shone A, (2006) ,Slater RA, (2004) ,Wang A, (1990) ,Weinstein D (1993) ,Yuh WTC, (1989))

Details of studies excluded on abstract or full text in the update review are available in Appendix E.

Table 25 outlines the PICO framework used. Table 26 describes the various types of classification tools evaluated in the included studies. Table 27 and Table 28, Table 29, Table 30, Table 31 and Table 32 contain the summary details of the included studies.

Full evidence tables and GRADE profiles are available in Appendix F and Appendix I respectively. Forest plots and ROC analyses are in Appendix H.

For tests to assess peripheral arterial disease (including assessing foot pulse and ankle brachial pressure index) in people with diabetes, see NICE clinical guideline 147. No studies were found in this review on tests to diagnose gangrene in the feet of people with diabetes.

Modified-GRADE approach

For included studies on classification tools for the severity of diabetic foot ulcer, the QUIP checklist (The Guideline Manual 2012) was used to appraise the quality of the evidence. The criteria of QUIP checklist were incorporated into the modified-GRADE framework to allow consistency of presentation of the guideline. Key criteria used for assessing the quality of evidence, for example, included study design (prospective or retrospective study), whether the PICO of the included study directly addressed the review protocol, whether the analysis was adjusted for baseline characteristics or any confounder, and other factors that may reduce the certainty of the effect estimates.

For included studies on diagnostic tests for soft tissue infection and osteomyelitis, the QUADAS-2 checklist (http://www.bris.ac.uk/quadas/quadas-2/ and The Guideline Manual 2012) was used to appraise the quality of the evidence. The criteria of QUADAS-2 checklist were incorporated into the modified-GRADE framework to allow consistency of presentation of the guideline. Key criteria used from the QUADAS-2 checklist were, for example, patient selection (prospective and consecutive), blinding (interpretation between the index test and reference standard), appropriate reference standard used, flow and timing between the index test and reference standard, lost-to follow-up, and other factors that may reduce the certainty of the estimated accuracy.

Summary of quality and methodological issues

For systems that classified the severity of diabetic foot ulcers, 15 studies were included that covered 9 different severity classification systems (see Table 26).

The majority of the included studies were of low or very low quality due to methodological issues such as:

- Study design (retrospective cohort study)
- Baseline characteristics of study sample or potential confounder were not adjusted in the analysis
- Small sample size
- Incomplete data analysis or loss to follow up
- And others

For the diagnostic test accuracy of different tests for soft tissue infection, osteomyelitis and gangrene, there were 42 included studies in total. None of the 42 included studies were on the diagnosis of gangrene (see Table 28).

Most of the included studies were of low or very low quality. A decision not to conduct a meta-analysis for this review question was made due to the methodological issues such as:

- Patient selection (unclear study sample was recruited consecutively or not in most included studies)
- Lack of blinding in most studies (between index test and reference standard)
- Small sample size (particularly in tests with only one included study)
- Variability of the prevalence of the study sample among included studies (with no information on the prevalence of the actual population of interest)
- Variability of reference standards being used (between included studies as well as within individual included studies)

Although a 'point summary' (or pooled estimate) was not produced for this review question, a summary of ROC (without pooled estimates) was provided where appropriate as a visual guide to aid discussion, but not as a sole decision tool for recommendations.

4.7.2.1.1 *Table 25: PICO framework*

Population	People with diabetic foot ulcer in any setting
Intervention	Ulcer classification tools and tests for diagnosing soft tissue infection, osteomyelitis and gangrene
Comparator	Classification tool: Clinical follow up Soft tissue infection: deep tissue biopsy Osteomyelitis: bone biopsy or imaging Dry gangrene; clinical judgement Wet gangrene: culture or clinical judgement
Outcome	Ulcer healing Amputation Mortality Hospitalisation Diagnostic accuracy Inter and intra reliability
Inclusion	Test and treat RCT, cohort or case-control studies Cross sectional studies were included for studies on diagnostic tests
Exclusion	Case series Papers reporting derivation of classification tools or diagnostic tests

4.7.2.1.2   *Table 26:   Description of identified classification tools*

The table below describes the various classification tools identified in the review:

System	Description
Wagner	Based on depth or penetration of ulcer and presence gangrene: Grade 0 Pre- or post-ulcerative site Grade 1 Superficial ulcer Grade 2 Ulcer penetrating to tendon or joint capsule Grade 3 Lesion involving deeper tissues Grade 4 Forefoot gangrene Grade 5 Whole foot gangrene involving more than two-thirds of the foot
University of Texas	Based on depth of ulcer as well as presence of soft tissue infection and ischemia. Grade 0 Pre- or post-ulcerative site Grade 1 Superficial wound not involving tendon, capsule or bone Grade 2 Wound penetrating to tendon or capsule Grade 3 Ulcer penetrating to bone or joint Stage A Lesion without infection or ischemia Stage B Infected / non-ischemic lesion Stage C Ischemic non-infected lesion Stage D Ischemic infected lesion

S(AD) SAD — Scored on ulcer size (area, depth), infection, arteriopathy and denervation.

Grade	Area	Depth	Sepsis	Arteriopathy	Denervation
0	Skin intact	Skin intact	NA	Pedal pulses present	Intact
1	Lesion <1cm2	Superficial	No infected lesions	Pedal pulses reduced or one missing	Reduce
2	Lesion 1 to 3cm2	Lesion penetrating to tendon, periosteum and joint capsule	Cellulitis-associated lesions	Absence of both pedal pulses	Absent
3	Lesion >3cm2	Lesion in bones or joint space	Lesion with osteomyelitis	Gangrene	Charcot joint

SINBAD — Scoring based on site, ischemia, neuropathy, bacterial infection, area, depth.

	Site	Ischemia	Neuropathy	Bacterial infection	Area	Depth
0	Forefoot	Pedal blood flow intact	Sensation intact	None	<1cm2	Confined to skin and subcutaneous tissue
1	Midfoot	Reduced pedal blood flow	Sensation lost	Present	>=1cm2	Reaching muscle, tendon or deeper

IDSA / IWGDF — System for classification of infection severity

IDSA	IWGDF	Clinical description
Uninfected	1	Wound without purulence or any manifestations of inflammation
Mild	2	>=2 Manifestations of inflammation (purulence or erythema, pain, tenderness, warmth, or induration); any

System	Description		
			cellulitis or erythema extends <= 2 cm around ulcer, and infection is limited to skin or superficial subcutaneous tissues; no local complications or systemic illness
	Moderate	3	Infection in a patient who is systemically well and metabolically stable but has >=1 of the following: cellulitis extending 12 cm; lymphangitis; spread beneath fascia; deep tissue abscess; gangrene; muscle, tendon, joint, or bone involvement
	Severe	4	Infection in a patient with systemic toxicity or metabolic instability (e.g., fever, chills, tachycardia, hypotension, confusion, vomiting, leukocytosis, acidosis, hyperglycemia, or azotemia)
PEDIS	Designed specifically to provide a framework for defining ulcer populations in research. Graded according to Perfusion, Extent, Depth, Infection and Sensation.		
MAID	Grades 0 to 4 based on: Presence of pedal pulses Wound area (<> 4cm2) Wound duration (<>130 days) Number of ulcers (single or multiple).		
DUSS	Score 0 to 4 based on: Presence of pedal pulses Bone involvement Site (toe or foot) Number of ulcers (single or multiple).		
CSI	Novel Composite Severity Index (CSI) for foot infection in conjunction with 99mTc-WBC SPECT/CT. CSI scored on number of lesions, stage and intensity.		

4.7.2.2 **Included studies on classification tools**

4.7.2.2.1 *Table 27:* *Classification tools*

The table below summarises the studies included in the review. For full details see Appendix F.

Study	Study design	Population	Tool	Summary of results
Erdman (2012) USA	Retrospective cohort	People with foot ulcer and suspected infection undergoing [99]mTc-WBC SPECT/CT in a large municipal hospital setting.	Composite Severity Index (CSI) for foot infection in conjunction with 99mTc-WBC SPECT/CT.	Prediction of positive clinical outcome reduced as CSI increased. Not statistically significant.
Beckert (2009) Germany	Prospective cohort	People with lower extremity ulcers attending an outpatient wound care unit.	MAID severity score.	With increasing MAID score, the probability of healing at 365d decreased. Statistically significant.
Abbas (2008) Tanzania	Retrospective cohort	People referred to specialist multidisciplinary foot clinic	Wagner University of Texas S(AD) SAD PEDIS	Strongest significant statistical association observed between healing and: Wagner score Depth (S(AD) SAD, PEDIS and UT grade) Infection (S(AD) SAD, PEDIS) UT Stage
Ince (2008) UK Germany Tanzania Pakistan	Retrospective cohort	People with diabetic foot ulcers referred to specialist clinics in four countries	SINBAD	Statistical significance between all 6 variables and healing. Trend to increased healing time with greater score.
Parisi (2008) Brazil	Prospective cohort	People with diabetic foot ulcers in a specialist multi-disciplinary unit in an Endocrinology Division	University of Texas Wagner S(AD) SAD	Statistically significant association between chance of healing and lower grade, stage or score on UT, Wagner and S(AD) SAD.
Lavery (2007) USA and Netherlands	Prospective cohort	People with diabetic ulcer in a diabetes management programme foot clinic.	IDSA / IWGDF Infection classification	With an increasing IDSA-IWGDF severity there was a statistically significant trend toward increased risk of amputation, an increased atomic level of amputation and an increased need for lower extremity related hospitalisation.
Beckert (2006)	Prospective	People with diabetic foot ulcer	Diabetic ulcer severity	Increasing probability of amputation with increasing

Study	Study design	Population	Tool	Summary of results
Germany	cohort	attending an out-patient wound care.	score (DUSS)	DUSS score. Not statistically significant.
Gul (2006) Pakistan	Retrospective cohort	People with diabetic foot ulcer visiting a foot clinic.	University of Texas Wagner	Higher grades of Wagner system associated with higher likelihood of amputation. Not statistically significant. Higher grades of UT system associated with higher likelihood of amputation. Not statistically significant. Higher stages of UT system also associated with higher likelihood of amputation. Statistically significant.
Treece (2004) UK	Prospective cohort	People with diabetic foot ulcers at a multi-disciplinary clinic at a hospital.	S(AD) SAD	Statistically significant differences in outcome according to area, depth, sepsis and arteriopathy.
Oyibo (2001) UK and USA	Prospective cohort	People presenting with a new foot ulcer to two specialist diabetic foot centres	University of Texas Wagner	Wagner system (grade) showed a statistically significant positive trend with increased number of amputations. UT system showed a statistically significant positive trend for grade and stage with increased number of amputations.
Armstrong (1998) USA	Retrospective cohort	People with diabetic foot wound in a multidisciplinary tertiary care diabetic foot clinic.	University of Texas	Overall trend towards statistically significant increased prevalence of amputation as wounds increased in depth and stage. Significantly increased risk of amputation if wound probed to bone and in patients with both ischemia and infection.
Wukich (2013) USA	Retrospective cohort	Patients hospitalised for diabetic foot infection	IDSA / IWGDF Infection classification	Length of stay was significantly longer for those with severe infection with a non-significant trend indicating higher rates of limb salvage in patients with moderate infections compared to patients with severe infections.
Tsai (2013) Taiwan	Retrospective cohort	diabetic patients admitted to the diabetic foot care centre	Wagner	Wagner proved a significant risk factor for lower extremity amputation in non-dialysis groups however seemed to lose its predictive power in the dialysis group. This is likely due to the rapid increase in wound severity amongst dialysis patients.
Won (2014) Korea	Retrospective cohort	patients with diabetic foot ulcers who visited or were referred to a tertiary centre for	Wagner	Severity of ulcer as defined by Wagner criteria was the strongest risk factor for amputation after multivariate analysis.

Study	Study design	Population	Tool	Summary of results
		complex foot and ankle disease		
Wang (2014) China	Retrospective case control	patients hospitalised with diabetic foot ulcers	Wagner	Severity of ulcer as defined by Wagner criteria was negatively correlated to diabetic foot prognosis after multivariate analysis

4.7.2.3 Included studies on diagnostic tests

The tables below summarise the studies included in the review. For full details see Appendix F

4.7.2.3.1 *Table 28:* *Swab tests for soft tissue infection*

Study	Study design	Population	Index test	Reference test	Results
Mutluogu (2012b) Israel	Retrospective cohort	Patients seen with diabetic foot ulcer in a teaching Military Medical Academy who had both superficial swab and deep tissue biopsy.	Swab of base of ulcer for soft tissue infection.	Deep tissue biopsy	Swab and biopsy identical 73% Extra isolates on swab 11% Isolates missed on swab 9% Completely different 7% Identical or extra isolates on swab 84%
Slater (2004)	Cohort	People with diagnosed infected diabetic foot wounds	Swab culture	Deep tissue biopsy	Swab and biopsy identical 62% Extra isolates on swab 20% Isolates missed on swab 18% Identical or extra isolates on swab 82%

4.7.2.3.2 *Table 29:* *Swab and tissue culture for osteomyelitis*

Study	Design	Population	Index test	Reference test	Results

Study	Design	Population	Index test	Reference test	Results
Bernard (2010) Switzerland	Cross sectional	Patients with diabetic toe osteomyelitis with bone contact seen in an Orthopaedic Surgery Service	Culture from bone contact swabbing for osteomyelitis	Bone biopsy culture	Se 96, Sp 79
Elamurugan (2010) India	Cross sectional	People with foot ulcer and suspicion of osteomyelitis attending casualty or surgical outpatients.	Culture from swab of base of ulcer for osteomyelitis	Bone biopsy culture	Swab and bone biopsy identical 12% At least one organism similar 26% Different 62%
Morales Lozano (2010) Spain	Cross sectional	People with diabetic foot lesion in a diabetic foot clinic.	Swab and soft tissue culture (Study also assessed clinical signs, probe to bone and plain film radiography)	Histological examination of bone biopsy	Se 86, Sp 19

4.7.2.3.3   Table 30:   Probe to bone tests for osteomyelitis

Study	Design	Population	Index test	Reference test	Results
Mutluogu (2012a) Turkey	Cross sectional	Inpatients and outpatients with infected foot ulcer and suspicion of osteomyelitis in a Military Medical Academy.	Probe to bone testing for osteomyelitis	Bone biopsy or MRI	Se 66, Sp 84
Garcia-Morales (2011) Spain	Cross sectional	People with diabetic foot ulcer and clinical suspicion of infection attending podiatric clinic.	Probe to bone testing for osteomyelitis	Inter-observer reliability	Inter-observer reliability. Kappa concordance index relative: 1 to 2: 0.593 1 to 3: 0.397 2 to 3: 0.53
Morales Lozano (2010)	Cross sectional	People with diabetic foot lesion in a diabetic foot clinic.	Probe to bone test for osteomyelitis (Study also assessed clinical signs,	Histological examination of bone	Se 98, Sp 78

Study	Design	Population	Index test	Reference test	Results
Spain			swab and soft tissue culture, probe to bone and plain film radiography)	biopsy	
Lavery (2007) USA	Prospective cohort	People with a diabetic foot wound in a primary care diabetic management programme	Probe to bone test for osteomyelitis	Microbiological culture from bone biopsy	Se 87, Sp 83
Shone (2005)	Cross sectional	People with diabetic foot ulcer attending an outpatient clinic	Probe to bone testing for osteomyelitis	Clinical signs of osteomyelitis, supported by MRI and microbiological analysis of deep tissue samples	Se 38, Sp 91
Grayson (1995)	Cohort	People with diabetic foot ulcer and clinical suspicion of infection attending hospital	Probe to bone testing for osteomyelitis	Histological sample	Se 66, Sp 85

4.7.2.3.4   Table 31:   Imaging tests for osteomyelitis

Study	Design	Population	Index test	Reference test	Results
Saeed (2013) Pakistan	Prospective cohort	Patients with diabetic foot ulcer and suspected osteomyelitis.	99mTc-UBI 29-41 scintigraphy following three phase bone scan (99mTc-MDP) for osteomyelitis	Culture from bone biopsy or clinical decision.	Se 100, Sp 100
Alcaro-Afonso (2013) Spain	Prospective cohort	Patients with diabetic foot ulcers and clinical suspicion of osteomyelitis admitted to Diabetic Foot Unit.	Plain film radiography for osteomyelitis	Inter and intra observer reliability	Inter-rater reliability concordance: 2 x very experienced K=.35, 2 x moderate experienced K=.39, 2 x inexperienced K=.40 Intra-observer agreement (repeated measure: 2 months later) in very experienced K=.75, mod experienced K=.61 and inexperienced K=.57.

Study	Design	Population	Index test	Reference test	Results
Kagna (2012) Israel	Prospective cohort	Patients with diabetic foot ulcer referred to Nuclear Medicine with suspected infection	FDG PET/CT for osteomyelitis	Histological examination of bone biopsy, clinical examination of bone during surgery or clinical decision	Se 100, Sp 93
Asli (2011) Iran	Cross sectional	Patients with foot lesion and clinical suspicion of osteomyelitis referred to nuclear medicine.	5 and 24h 99mTc-IgC scintigraphy. 99mTc-MDP scintigraphy.	Consensus of clinical opinion based on MRI, culture, histopathology and presentation.	5h Tc-IgC Se 100, 69 24h Tc-IgC Se 60, Sp 77 99mTc-MDP Se 100, Sp 54
Morales Lozano (2010) Spain	Cross sectional	People with diabetic foot lesion in a diabetic foot clinic.	Plain film radiography (Study also assessed clinical signs, swab and soft tissue culture and probe to bone)	Histological examination of bone biopsy	Se 90, Sp 22
Heiba (2010) USA	Retrospective cohort	People with foot ulcer and suspicion of osteomyelitis referred to nuclear imaging.	DI SPECT/CT BS SPECT/CT WBCS SPECT/CT DI planar DI SPECT DI SPECT/CT Step 1 and 2.	Bone and tissue sample (culture or histology) or clinical examination and other imaging (CT and MRI).	DI SPECT/CT Se 95, Sp 94 BS SPECT/CT Se 94, Sp 47 WBCS SPECT/CT Se 87, Sp 68 DI planar Se 93, Sp 66 DI SPECT Se 93, Sp 77 DI SPECT/CT Step 1 Se 94, Sp 58 DI SPECT/CT Step 2 Se 97, Sp 94
Nawaz (2010) USA	Prospective cohort	People with diabetic foot disease attending a hospital medical centre	FDG-PET Plain film radiography MRI	Histological examination and microbiological culture of bone biopsy. Clinical examination	FDG-PET Se 81, Sp 93 PFR Se 63, Sp 87 MRI Se 91, Sp 78
Rozzanigo (2009)	Cross sectional	People with infected foot ulcer in a hospital setting	MRI	Bacteriological and/or histological tests in detecting osteomyelitis	Se 100, Sp 67
Al-Khawari (2007)	Cross sectional	People with suspected diabetic foot infection in a hospital setting	MRI	Culture growth or characteristic histological findings in diagnosing osteomyelitis	Se 100, Sp 63

Study	Design	Population	Index test	Reference test	Results
Ertugrul (2006)	Cross sectional	Patients with >grade 3 diabetic foot lesion attending a hospital setting	MRI 99mTc-MDP-labelled leukocyte scan	Histopathological findings in diagnosing osteomyelitis	MRI Se 78, Sp 60 99m-Tc-MDP Se 91, Sp 67
Rubello (2004)	Cross sectional	People with diabetic foot ulcer. No setting specified.	LeukoScan (4 h and 18–24h)	Microbiological findings or other laboratory and imaging techniques in detecting bone infection	4h Se 92, Sp75 24h Se 91, Sp 88
Palestro (2003)	Cross sectional	People with diabetic foot ulcer in a hospital setting.	99mTc-labelled monoclonal antibody In-WBC 3-phase (99mTc-MDP-labelled bone scintigraphy)	Bone biopsy examination and culture in diagnosing osteomyelitis and clinical judgement	99mTc-labelled monoclonal antibody Se 90, Sp 67 In-WBC Se 80, Sp 67 99mTc-MDP Se 90, Sp 27 99mTc-MDP + WBC Se 80, Sp 75 99mTc-labelled monoclonal antibody + 99mTc-MDP Se 90, Sp 67
Poirier (2002)	Cross sectional	People with diabetic foot ulcer and suspected osteomyelitis in a hospital setting	99mTc-MDP bone scintigraphy 99mTc-HMPAO-labelled leukocyte scan	Radiological examination, bacteriological and histological studies in diagnosing osteomyelitis	99mTc-MDP Se 100, Sp 28 99mTc-HMPAO/MDP Se 93, Sp 98
Harwood (1999)	Cross sectional	People with suspected infected diabetic foot ulcer in an outpatient hospital setting.	99m-Tc HMPAO In-WBC 99m-Tc MDP	Histology and/or microbiological cultures in detecting osteomyelitis	99m-Tc HMPAO Se 91, Sp 56 In-WBC Se 79, Sp 67 99m-Tc MDP Se 94, Sp 21
Devillers (1998)	Cross sectional	People with infected diabetic foot ulcer attending an endinocrinology unit.	Plain film radiography 3 -phase 99mTc-MDP-labelled bone scintigraphy 99mTc-HMPAO-labelled leukocyte scintigraphy	Radiographic and/or bacteriological or histological results or clinical follow up in diagnosis of diabetic foot infection	PFR Se 54, Sp 83 3 -phase 99mTc-MDP Se 100, Sp 30 99mTc-HMPAO Se 88, Sp 97
Remedios (1998)	Cross sectional	People with diabetic foot ulcer in a hospital setting.	99m-Tc nanocolloid MRI	Histological and microbiology tests in detecting osteomyelitis	99m-Tc nanocolloid Se 100, Sp 60 MRI Se 100, Sp 80

Study	Design	Population	Index test	Reference test	Results
Harvey (1997)	Cross sectional	People with diabetic foot problems attending a Veterans Centre	99mTc-HMPAO-labelled leukocyte scintigraphy 99mTc-MDP-labelled bone scintigraphy	Histology, bone cultures and radiographic results in diagnosing osteomyelitis	99mTc-HMPAO Se 86, Sp 90 99mTc-MDP Se 91, Sp 40
Croll (1996)	Cross sectional	Inpatients with diabetic foot infections	MRI 99mTc-MDP bone scan In-WBC Plain radiographs	Pathological specimen, or bone culture in diagnosing osteomyelitis	MRI Se 89, Sp 100 99mTc-MDP Se 50, Sp 50 In-WBC Se 33, Sp 69 PFR Se 22, Sp 94
Morrison (1995)	Cross sectional	People with suspected osteomyelitis in a hospital setting	MRI	Histological analysis of biopsy specimen or clinical and radiographic demonstration of progression.	Se 82, Sp 94
Levine (1994)	Cross sectional	People with diabetic foot ulcer. No setting specified.	MRI Plain-film radiography 111-In-WBC scintigraphy 99mTc bone scan	Pathological and histological determination, surgical observation and clinical resolution in diagnosing osteomyelitis	MRI Se 77, Sp 100 Plain-film Se 60, Sp 81 111-In-WBC Se 80, Sp 29 99mTc bone scan Se 100, Sp 25
Weinstein(1993)	Cross sectional	People with suspected osteomyelitis, non-healing ulcer or soft tissue infection.	MRI Plain radiographs 99mTc/Ga scan	Histological examination in diagnosing osteomyelitis	MRI Se 100, Sp 81 PFR Se 69, Sp 83 99mTc/Ga scan Se 52, Sp 81
Newman (1992)	Cross sectional	People with diabetic foot ulcer attending a medical centre.	MRI Leukocyte scanning	Bone biopsy and culture in diagnosing osteomyelitis	MRI Se 29, Sp 78 Leukocyte scan Se 100, Sp 67
Newman (1991)	Cross sectional	Inpatients and outpatients at a medical centre.	Plain film radiograph Bone scan Leukocyte 4h Leukocyte 24h	Bone biopsy and culture	Plain film radiograph Se 28, Sp 92 Bone scan Se 69, Sp 39 Leukocyte 4h Se 77, Sp 77 Leukocyte 24h Se 89, Sp 69
Larcos (1991)	Cross sectional	People with suspected infected diabetic foot ulcer. No setting specified.	111-In-WBC 99mTc-MDP-labelled bone scintigraphy Radiographs	Surgery (bone culture or biopsy) and clinical follow-up in diagnosing osteomyelitis	111-In-WBC Se 79, Sp 78 99mTc-MDP Se 93, Sp 43 PFR Se 43, Sp 83

Study	Design	Population	Index test	Reference test	Results
Beltran (1990)	Cohort	People with diabetic foot problems. No setting specified	MRI	Aspiration, pathological examination, and plain radiographs in detecting osteomyelitis	8 diagnoses of osteomyelitis made. 6 confirmed by reference test.
Wang (1990)	Cross sectional	People with suspected osteomyelitis in a medical centre setting.	MRI Plain radiographs	Histological examination in detecting osteomyelitis	MRI Se 98, Sp 81 PFR Se 52, Sp 69
Keenan (1989)	Cross sectional	People with diabetes with suspected foot infection referred to nuclear medicine.	3-phase 99mTc-MDP bone scintigraphy In-WBC	Culture and/or histological examination in diagnosing osteomyelitis	99mTc-MDP Se 100, Sp 38 In-WBC Se 100, Sp 78 99mTc-MDP + In-WBC Se 100, Sp 79
Yuh (1989)	Cross sectional	People with diabetic foot problem. No setting specified.	MRI 99mTc-MDP bone scintigraphy Plain radiographs	Pathological tests detecting osteomyelitis	MRI Se 100, Sp 89. 99mTc-MDP bone scintigraphy Se 94, Sp 100 PFR Se 75, Sp 75

4.7.2.3.5 *Table 32:* *Blood tests for osteomyelitis*

Study	Design	Population	Index test	Reference test	Results
Ertugrul (2009)	Cohort	Inpatients with diabetic foot ulcer	ESR	Histopathology, microbiology or MRI with conventional spin echo in diagnosing osteomyelitis	ESR >=60 Se 92, Sp 68 ESR >=65 Se 88, Sp 73 ESR >=70 Se 83, Sp 77 ESR >=75 Se 79, Sp 82 ESR >=80 Se 71, Sp 91
Malabu (2007)	Cross sectional	People with diabetic foot ulcer in a hospital setting.	ESR Haematocrit Haemoglobin Platelet count Red cell distribution width White cell count	Pathological and histological determination, surgical observation and clinical resolution in diagnosing osteomyelitis	ESR >70 Se 90%, Sp 94% Hematocrit >36% Se 95%, Sp 84% Hemoglobin < 12 g/dl Se 81%, Sp 90% Platelet count > 400 x 109/L Se45% Sp 95% RDW >14.5 Se 67%, Sp 63% White cell count >400x109/L Se 52%, Sp 80%
Kaleta	Cross	People with diabetic	ESR	Histological	ESR >=60 Se 90, Sp 90

Study	Design	Population	Index test	Reference test	Results
(2001)	sectional	foot ulcer in a medical centre setting.		examination (pathological reports) in diagnosing osteomyelitis	ESR >=65 Se 90, Sp 90 ESR >=70 Se 90, Sp 90 ESR >=75 Se 84, Sp 100 ESR >=80 Se 79, Sp 100
Newman (1991)	Cross sectional	Inpatients and outpatients at a medical centre	ESR >70 and >100	Bone biopsy and culture to diagnose osteomyelitis	ESR >70 Se 28, Sp 100 ESR >100 Se 23, Sp 100
Michail (2013)	Cross sectional	Consecutive patients with diabetic foot infection from outpatient clinics of two hospitals	ESR WCC CRP PCT	Clinical examination(probe to bone test), X-ray, Scintigraphy and MRI	White cell count >14x10^9/L Se 74 Sp 82 ESR >67 mm/h Se 84 Sp 75 CRP >14 mg/L Se 85 Sp 83 PCT >0.30 ng/mL Se 81 Sp 71

(a) ESR = Erythrocyte Sedimentation Rate
(b) WCC= White cell count
(c) CRP= C-reactive protein
(d) PCT= Procalcitonin

4.7.3 Health Economic Evidence

A literature search was conducted for the question using standard health economics filters appplied to the clinical search strategies. No relevant cost-utility analyses were found. Health economic modelling was not prioritised for this review question

4.7.4 Evidence Statements

Classification tools

Seven observational studies, ranging from 105 to 658 participants presented moderate to very low quality evidence that increasing grade of Wagner classification was associated with worsening patient outcomes in terms of amputation rate and rate of healing.

Five observational studies, ranging from 105 to 383 participants presented moderate to very low quality evidence that increasing grade of University of Texas classification was associated with worsening patient outcomes in terms of amputation rate and rate of healing.

Three observational studies, ranging from 105 to 326 participants presented moderate to very low quality evidence that increasing grade of SAD classification was associated with worsening patient outcomes in terms of rate of healing.

One observational study of 1340 participants presented low quality evidence that increasing grade of SINBAD classification was associated with worsening patient outcomes in terms of rate of healing, death and amputation.

One observational study of 1000 participants presented moderate quality evidence that increasing grade of DUSS classification was associated with worsening patient outcomes in terms of rate of healing.

Two observational studies, ranging from 100 to 247 participants presented low to very low quality evidence that increasing grade of IDSA/IWGDF classification was associated with worsening patient outcomes in terms of risk of amputation and hospital length of stay.

One observational study of 326 participants presented very low quality evidence that increasing grade of PEDIS classification was associated with worsening patient outcomes in terms of rate of healing and infection.

One observational study of 2019 participants presented moderate quality evidence that increasing grade of MAID classification was associated with worsening patient outcomes in terms of rate of healing.

One observational study of 77 participants presented very low quality evidence that increasing grade of CSI classification was associated with worsening patient outcomes in terms of rate of healing.

Swab and tissue culture

Two observational studies, with 54 and 56 participants, presented low quality evidence that 82 to 84% of superficial swabs of diabetic foot ulcer found an identical number or more isolates than were found in deep tissue biopsies.

One observational study, with 132 participants, presented very low quality evidence that superficial swab and soft tissue culture had sensitivity of 86% and specificity of 19% in diagnosing osteomyelitis when compared to bone biopsy.

One observational study, with 68 participants, presented moderate quality evidence that superficial swab had sensitivity of 96% and specificity of 79% in diagnosing the main pathogen of osteomyelitis when compared to bone biopsy.

One observational study, with 144 participants, presented very low quality evidence that 12% of bone contact swabbing found identical isolates to those found on bone biopsy.

Probe to bone testing

Five observational studies, ranging from 65 to 247 participants, presented very low quality evidence that probe to bone testing had sensitivity ranging from 38 to 98% and specificity ranging from 78% to 92% in diagnosing osteomyelitis when compared to bone biopsy or imaging tests.

Two observational studies presented moderate quality evidence that probe to bone testing inter rater reliability ranged from 0.31 to 0.593.

Imaging tests

Twelve observational studies of 99mTc-MDP-labelled scintigraphy, with a range of 22 to 94 participants, presented low quality evidence of sensitivities ranging from 50% to 100% and of specificities ranging from 0 to 67% in diagnosing osteomyelitis. These studies varied in type of reference test.

Eleven observational studies of MRI, with a range of 14 to 94 participants, presented low quality evidence of sensitivities ranging from 77% to 100% and of specificities ranging from 60% to 100% in diagnosing osteomyelitis. These studies varied in type of reference test.

Ten observational studies of plain radiography, with a range of 26 to 200 participants, presented low quality evidence of sensitivities ranging from 22% to 90% and of specificities ranging from 17% to 94% in diagnosing osteomyelitis. These studies varied in type of reference test.

Eight observational studies of In-WBC, with a range of 12 to 111 participants, presented low quality evidence of sensitivities ranging from 33% to 100% and of specificities ranging from 22% to 78% in diagnosing osteomyelitis. These studies varied in type of reference test.

Three observational studies of 99mTc-HMPAO-labelled scintigraphy, with a range of 52 to 122 participants, presented moderate quality evidence of sensitivities ranging from 86% to 91% and of specificities ranging from 56% to 95% in diagnosing osteomyelitis. These studies varied in type of reference test.

Two observational studies of FDG-PET, with 39 and 106 participants, presented low quality evidence of sensitivities ranging from 81% to 100% and specificities of 93% in diagnosing osteomyelitis compared with histological analysis of bone biopsy or clinical examination.

A further four observational studies presented very low to low quality evidence on 10 other imaging techniques for the diagnosis of osteomyelitis. Each of these different imaging techniques was assessed in only one paper.

Blood tests

Five observational studies presented low to moderate quality evidence showing varying degrees of the accuracy of blood tests in diagnosing infection. Data could not be pooled.

4.7.5 Evidence to Recommendations

Table 33: Linking evidence to recommendations table

Relative value of different outcomes	The GDG considered the predictive accuracy of the different scores, tests and tools. The group agreed that they would be prepared to accept lower specificity in exchange for higher sensitivity in order to ensure all patients with active disease receive the treatment they require. The group felt that false positives were preferable to false negatives given the impact that foot ulcer and subsequent consequences can have on a person's life, such as amputation, mortality and hospitalisation. The importance of healing ulceration and reducing re-ulceration rates was again paramount in this question as in previous questions. This could be addressed by making sure that those who have developed ulceration receive the correct treatment (see section 4.10), and that any subsequent complications such as infection and osteomyelitis are correctly diagnosed as soon as possible to allow for early treatment and follow up. Few reported the outcomes of rate of re-ulceration, soft tissue infection, and gangrene.
Trade-off between benefits and harms	The GDG considered that, in instances of a true positive, referral to appropriate services and appropriate care results in decreased risk of ulceration, re-ulceration, infection, both minor and major amputation, and death (see Section 4.3 Protocols and DFS and MDS) In instances of true negatives, reassurance and ongoing monitoring by appropriate health care professionals in the appropriate setting or service is appropriate. (see Section 4.3 Protocols and DFS and MFS) The consequences of a false negative include increased probability of worsening ulceration, infection, both minor and major amputation, and death, whereas the consequences of a false positive include increased assessment and discharge from one service to another. (see Section 4.3 Protocols and DFS and MFS) Because of the consequences outlined above, both for the patient and for the services provided, the GDG considered that all patients and not just those at high risk were to be categorised correctly by stratification systems. And also that a false negative could have potentially more severe consequences than a false positive for both the assessment tools and the diagnostic tests. Given that both plain radiograph and probe to bone tests had particularly variable findings for sensitivity. It was decided that a recommendation should be made to make clear that when osteomyelitis is suspected the diagnosis should not be ruled out on the basis of a negative probe to bone or plain radiographic finding.
Economic considerations	The cost of retraining healthcare professionals to use a classification system not widely employed was considered an important factor in recommending the most appropriate classification system. Cost and availability of the MRI investigation was also taken into consideration.

Quality of evidence	The quality of the evidence for both the classification tools and the diagnostic tools were found to be majority low and very low quality. Due to the variability of reference standards used in the studies and other important issues such as lack of blinding, patient selection, small sample sizes, unadjusted baseline characteristics, and poor reporting of information, the decision was made not to pool the data and provide a pooled estimate of the findings. Decisions were therefore aided by the use of forest plots and ROC curves but these were not used as the sole decision tool for creating recommendations. Group informal consensus and experience remained an important tool for crafting recommendations.
Other considerations	There was difficulty in proving the superiority of one form of classification system over another. Results seemed to show that all classifications systems successfully associated an increase in the severity of grading with worse outcomes for the patient. Evidence to suggest which systems were superior to others was inconclusive. Taking into account other important factors such as applicability to UK practice, implementability and widespread use, GDG agreement was employed to recommend the University of Texas classification system or SINBAD. Both these classification systems were felt to be simple and widely used in the UK population.

A negative recommendation was employed against the use of WAGNER as it was felt to be unsophisticated and not as clinically useful for grading the severity of ulcer in the UK population. This was largely due to the poor gradation of disease severity in the Wagner tool compared to other available grading tools, the Wagner classification system was also felt to provide less clinically useful information such as the ischaemic status of the patient's leg/foot.

The GDG discussed the use of various diagnostic tests for the identification of Osteomyelitis and deep infection of the diabetic foot. Evidence was presented comparing different methods of culture, imaging and blood tests for sensitivity and specificity. The GDG felt there was strong evidence to show that MRI performed well for diagnosis of osteomyelitis in terms of sensitivity and specificity. While plain radiograph was felt to be inferior in terms of diagnostic accuracy, it was recognised that diagnosis was very possible with plain X-ray and that this investigation was cheap and widely available, not to mention necessary for monitoring disease progression. A negative finding on plain radiograph however should be cross checked by MRI when osteomyelitis is suspected.

The GDG reviewed the evidence for infection sampling and considered bone sampling and tissue culture to be the most useful microbiological sampling techniques. When a wound is debrided the GDG noted that it should be entirely possible to gain a good sample from the base of the wound. Recognising that not all wounds would be suitable for debridement the GDG recommended deep swab as the next best option. It was noted that the evidence showed that superficial swab sampling could pick up the major pathogen in infection but that it can also pick up a large proportion of additional organisms which could lead to the overuse of broad spectrum antibiotics. For this reason the GDG recommended that a swab, if used, should be deep rather |

than superficial.

The use of various types of blood test for the diagnosis of osteomyelitis and soft tissue infection were considered. The GDG felt it was necessary to make a recommendation regarding the use of these blood tests as they are commonly employed in practice and should form a part of the complete clinical picture rather than being used for diagnosis as a stand-alone test. The GDG stated that osteomyelitis should not be ruled out based on normal inflammatory markers since these tests have a variable sensitivity and specificity for this disease.

4.7.6 Recommendations

25. **If a person has a diabetic foot ulcer, assess and document the size, depth and position of the ulcer.**

26. **Use a standardised system to document the severity of the foot ulcer, such as the SINBAD (Site, Ischaemia, Neuropathy, Bacterial Infection, Area and Depth) or the University of Texas classification system.**

27. **Do not use the Wagner classification system to assess the severity of a diabetic foot ulcer.**

28. **If a diabetic foot infection is suspected and a wound is present, send a soft tissue or bone sample from the base of the debrided wound for microbiological examination. If this cannot be obtained, take a deep swab because it may provide useful information on the choice of antibiotic treatment.**

29. **Consider an X-ray of the person's affected foot (or feet) to determine the extent of the diabetic foot problem.**

30. **Think about osteomyelitis if the person with diabetes has a local infection, a deep foot wound or a chronic foot wound.**

31. **Be aware that osteomyelitis may be present in a person with diabetes despite normal inflammatory markers, X-rays or probe-to-bone testing.**

32. **If osteomyelitis is suspected in a person with diabetes but is not confirmed by initial X-ray, consider an MRI to confirm the diagnosis.**

4.7.7 Research recommendations

No research recommendations were drafted for this review question.

4.8 Monitoring of people with diabetic foot problems

4.8.1 Review Question

How often should people with diabetes who have foot ulcers, soft tissue infections, osteomyelitis or gangrene be reviewed?

4.8.2 Evidence Review

The aim of this review question was to determine the appropriate review frequency for people with diabetes who have foot ulcers, soft tissue infections, osteomyelitis or gangrene. This clinical issue was previously considered in Clinical Guideline 10 however, no appropriate evidence was identified at that time. The review protocol for this question can be found in Appendix C (under review question 8)

The original and rerun searches identified 9738 abstracts 15 papers were identified. 14 papers were subsequently excluded because they did not fit the inclusion criteria (see Appendix F for a full list of excluded studies). 1 paper was included in the final review (Warriner, 2012). A list of excluded studies and the reasons for exclusion can be found in Appendix E.

Table 34 outlines the PICO framework used for this review question and Table 35 provides a summary of the included paper. A GRADE profile for this study is shown in Appendix I. An evidence table is shown in Appendix F.

Table 34: PICO Framework

Population	Children, young people and adults with type 1 or type 2 diabetes
Intervention	Review schedules of varying frequency
Comparator	Standard care based on different risk category
Outcomes	Rates and extent of amputation (major or minor Rates of healing / cure Time to further ulceration Rates of foot ulceration, infection and gangrene resulting from diabetes Resource use and costs Rates of A & E/ hospital admission for foot problems resulting from diabetes Mortality Time to healing/ cure
Include	Systematic reviews and randomised controlled trials. If insufficient evidence is available progress to non-randomised controlled trials and cohort studies
Exclude	Studies of children, young people and adults with diabetes and foot problems who are admitted to hospital

Table 35: Summary table of included studies for monitoring of people with diabetic foot infections

Author (year)	Study type	Participants	Review schedule frequency	Outcomes of interest	Length of follow up	Study Location
Warriner (2012)	Retrospective cohort	**Patient characteristics:** Patients with type 1 or type 2 diabetes and Wagner grade 1 or 2 diabetic foot ulcers **Evaluable total:** 206 patients (105 received care once a week; 101 received care once every two weeks) **Age:** Mean age 68 years	Routine care once a week versus Routine care once every two-weeks	• Rates of healing/ cure • Time to healing/ cure (days)	Not specified	USA

4.8.3 Health Economic Evidence

A literature search was conducted for the question using standard health economics filters appplied to the clinical search strategies. No relevant cost-utility analyses were found. Health economic modelling was not prioritised for this review question

4.8.4 Evidence Statements

One very low quality observational study with 206 patients reported that the closure of diabetic foot ulcers and median time to closure was significantly improved for patients who visited a wound clinic at least once a week compared to patients who visited a wound specialist at least once every other week.

4.8.5 Evidence to recommendations

Table 36: Linking evidence to recommendations table

Relative value of different outcomes	This review assessed the effects of different frequencies of monitoring on the rates of healing/cure, reulceration, admission, infection, gangrene, minor and major amputation. The GDG felt that the primary outcome that clinicians seek to avoid is the non-healing or recurrence of ulcer. Infection, gangrene, amputation and death can be preventable secondary outcomes of having an ulcer. Reducing the rates of these outcomes will also result in improved rates of hospital admission and resource use.
Trade-off between benefits and harms	For the patient, the primary benefits from increased frequencies of monitoring include more contact with appropriately skilled health care professionals and the increased probability that timely appropriate care will be available should problems worsen or new complications develop. This could result in increased rates of ulcer healing leading to lower rates of infection gangrene and amputation with a resultant lower rate of hospital admission and resource use/cost. For the NHS, the early treatment of developing foot problems can help avoid un-necessary hospitalisation and longer term management of complications such as infection, gangrene and amputations. The harms associated with increased frequency of monitoring include the inconvenience to the patient which may result in dissatisfaction and missed appointments with resulting increases in late presenting complications and possible hospitalisation. For the NHS, the resource implications needed to support increased number of appointments and treatment were considered.
Economic considerations	For the NHS, the early treatment and regular review of foot problems can help avoid un-necessary hospitalisation and longer term management of complications such as infection, gangrene and amputations. This will also help avoid unnecessary resource use. The harms associated with increased frequency of monitoring include inconvenience to the patient which may result in

| | dissatisfaction and missed appointments with resulting increases in late presenting complications and possible hospitalisation. For the NHS, the resource implications needed to support increased number of appointments and treatment were considered.

Therefore a careful choice in monitoring frequency is clearly required to achieve the necessary balance. |
|---|---|
| **Quality of evidence** | The GDG recognised the limited evidence from one retrospective study meant it was difficult to be specific about time periods for review frequency. They felt it was important to reflect this in the wording of the recommendations. |
| **Other considerations** | The GDG acknowledged the limitations of the review based upon one paper, but this prompted a discussion into the need to provide best practice guidelines for all conditions covered by this review. The GDG recognised the importance of speed in the referral of patients with more complicated wounds and agreed there was a need to urgently refer patients with soft tissue infections, gangrene and osteomyelitis to a specialist service. The GDG noted the importance of prompt referral for patients with a foot ulcer but acknowledged that this need was less urgent than the speed of referral for the other emergency or life threatening conditions considered by this guideline (see section 4.14).

They agreed it was appropriate to keep the wording of recommendations broad, thus ensuring frequency for care for people with a diabetic foot problem is determined by health professionals with specialist knowledge. This was because the triage of care for these patients may differ regionally. The recommendation allowed for flexibility by stating that the frequency of review should take into account the overall health of the person, how healing has progressed, and any deterioration. It was agreed that a patient's frequency of review should be maintained with good communication and integration across community and hospital based care.

The GDG recognised the importance of the pathway of care and felt it was important to link both primary care and specialist services in defining time frames for review frequency. They felt it was important to note that different patient needs can influence review frequency and this would need to be reflected in the wording of recommendations. The committee also acknowledged that each grade of ulcer will require a different timing for care and therefore felt it was important to consider the severity of ulcer when implementing a treatment plan and defining a timeframe for follow-up care. The GDG also recognised review frequency should be based upon each patient's individual need and care plans would need to reflect the change in condition of wound or ulcer over time.

In section 4.14 the GDG also defined what they would consider to be severe/complex problems in need of immediate attention to be treated under secondary care. |

4.8.6 Recommendations

33. **When deciding the frequency of follow-up as part of the treatment plan, take into account the overall health of the person with diabetes, how healing has progressed, and any deterioration.**

34. **Ensure that the frequency of monitoring set out in the person's individualised treatment plan is maintained whether the person with diabetes is being treated in hospital or in the community.**

4.8.7 Research recommendations

How often should people with diabetic foot problems (foot ulcers, soft tissue infections, osteomyelitis or gangrene) be reviewed?

Why this is important

The evidence surrounding different monitoring frequencies for those who have developed diabetic foot problems was limited. It is proposed that a randomised controlled trial is undertaken to explore this question. The proposed study would monitor and evaluate the cure rates of foot ulcer or infection resulting from diabetes, rates of re-ulceration, time to further ulceration, rates and extent of amputation (major or minor), and hospital and emergency admission rates and mortality as a result of different monitoring frequencies.

4.9 Management strategies for people with diabetic foot problems

4.9.1 Review Question

What is the effectiveness of different management strategies for people with diabetes who have foot ulcers, soft tissue infections, osteomyelitis or gangrene? This includes information, advice and education about self-monitoring and preventing further foot problems, blood glucose management, and skin and nail care.

4.9.2 Evidence Review

The aim of this review question was to determine the effectiveness of strategies to manage foot ulcers, soft tissue infections, osteomyelitis or gangrene in people with diabetes, by considering the effectiveness of   information, advice and education provided to patients about looking after their feet, blood glucose management and provision of skin and nail care treatments and other management strategies. The review protocol for this question can be found in Appendix C (under review question 9)

The original and rerun searches identified 9738 abstracts 45 papers were identified. 37 papers were subsequently excluded because they did not fit the inclusion criteria (see Appendix E for a full list of excluded studies). 8 new papers were included in the final review. 1 additional paper has been included in this review from evidence identified in Clinical Guideline 10. (Malone,J.M.(1989), Al-Wahbi,A.M. (2010), Rerkasem,K. (2007), Weck,M. (2013), Aragon-Sanchez,J. (2011), Markuson,M. (2009), Young,M.J. (2008), Flahr, D (2010), Alzahrani, H. (2013)).

Table 37 outlines the PICO framework used for this review question and Table 38 provides a summary of all studies included in the review. The GRADE profiles for these studies are shown in Appendix I. The evidence tables for the studies included in the review are shown in Appendix F.

Table 37 – PICO Framework

Population	Children, young people and adults with type 1 or type 2 diabetes
Intervention	Information, advice and education on self-monitoring and skin and nail care Information, advice and education about foot wear Blood glucose management Provision of skin and nail care treatment Other management strategies
Comparator	Standard care
Outcomes	Rates and extent of amputation (major or minor) Rates of healing / cure Time to further ulceration Rates of foot ulceration, infection and gangrene resulting from diabetes Resource use and costs Rates of A & E/ hospital admission for foot problems resulting from diabetes Mortality Time to healing/ cure
Include	Systematic reviews and randomised controlled trials. If insufficient evidence is available progress to non-randomised controlled trials and cohort studies
Exclude	Strategies for management of foot problems in people without diabetes

Table 38: Summary table of included studies for management strategies for people with diabetic foot infections

Author (year)	Study type	Participants	Comparisons	Outcomes of interest	Length of follow up	Study Location
Information, advice & education about foot care						
Malone (1989)	RCT	203 patients with diabetes & a foot ulcer or foot infection (103 patients in intervention group; 100 patients in comparator)	Education programme versus standard care (no education programme)	• Ulcer healing rates • Ulcer incidence rates • Infection rates • Amputation rates • Level of amputation (major or minor) • Mortality rates	2 years	USA
Al-Wahbi (2010)	Retrospective cohort	41 patients with diabetic foot complications (21 in intervention group; 20 in comparator)	Before and after establishing an foot care training & education programme	• Amputation rates	Not specified	Saudi Arabia
Rerkasem (2007)	Retrospective cohort	171 patients receiving outpatient care for a diabetic foot ulcer (61 patients in intervention group; 110 patients in comparator)	Integrated diabetic foot care programme versus standard care	• Amputation rates • Level of amputation (major or minor)	Not specified	Thailand
Weck (2013)	Prospective cohort	1192 patients with a diabetic foot ulcer (684 patients received a structured	Structured healthcare programme versus non-integrated programme (usual	• Ulcer healing rates • Ulcer improvement rates	2 years	Germany

Author (year)	Study type	Participants	Comparisons	Outcomes of interest	Length of follow up	Study Location
		programme of inpatient, outpatient and rehabilitation care versus usual care; 508 controls received standard care without an interdisciplinary care programme)	care)	• Major amputation rates • Mortality rates		
Blood glucose control						
Aragon-Sanchez (2011)	Prospective cohort	81 patients with diabetes who underwent surgical treatment for diabetic foot osteomyelitis (21 with HBA1c 5.3%-7.3%; 60 with HBA1c 7.4%-14%)	HBA1c values and ulcer healing time	• Amputation rates • Time to ulcer healing • Length of hospital stay • Mortality rates	Not reported	Spain
Markuson (2009)	Retrospective cohort (correlation study)	46 patients with diabetic lower extremity ulcer attending an outpatient wound care centre (16 with HBA1c<7%; 20 with HBA1c 7%-10%)	HBA1c values and ulcer healing time	• Ulcer healing rates • Ulcer healing time	Not reported	USA
Other interventions- cardiovascular risk management						
Young (2008)	Retrospective cohort	655 patients with a diabetic foot ulcer attending a foot ulcer clinic (404 patents in cohort 1- prior to implementing cardiovascular risk	Before and after implementing a cardiovascular risk management programme	• Mortality rates	5 years	UK

Author (year)	Study type	Participants	Comparisons	Outcomes of interest	Length of follow up	Study Location
		programme; 251 patients in cohort 2- after implementation of programme)				
Other interventions- Exercise interventions						
Flahr (2010)	Prospective randomised pilot study	19 patients with a diabetic foot wound (10 patients completed exercise programme; 9 patients received usual care)	Foot exercise programme versus standard care	• Wound healing rates	12 weeks	Canada
Other interventions- Shellac for gangrene						
Alzahrani (2013)	Prospective randomised pilot study	Out of 26 patients included 23 patients completed the study (13 in the intervention group completed the study; 10 control patients received their standard care regimen)	Application of Shellac to dry gangrenous wounds Versus Application of 10% povidone-iodine (standard care)	• Amputation rates • Mortality rates	12 months	Saudi Arabia

4.9.3 Health Economic Evidence

A literature search was conducted for the question using standard health economics filters appplied to the clinical search strategies. No relevant cost-utility analyses were found. Health economic modelling was not prioritised for this review question

4.9.4 Evidence Statements

Information, advice & education about foot care

One low quality RCT with 203 participants reported that the number of healed foot ulcers, the number of unhealed foot ulcers and number of overall amputations was significantly improved for participants who received a foot care education programme compared to those who only received standard foot care. Whereas 1 very low quality observational study with 41 participants showed there was no significant difference in the number of amputations for participants who received a foot care education programme compared to those who received standard foot care.

In addition, 2 very low quality observational studies with 1363 participants found that the number of overall amputations, number of major amputations and mortality rate was significantly improved for participants who received an integrated foot care programme compared to those who received standard foot care.

Blood glucose control

One very low quality observational studies with 81 participants reported there was no significant differences in the number of healed foot ulcers, number of amputations, length of hospital stay or mortality for participants who had HBA1c levels of 5.3% to 7.3% compared to participants who had HBA1c levels of 7.4% to 14%.

Additionally, one very low quality observational study with 46 participants found there was no significant difference in the number of healed ulcers or time to healing for participants who had admission HBA1c levels of 4% to 7% compared to participants who had HBA1c levels of 7.1% to 10%.

Other interventions- Cardiovascular risk management

One very low quality observational studies with 655 participants reported there was no significant difference in overall mortality but that that the estimated 5 year mortality was significantly reduced for participants who received the cardiovascular risk management programme compared to participants who did not receive the programme.

Other interventions- Foot exercise intervention

One very low quality RCT with 19 participants reported there were no significant differences in wound healing rate for participants who completed a foot exercise intervention programme compared to participants who received usual foot care.

Other interventions- Shellac for prevention of wet gangrene

One very low quality RCT with 26 participants reported there were no significant differences in amputation rate or mortality rate for participants who received the application of shellac to dry gangrene compared to participants who received the application of 10% povidone-iodine solution to gangrenous areas as per usual care.

4.9.5 Evidence to Recommendations

Table 39: Linking evidence to recommendations table

Relative value of different outcomes	The GDG agreed that reducing ulceration and re-ulceration rates was paramount as the critical outcome for this question and the guideline. The GDG argued that if ulcers could be prevented then the subsequent likelihood of other outcomes such as infection, gangrene, amputation and death would be diminished.
	For this review question, all of the persons included will have already developed diabetic foot problems and to the emphasis will be on curing active foot ulceration and reducing the rate of reulceration. This would have long term impact in diminishing the likelihood of further complications from developing such as infection, gangrene, amputation and mortality rate. Reducing the incidence of these complications will also result in reduced rates of hospital admission with implications for resource use and cost.
Trade-off between benefits and harms	It was felt that the benefits of a good management strategy for people who have developed diabetic foot problems would include a clear improvement in clinical outcomes as listed above. The main complication that healthcare professionals are eager to avoid is ulceration. If patients can have their foot ulceration healed quickly and reulceration prevented this can protect against the development of further, more severe, complications such as infection, gangrene and amputation. It is also important that this therapy should be safe and do no harm. It should be available and implementable in the real world.
	Potential harm as a result of offering the above management strategies could include having a direct adverse effect as a result of using the therapy or where use of the treatment is found to worsen or slow the progress of healing. If a treatment has no effect, this too could lead to wasted resources and possible patient dissatisfaction. A poorly motivated patient may allow their disease to go unmanaged or poorly controlled which could lead to an increased likelihood of the development of diabetic foot complications such as ulceration/reulceration. This may, in turn, cause increased rates of infection, gangrene, amputation, hospital admission with resulting high resource use and costs.
Trade-off between net health benefits and resource use	The GDG considered the relative cost and effectiveness of each of the interventions presented and made recommendations with consideration of these factors.
Quality of evidence	The GDG noted the very low quality of the evidence presented for the role of blood glucose control in the management of people with diabetic foot infection. In addition, the GDG also acknowledged that patient education can include broader factors not included by the structured education programmes reviewed. For this reason, the GDG agreed it was appropriate to give reference to the broader diabetes guidelines for specific targets for blood glucose values and non-specific patient education needs.
Other considerations	The GDG felt the recommendations needed to reflect all

appropriate sources of information available for people with diabetic foot ulcers. They noted that information should be provided to all people involved in the patient's care. The GDG agreed that there is anecdotal evidence available to link good glycaemic control to better outcomes for people with diabetic foot infections and that it was important to raise awareness that the presence of diabetic foot infections can increase the risk of cardiovascular disease.

The GDG recognised the difficulties in specifying the types of information people with foot ulcers may need. They recognised the information should be tailored to individual patient needs and considered the importance of providing written, verbal and pictorial information. The GDG agreed it was appropriate to provide a list of useful information resources to assist patients in identifying foot problems.

The GDG agreed there was limited evidence presented for all conditions covered within the review question, but acknowledged that patients presenting with foot problems in one leg, may have an increased risk of problems in the alternate leg.

The evidence regarding better outcomes for those patients receiving a more integrated care pathway was covered in more detail under sections 4.3 and 4.14.

There was no convincing evidence to show that a foot exercise intervention offered any benefit in terms of wound healing rate.

The GDG wanted to capture the responsibilities of patients within the treatment plan. The committee recognised that patients need to make informed decisions about their own care, and noted the importance of providing comprehensive information and advice.

4.9.6 Recommendations

35. **Provide information and clear explanations as part of the individualised treatment plan for people with a diabetic foot problem. Information should be oral and written, and include the following:**
    - A clear explanation of the person's foot problem.
    - Pictures of diabetic foot problems.
    - Care of the other foot and leg.
    - Foot emergencies and who to contact.
    - Footwear advice.
    - Wound care.
    - Information about diabetes and the importance of blood glucose control (also see recommendation 23).

36. **If a person presents with a diabetic foot problem, take into account that they may have an undiagnosed, increased risk of cardiovascular disease that may need further investigation and treatment. For guidance on the primary prevention of cardiovascular disease, see the NICE guideline on lipid modification.**

4.9.7 Research recommendations

No research recommendations were drafted for this review question

4.10 Debridement, wound dressings and offloading

4.10.1 Review Question

What is the clinical effectiveness of surgical or non-surgical debridement, wound dressings and offloading for people with diabetic foot infections?

4.10.2 Evidence Review

The aim of this review question was to identify the most effective wound management strategies for diabetic foot problems by considering the effectiveness of surgical or non-surgical debridement, wound dressings, offloading and orthotic devices or footwear in people with diabetic foot ulcers (with or without soft tissue infection, osteomyelitis or gangrene). The review protocol for this question can be found in Appendix C (under review question 10)

This question aimed to update the existing evidence already identified previously in the NICE Clinical Guideline 119. Eleven papers were included in this review from evidence identified in that guideline. Five studies were included for wound dressings and 6 studies were included for offloading.

The original and rerun searches identified 1289 abstracts 108 papers were identified and 94 papers were subsequently excluded because they did not fit the inclusion criteria (see Appendix E for a full list of excluded studies). 14 newly identified papers were included in the final review. This included 7 papers for debridement and wound dressings and 7 papers for offloading. Tallis,A.(2013). Piaggesi,A. (1998). Jensen,J.L. (1997). Gottrup,F. (2013), Donaghue,V.M, (1998), Armstrong DG, (2005), Caravaggi,C. (2000), Caravaggi (2007, Faglia,E. (2010), Gutekunst,D.J. (2011), Zimny,S. (2003), Zhang, Y. (2014), Lavery, L. A. (2014), Foster AVM, (1994), Piaggesi A, (2001), Jude EB, (2007), Clever, H. U. (1996), Veves, A, (2002), Jeffcoate, (2009), Van De Weg, FB. (2008), Armstrong, DG, (2001), Piaggesi, A, (2007), Katz, IA, (2005), Mueller, MJ, (1989), Nube, VL, (2006))

Table 40 outlines the PICO framework used for this review question and Table 2 provides a summary of all studies included in the review. The GRADE profiles for these studies are shown in Appendix I and the evidence tables are shown in Appendix F. Any meta-analyses of outcomes are shown in Appendix H. For studies where pooling of data may not have been appropriate i.e. where there were large differences between the population characteristics or the interventions used meta-analysis was not performed.

Table 40: PICO Framework

Population	Children, young people and adults with type 1 or type 2 diabetes and foot ulcer (with or without soft tissue infection, osteomyelitis or gangrene)
Intervention	Surgical or non-surgical debridement Wound dressings Offloading devices and footwear
Comparator	Standard care Head to head comparisons
Outcomes	Cure rates of foot infection in people with diabetes Rates and extent of amputation (major or minor) Length of hospital stay Rates of hospital readmission Mortality Health-related quality of life (QOL) Complications (or other diabetic foot related outcomes) Re-ulceration

Population	Children, young people and adults with type 1 or type 2 diabetes and foot ulcer (with or without soft tissue infection, osteomyelitis or gangrene)
Include	Studies in which people with diabetes and foot ulcer are a subset of people with chronic wounds and data is presented separately.
Exclude	Non-randomised trials RCTs with less than 10 study sample Crossover studies with no washout period and no carry over effects analysis Studies on wound management for other conditions/diseases (other than diabetic foot problems)

Table 41: Summary table of included studies

Author (year)	Population	Comparisons	Outcomes of interest	Follow up	Study Location
Debridement and dressings					
Surgical versus non-surgical debridement					
Piaggesi (1998)	**Patient characteristics:** Patients with type 1 or type 2 diabetes with one or more painless foot ulcer **Evaluable total:** 41 patients (20 received non-operative treatment; 21 received surgical treatment) **Age:** Mean age 64 years	Non-operative treatment (including debridement and dressing) versus surgical conic ulcerectomy	• Wound closure • Healing time • Recurrence of ulceration • Complications	6 months	Italy
Alginate dressings versus control dressing					
Foster (1994)	**Patient characteristics:** Patients aged at least 18 years with a clean diabetic foot ulcer **Evaluable total:** 30 patients (30 received Alginate dressing; 30 received control dressing) **Age:** Mean age 65 years	Alginate dressing versus Foam dressing (control dressing)	• Wound healing • Healing time	28 weeks or until complete healing	UK
Hydrocolloid dressing versus control dressing					
Jensen (1997)	**Patient characteristics:** Patients with Wagner grade II diabetic foot ulcers **Evaluable total:** 31 patients (14 received Hydrogel wound dressing; 17 received control dressing) **Age:** Not reported	Hydrogel wound dressing versus Saline gauze dressing (control)	• Wound closure • Healing time • Adverse events	16 weeks	USA
Piaggesi	**Patient characteristics:**	Hydrofiber wound dressing	• Healing time	8 weeks (or	Italy

Author (year)	Population	Comparisons	Outcomes of interest	Follow up	Study Location
(2001)	Patients with type 1 or type 2 diabetes with foot ulceration of more than 3 weeks duration **Evaluable total:** 20 patients (10 received hydrofibre dressing; 10 received control dressing) **Age:** Mean age 62 years	versus Saline gauze dressing (control)	• Complications	until complete re-epithelisation	
Hydrocolloid dressing versus Alginate dressing					
Jude (2007)	**Patient characteristics:** Adults with type 1 or type 2 diabetes with Wagner grade I or II non-ischaemic diabetic foot ulcers **Evaluable total:** 134 patients (67 received hydrofibre dressing; 67 received calcium alginate dressing) **Age:** Mean age 59 years	Hydofiber wound dressing versus Calcium alginate dressing	• Wound healing • Wound reduction • Healing time • Complications • Adverse events • Withdrawals due to adverse events	8 weeks	18 sites in UK, France, Germany, Sweden
Hydroactive dressing versus hydrophilic dressing					
Clever (1996)	**Patient characteristics:** Patients aged 18-80 years with a pure neuropathic diabetic ulcer of 1-5 cm diameter **Evaluable total:** 40 patients (20 received hydroactive dressing; 20 received hydrophilic dressing) **Age:** Mean age 56 years	Hydroactive dressing versus Hydrophilic dressing	• Healing time • Wound reduction	4 weeks	
Collagen dressing versus control dressing					
Tallis (2013)	**Patient characteristics:** Patients with T1 or T2 diabetes aged 18 years or over with a neuropathic foot ulcer of 0.5-10cm^2 area **Evaluable total:** 48 patients (24 received collagenese	Clostridial collagenase debridement dressing versus saline gauze dressing	• Change in ulcer area	12 weeks	

Author (year)	Population	Comparisons	Outcomes of interest	Follow up	Study Location
	dressing; 24 received saline gauze dressing) **Age:** Mean age 61 years				
Gottrup (2013)	**Patient characteristics:** Patients with a diabetic foot ulcer of at least 30 days duration **Evaluable total:** 39 patients (24 received collagen/ORC/silver dressing; 20 received control dressing) **Age:** Mean age 60 years	Collagen/oxidised regenerated cellulose/silver dressing versus Control dressing	• Wound healing • Adverse events • Withdrawals due to infection	14 weeks	Denmark
Veves (2002)	**Patient characteristics:** Patients aged 18 years or over with a diabetic foot ulcer of at least 30 days duration **Evaluable total:** 188 patients (104 received collagen/ORC dressing; 88 received control dressing) **Age:** Mean age 58 years	Collagen/ oxidised regenerated cellulose dressing versus saline gauze dressing (control dressing)	• Wound healing • Wound surface reduction • Adverse events	12 weeks	USA
Donaghue (1998)	**Patient characteristics:** Patients with diabetes aged at least 21 years being treated for foot ulcerations **Evaluable total:** 61 patients (44 received collagen/alginate dressing; 17 received control dressing) **Age:** Mean age 60 years	Collagen/Alginate dressing versus Saline gauze dressing (control dressing)	• Wound healing • Healing time • Wound reduction	8 weeks	USA
Other dressings					
Jeffcoate (2009)	**Patient characteristics:** Patients with diabetes aged 18 years or over with a chronic full thickness foot ulcer of at least 6 weeks duration **Evaluable total:**	Antiseptic dressing versus Hydrocolloid dressing versus	• Wound healing • Healing time • Amputations • Complications	24 weeks	UK

Author (year)	Population	Comparisons	Outcomes of interest	Follow up	Study Location
	229 patients (87 received inadine dressing;73 received aquacel dressing; 69 received control dressing) **Age:** Mean age 60 years	Non-adherent dressing	• Withdrawals due to adverse events		
Zhang (2014)	**Patient characteristics:** Patients 18 years of age ro older, with evidence of peripheral neuropathy, Wagner Grade I or II, ankle brachial pressure index of >0.5 and a diabetic foot ulcer of ≥ 4 weeks duration **Evaluable total:** Randomised=50 Silicone dressing = 24 Vaseline gauze = 26 **Age:** Mean 61.5 ± 8.3 years	Soft silicone dressing Versus Vaseline gauze	• wound healing, • healing time • wound pain • adverse events	12 weeks	China
Offloading					
Irremovable versus removable offloading devices					
Faglia (2010)	**Patient characteristics:** Adult patients with non-infected University of Texas grade 1A diabetic plantar ulcers **Evaluable total:** 45 patients (23 received total contact cast; 22 received Removable cast walker) **Age:** Mean age 60 years	Nonremovable fiberglass off-bearing cast versus Removable cast walker	• Wound healing • Ulcer reduction	90 days	Italy
Caravaggi (2000)	**Patient characteristics:** Patients with diabetic plantar ulcers **Evaluable total:** 50 patients	Nonremovable fiberglass off-bearing cast versus Therapeutic shoe	• Wound healing	30 days	Italy

Author (year)	Population	Comparisons	Outcomes of interest	Follow up	Study Location
	(26 received fiberglass cast; 24 received therapeutic shoe) **Age:** Mean age 60 years				
Caravaggi (2007)	**Patient characteristics:** Patients with diabetic plantar ulcers **Evaluable total:** A total of 60 patients were randomised to treatment (29 patients received non-removable fiberglass offloading cast; 29 patients received removable pneumatic cast). **Age:** **Mean age not reported**	Non-removable fibreglass offloading cast Versus Removable pneumatic cast	• Wound healing	90 days	Italy
Armstrong (2005)	**Patient characteristics:** Patients with University of Texas grade 1A diabetic foot ulcerations **Evaluable total:** 50 patients (23 received Instant total contact cast 27 received Removable cast walker) **Age:** Mean age 65 years	Instant total contact cast versus Removable cast walker	• Wound healing • Healing time	12 weeks or until complete wound healing	USA
Van de Weg (2008)	**Patient characteristics:** Patients with diabetes and Wagner grade I or II plantar ulcers **Evaluable total:** 43 patients (23 received total contact cast; 20 received custom made shoes) **Age:** Mean age 61 years	Total contact cast versus Custom made temporary footwear	• Wound healing • Wound reduction • Healing time	16 weeks	Denmark
Gutekunst (2011)	**Patient characteristics:** Patients with diabetes and Wagner grade I or II plantar ulceration **Evaluable total:**	Total contact cast versus Removable cast walker boot	• Wound healing • Healing time	Not reported	USA

Author (year)	Population	Comparisons	Outcomes of interest	Follow up	Study Location
	23 patients (11 received Total contact cast; 12 received Cast walker boot) **Age:** Mean age 54 years				
Armstrong (2001)	**Patient characteristics:** Patients with non-infected diabetic plantar ulcers **Evaluable total:** 39 patients (19 received total contact cast; 20 received removable cast walker) **Age:** Not reported	Total contact cast versus Removable cast walker	• Wound healing • Healing time	12 weeks or until complete epithelisation	USA
Lavery (2014)	**Patient characteristics:** Diabetic patients with grade 1A or 2A fore foot ulcers (University of Texas Classification System) on the sole of the foot were enrolled. **Evaluable total:** A total of 73 patients were randomised to treatment (23 patients received healing sandles; 23 patients received total contact casting and 27 patients received shear reducing removable walker). **Age:** Not reported	Patients received a removable healing sandal Versus Patients received a shear reducing removable walker	• Wound healing • Healing time	12 weeks	USA
Irremovable versus irremovable offloading devices					
Piaggesi (2007)	**Patient characteristics:** Patients with forefoot diabetic plantar ulcer of at least 3 weeks duration **Evaluable total:** 40 patients (20 received total contact cast; 20 received instant total contact cast) **Age:** Mean age 60 years	Total contact cast versus Instant total contact cast	• Wound healing • Healing time • Adverse events	12 weeks and up to complete re-epithelialisation	Italy

Author (year)	Population	Comparisons	Outcomes of interest	Follow up	Study Location
Katz (2005)	**Patient characteristics:** Patients with noninfected University of Texas grade 1A or IIA diabetic foot ulcers **Evaluable total:** 41 patients (20 received total contact cast; 21 received instant total contact cast) **Age:** Mean age 50 years	Total contact cast versus Instant total contact cast	• Wound healing • Complications	12 weeks	USA
Irremovable offloading devices versus control dressing					
Mueller (1989)	**Patient characteristics:** Patients with a diabetic plantar ulcer **Evaluable total:** 40 patients (21 received total contact cast; 19 received traditional dressing) **Age:** Mean age 55 years	Total contact cast versus Traditional wet to dry dressing	• Wound healing	6 weeks	USA
Padding versus conventional offloading					
Zimny (2002)	**Patient characteristics:** Patients with Wagner grade I or II diabetic neuropathic forefoot ulcers **Evaluable total:** 54 patients (20 received half shoe; 24 received felted foam; **Age:**	Felted padding Versus half shoe	• Healing time • Wound reduction	10 weeks	Germany
Padding versus padding					
Nube (2006)	**Patient characteristics:** Patients with University of Texas grade 1 plantar ulcers **Evaluable total:** 32 patients (15 received padding to the skin;	Felt deflective padding to skin versus Felt deflective padding in shoe	• Wound reduction	4 weeks or until healed	Australia

Author (year)	Population	Comparisons	Outcomes of interest	Follow up	Study Location
	17 received padding to the shoe) **Age:** Mean age 58 years				

4.10.3 Health Economic Evidence

A literature search was conducted for the question using standard health economics filters appplied to the clinical search strategies. No relevant cost-utility analyses were found. Health economic modelling was not prioritised for this review question

4.10.4 Evidence Statements

Surgical versus non-surgical debridement

One low quality randomised control trial with 41 participants found there was no significant difference between ulcer healing, ulcer recurrences or the number of adverse events for participants receiving surgical or non-surgical debridement.

Alginate dressings versus control dressings

One low quality randomised control trial with 60 participants found there was no significant difference between ulcer healing for diabetic foot ulcers treated with an alginate dressing or a foam dressing.

Hydrofibre dressings versus control dressings

Two very low quality randomised control trial with 51 participants found there was no significant difference between ulcer healing, the number of adverse events or the number of complications for diabetic foot ulcers treated with a hydrofibre dressing or a saline gauze dressing

One very low quality randomised controlled trial with 20 participants found diabetic foot ulcers treated with a hydrofibre dressing healed significantly faster than those treated with a saline gauze dressing.

Hydrocolloid dressings versus Alginate dressings

One low quality randomised control trial with 134 participants found there was no significant difference between ulcer healing, ulcer healing time, number of adverse events or number of complications for diabetic foot ulcers treated with a hydrocolloid dressing or a calcium alginate dressing.

Hydroactive dressings versus hydrophilic dressings

One very low quality randomised control trial with 40 participants found there was no significant difference between ulcer healing time or the change in ulcer size for diabetic foot ulcers treated with a hydroactive dressing or a hydrophilic dressing.

Collagen dressings versus control dressings

Two low to very low quality randomised control trials with 123 participants found the wound size decreased significantly for diabetic foot ulcers treated with a collagen dressing compared to those treated with a saline gauze dressing.

In addition one very low quality randomised controlled trial with 75 participants found there was no significant difference in ulcer healing or ulcer healing time for diabetic foot ulcers treated with a collage/alginate dressing compared to those treated with a saline gauze dressing.

Collagen/oxygen regenerated cellulose/silver dressings versus control dressings

One very low quality randomised control trials with 188 participants found there was no significant difference between changes in ulcer size for diabetic foot ulcers treated with a collagen/oxygen regenerated cellulose/silver dressing or a saline gauze dressing.

A low quality meta-analysis of 2 randomised controlled trials with 224 participants found there was no significant difference in ulcer healing or the number of adverse events for foot ulcers treated with a collagen/oxygen regenerated cellulose/silver dressing compared to a saline gauze dressing.

Other dressings

One moderate quality randomised control trial with 229 participants found there was no significant difference between ulcer healing, healing time, number of amputations, adverse events or complications for diabetic foot ulcers treated with a hydrofibre dressing, impregnated dressing or a non-adherent dressing.

One moderate to low quality randomised control trial with 50 participants found there was no significant difference between adverse events and cure rates for those treated with soft silicone dressing or a Vaseline gauze dressing.

Irremovable versus removable offloading devices

One low quality randomised control trials with 45 participants found there was no significant difference between change in wound size for diabetic foot ulcers treated with a non-removable cast or a removable cast walker.

A very low quality meta-analysis of five randomised control trials with 215 participants found significantly more ulcers healed for non-ischaemic plantar diabetic foot ulcers treated with a non-removable cast compared to a removable cast walker.

A further low quality meta-analysis of three randomised controlled trials with 112 participants found that time to healing was significantly reduced for non-ischaemic plantar diabetic foot ulcers treated with a non-removable cast compared to a removable cast walker.

One low quality randomised control trial with 43 participants found there was no significant difference between change in ulcer size for diabetic foot ulcers treated with a non-removable cast or customised footwear. Ulcers treated with a non-removable cast healed significantly quicker than ulcers treated with customised footwear.

A meta-analysis of 2 low quality randomised control trials with 93 participants found there was no significant difference in ulcer healing for diabetic foot ulcers treated with a non-removable cast or customised footwear.

One low quality randomised control trial with 50 participants found that rate of cure was significantly reduced in those treated with a total contact cast than those treated with a shear reducing removable walker. There was no significant difference in terms of time to healing between groups.

One low quality randomised control trial with 46 participants found that time to healing was significantly reduced in those treated with a total contact cast than those treated with a healing sandal. There was no significant difference in terms of cure rate between groups.

Irremovable versus irremovable offloading devices

One low quality randomised controlled trial with 43 participants found there was no significant difference in ulcer healing time for diabetic foot ulcers treated with a total contact cast versus an instant total contact cast.

A meta-analysis of 2 low quality randomised control trials with 81 participants found there was no significant difference in ulcer healing for diabetic foot ulcers treated with a total contact cast versus an instant total contact cast.

A further meta-analysis of the same studies also found no significant difference in the number of adverse events for diabetic foot ulcers treated with a total contact cast versus an instant total contact cast.

Irremovable offloading devices versus dressings

One low quality randomised control trials with 25 participants found there was no significant difference in ulcer healing for diabetic foot ulcers treated with a total contact cast or a traditional dressing.

Padding versus conventional therapy

One low quality randomised control trials with 54 participants found that healing time was significantly shorter for diabetic foot ulcers treated with a felted foam padding compared to a half shoe but there was no significant difference in change in ulcer size between groups.

Padding versus padding

One low quality randomised control trials with 32 participants found there was no significant difference in change in ulcer size for diabetic foot ulcers treated with felted padding to the skin compared to felted padding within a shoe.

4.10.5 Evidence to Recommendations

Table 42: Linking Evidence to Recommendations Table

Relative value of different outcomes	The guideline development group (GDG) agreed that improving ulceration and re-ulceration rates was the critical outcome for this question and the whole guideline. The GDG argued that if these could be prevented then the subsequent likelihood of other outcomes such as infection, gangrene, amputation and death would be diminished.
	In this review all of the persons will have already developed diabetic foot problems and it will be a case of trying to cure active foot ulceration and reduce the rate of reulceration. This will have long term impact in diminishing the likelihood of further complications from developing such as infection, gangrene, amputation and mortality rate. Reducing the incidence of these complications will also result in reduced rates of hospital admission and improved health-related quality of life.
Trade-off between benefits and harms	It was felt that the benefits of a good treatment strategy for people who have developed diabetic foot problems would include a clear improvement in clinical outcomes as listed above. As mentioned, the main complication that we are eager to be treated is ulceration. If patients can have their foot ulceration heal quickly and reulceration prevented this can protect the development of more severe complications such as

	infection, gangrene and amputation. Secondly that this therapy should be safe and do no harm. Thirdly that it should be available and implementable in the real world. Potential harm as a result of offering the above treatment strategies could be a direct adverse effect as a result of the therapy or if use of the treatment is found to worsen or slow the progress of healing. If a treatment has no effect, this too could lead to wasted resources and possible patient dissatisfaction if the person sees that the diabetic foot problem is not responding to therapy. A poorly motivated patient may allow their disease to go unmanaged or poorly controlled which could lead to an increased likelihood of the development of diabetic foot complications such as ulceration/reulceration. This may, in turn, cause increased rates of infection, gangrene, amputation, hospital admission with the resulting burden on health-related quality of life.
Trade-off between net health benefits and resource use	The GDG considered the cost and clinical effectiveness of each of the interventions discussed and made recommendations with these factors in mind.
Quality of evidence	The group felt the quality rating of evidence needed to reflect the use of certain types of dressings not commonly used in the UK population. The GDG agreed that the use of saline gauze dressings was not common practice in the UK and therefore felt the quality of studies that used this type of dressing needed to be downgraded to reflect this indirect comparison. The GDG felt that the comparison reported by Ganguly et al (2008) was inappropriate (total contact casting vs. conventional dressing) and therefore requested this study was removed from the evidence review.
Other considerations	Debridement: The GDG acknowledged that debridement could be conducted in both community and hospital settings by different healthcare teams. The GDG also agreed the most important issue was that debridement was only conducted by appropriately trained health care professionals and therefore felt it was important to state this in a separate recommendation. Dressings: The group felt that patient decisions, dressing availability, wound severity, and factors such as infection control were all issues that contribute to decisions about the choice of dressing. They therefore felt it was inappropriate to recommend specific types of dressing. The group did however acknowledge that the lowest cost dressings may not necessarily be the most appropriate dressings for patient needs and therefore reflected this in the recommendations. Offloading: The GDG acknowledged that the effectiveness of offloading devices depends, in part, upon patient tolerability and compliance of use. They also noted that custom made footwear was not a standardised practice within the UK, and that removable cast walkers were all very different. They therefore felt it was inappropriate to recommend specific devices. The GDG felt it was inappropriate to generalise the use of total

contact casting to the broad diabetic foot ulcer population, but recognised the findings of the evidence review provided an appropriate guide. They therefore agreed that the recommendation for using total contact non-removable casting should be guided by the population identified within the evidence review namely non-infected, non-ischaemic plantar diabetic foot ulcers.

The GDG agreed it was necessary to provide a comprehensive overview by linking the recommendations made for this evidence review to earlier sections of the guideline.

The GDG also felt it was appropriate to acknowledge the development of pressure ulcers within people who have neuropathic foot ulcers. They therefore provided a cross-reference to recommendations made within the Pressure Ulcers guideline (NICE Clinical guideline 179)

4.10.6   Recommendations

37. Offer 1 or more of the following as standard care for treating diabetic foot ulcers:

- Offloading.
- Control of foot infection.
- Control of ischaemia.
- Wound debridement.
- Wound dressings.

38. Offer non-removable casting to offload plantar neuropathic, non-ischaemic, uninfected forefoot and midfoot diabetic ulcers. Offer an alternative offloading device until casting can be provided.

39. In line with the NICE guideline on pressure ulcers, use pressure-redistributing devices and strategies to minimise the risk of pressure ulcers developing.

40. When treating diabetic foot ulcers, debridement in hospital should only be done by healthcare professionals from the multidisciplinary foot care service, using the technique that best matches their specialist expertise and clinical experience, the site of the diabetic foot ulcer and the person's preference.

41. When treating diabetic foot ulcers, debridement in the community should only be done by healthcare professionals with the relevant training and skills, continuing the care described in the person's treatment plan.

42. When deciding about wound dressings and offloading when treating diabetic foot ulcers, take into account the clinical assessment of the wound and the person's preference, and use devices and dressings with the lowest acquisition cost appropriate to the clinical circumstances.

4.10.7 Research recommendations

What is the clinical effectiveness of different dressing types in treating diabetic foot problems?

Why this is important

The evidence surrounding different dressing types for diabetic foot ulcer was often limited or inconclusive. It is proposed that more randomised controlled trials are undertaken to explore this question, but alternative methodologies may also be considered in the case of treating a complex wound. The proposed study would monitor and evaluate the cure rates of foot ulcer resulting from diabetes, rates and extent of amputation (major or minor), health-related quality of life, adverse events and hospital admission rates and length of stay.

4.11 Antibiotic regimens and antimicrobial therapies

4.11.1 Review question

What is the clinical effectiveness of different antibiotic regimens and antimicrobial therapies for foot infection (with or without osteomyelitis) in people with diabetes?

4.11.2 Evidence review

The aim of this review question was to identify the most effective antibiotic and antimicrobial treatments for foot infection in people with diabetes. This clinical issue has previously been considered in NICE Clinical Guidelines 10 & 119. This question aimed to update the previously published guidelines.The review protocol for this question can be found in Appendix C (under review question 11).

The original and rerun searches identified 9738 abstracts, 56 papers were identified. 35 papers were subsequently excluded because they did not fit the inclusion criteria (see Appendix E for a full list of excluded studies). 21 identified papers were included in the final review. (Clay,P.G. (2004), Schaper,N.C. (2012), Saltoglu,N. (2010), Siami,G. (2001), Vick-Fragoso,R. (2009), Lipsky,B.A. (2012), File, Jr (1983), Bradsher, T (1984), Lipsky, BA, (1997), Grayson, ML, (1994), Erstad, BL (1997), Harkless, L, (2005), Tan, JS, (1993), Bouter, KP, (1996), Lipsky, BA, (2007), Lipsky, BA, (2004), Lipsky, BA, (2005), Lipsky, BA (2005), Hughes, CE (1987), Lipsky BA,(1990), Lauf, L. (2014))

Table 43 outlines the PICO framework used for this review question and Table 44 outlines the class of antibiotics included in this review and their bacterial spectrum of coverage. Table 45 provides a summary of all studies included in the review. The GRADE profiles for these studies are shown in Appendix I. The evidence tables for the newly identified studies and evidence tables for papers used in previous guidelines are shown in Appendix G.

Table 43: PICO framework

Population	Children, young people and adults with type 1 or type 2 diabetes and foot ulcer with soft tissue infection (with or without osteomyelitis or gangrene)
Intervention	Any antibiotic regimen or antimicrobial therapy
Comparator	Standard care Placebo No treatment Head to head comparison Topical antibiotics
Outcomes	Cure rates of foot infection in people with diabetes Rates and extent of amputation (major or minor) Adverse events (treatment failure, healthcare assoc. infections, side effects of antibiotics, mortality, sepsis) Length of stay Health-related quality of life
Include	Studies in which people with diabetes are a subset of the people with foot infection and data is presented separately.
Exclude	Studies on antibiotic regimens and antimicrobial therapies for people with diabetes and infection in a site other than the foot. Studies in which people with foot infection is not a subset of the population or where data is not presented separately.

Table 44: Antibiotics & spectrum of activity

Table showing class of antibiotics identified in the review
and their spectrum of activity

Antibiotic	Broad spectrum[a]	Narrow spectrum[b]
Penicillins		
Amdinocillin		✓
Cloxacillin		✓
Flucloxacillin		✓
Nafcillin		✓
Amoxicillin/Clavulanate	✓	
Ampicillin/Sulbactam	✓	
Piperacillin/Clindamycin	✓	
Piperacillin/Tazobactam	✓	
Ticarcillin/Clavulanate	✓	
Cephalosporins		
Cefoxitin	✓	
Ceftizoxime	✓	
Ceftriaxone	✓	
Cephalexin	✓	
Quinolones		
Clinafloxacin	✓	
Levofloxacin	✓	
Moxifloxacin	✓	
Ofloxacin	✓	
Carbapenems		
Ertapenem	✓	
Imipenem/Cilastatin	✓	
Nitroimidazoles		
Metronidazole	✓	
Lincosamides		
Clindamycin		✓
Oxazolidinones		
Linezolid		✓
Lipopeptide antibiotics		
Daptomycin		✓
Glycoceptide antibiotics		
Vancomycin		✓

(a) Active against both Gram positive & Gram negative bacteria plus specific families of bacteria

(b) Active against either Gram positive or Gram negative bacteria plus specific families of bacteria

Table 45: Summary table of included studies for antibiotic & antimicrobial therapies for diabetic foot infections

Author (year)	Study type	Participants	Class of antibiotic	Drug comparisons	Route	Outcomes	Follow up	Location
Broad spectrum vs. broad spectrum								
Tan et al (1993)	Multi centre double blind RCT	**Patient characteristics:** Hospitalised patients with complicated skin & skin structure bacterial infections **Evaluable total:** 111 patients (67 received Piperacillin-Tazobactam; 44 received Ticarcillin-Clavulanate). 32% had diabetic foot ischaemia **Age:** Mean age 54 years	Ureidopenicilin/ beta lactam inhibitor vs. Carboxypenicilin/ beta lactam inhibitor	Piperacillin-Tazobactam vs. Ticarcillin-Clavulanate	IV[1] vs. IV	• Cured or improved condition of ulcer	10-14 days	USA Inpatient
Lauf (2014)	Multi centre double blind RCT	**Inclusion criteria:** hospitalised men and women with diabetes mellitus who had a foot infection. **Evaluable total:** 111 patients (67 received Piperacillin-Tazobactam; 44 received Ticarcillin-Clavulanate). 32% had diabetic foot ischaemia **Age:** Mean age 59 years	Glycylcycline-class antimicrobial agent Vs Carbapenem	150 mg once-daily, parenteral intravenous [IV] tigecycline Vs 1 g once-daily intravenous [IV] ertapenem ± vancomycin	IV vs IV	• Clinical cure • Adverse events	Follow up was at the test of cure assessment: (12 to 92 days after the last dose for those without osteomyelitis) (25-27 weeks for subjects in the substudy arm with osteomyelitis).	USA Inpatient
Paul-Bouter et al (1996)	Double blind RCT	**Patient characteristics:** Hospitalised patients with	Carbapenem/ beta lactam	Imipenem/ Cilastatin	IV vs. IV	• Cured or improved	10 days	Netherlands Inpatient

Author (year)	Study type	Participants	Class of antibiotic	Drug comparisons	Route	Outcomes	Follow up	Location
		Wagner classified diabetic foot lesions stage II, III or IV **Evaluable total:** 185 patients (96 received Piperacillin/Tazobactam; 89 received ampicillin/Sulbactam **Age:** Mean age 59 years	inhibitor vs. Ureidopenicillin/ clindamycin	vs. Piperacillin/ clindamycin		condition of ulcer • Eradication of pathogens • Adverse events		
Grayson et al (1994)	Double blind RCT	Patient characteristics: Diabetic patients with limb-threatening infection of a lower-extremity **Evaluable total:** 93 patients (47 received ampicillin/subactam; 46 received imipenem/Cilastatin **Age:** Mean age 60 years	Carbapenem/ beta lactam inhibitor vs. Aminopenicillin/ beta lactam inhibitor	Imipenem/ Cilastatin. Vs. Ampicillin/ Sulbactam	IV vs. IV	• Cured or improved condition of ulcer • Adverse events • Eradication of pathogens	6 days	USA Inpatient
Harkless et al (2005)	Multi centre open label RCT	**Patient characteristics:** Adult patients with diabetes mellitus & open infected foot ulcers **Evaluable total:** 185 patients (96 received Piperacillin/Tazobactam; 89 received ampicillin/Sulbactam **Age:** Mean age 59 years	Ureidopenicillin/ beta lactam inhibitor vs. Aminopenicillin/ beta lactam inhibitor	Piperacillin/ Tazobactam vs. Ampicillin/ Sulbactam	IV vs. IV	• Cured or improved condition of ulcer • Eradication of pathogens • Adverse events • Withdrawals due to Adverse event	14-21 days	USA Inpatient
Hughes et al (1987)	Dual centre double blind RCT	**Patient characteristics:** Patients with a history or clinical evidence of peripheral arterial insufficiency or diabetes &	Cephalosporin vs. Cephalosporin	Cefoxitin vs. Ceftizoxime	IV vs. IV	• Cured or improved condition of ulcer • Adverse events	Up to 3 months	USA Inpatient

Author (year)	Study type	Participants	Class of antibiotic	Drug comparisons	Route	Outcomes	Follow up	Location
		two or more signs of lower extremity infection **Evaluable total:** 53 patients (28 received ceftizoxim 25 received cefoxitin. 80% had diabetes; 32% had soft tissue infections & 30% had osteomyelitis. **Age:** Mean age 64.2 years				• Eradication of pathogens		
Lipsky et al (2005)	Multi centre double blind RCT	**Patient characteristics:** Patients with diabetes mellitus & a foot infection & requiring IV antibiotics **Evaluable total:** 445 patients (226 received ertapenem; 219 received Piperacillin/ Tazobactam) **Age:** Mean age 58 years	Ureidopenicillin/ beta lactam inhibitor vs. Carbapenem	Piperacillin/ Tazobactam vs. Ertapenem	IV vs. IV	• Cured or improved condition of ulcer	Up to 5 days	USA Inpatient
Saltoglu et al (2010)	Open label RCT	**Patient characteristics:** Hospitalised adults with a clinical diagnosis of moderate to severe diabetic lower-extremity infection. **Evaluable total:** 62 patients (30 received Piperacillin/Tazobactam; 32 received imipenem/Cilastatin **Age:** Mean age 58.4 years	Ureidopenicillin/ beta lactam inhibitor vs. Carbapenem/ beta lactam inhibitor	Piperacillin/ Tazobactam vs. Imipenem/ Cilastatin	IV vs. IV	• Cured or improved condition of ulcer • Isolated microorganisms • Adverse events	2 months	Turkey Inpatient
Erstad & McIntyre	Double-blind RCT	**Patient characteristics:** Adults who required	Cephalosporin Vs.	Cefoxitin vs.	IV vs. IV	• Cured or improved	At least 5 days	USA Inpatient

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Author (year)	Study type	Participants	Class of antibiotic	Drug comparisons	Route	Outcomes	Follow up	Location
(1997)		hospitalisation for a diabetic foot infection. Evaluable total:36 patients (18 received Ampicillin/Sulbactam; 18 received cefoxitin **Age:** Mean age 59 years	Aminopenicillin/ beta lactam inhibitor	Ampicillin/ Sulbactam		condition of ulcer • Length of hospital stay • Eradication of pathogens		
Schaper et al (2013)	Multi centre double blind RCT	**Patient characteristics:** Hospitalised adults with a diabetic foot infection requiring surgery & antibiotics3. **Evaluable total:** 206 patients (110 received moxifloxacin; 96 received Piperacillin/Tazobactam & amoxicillin/clavulanate **Age:** Mean age 64 years	Quinolone vs. Ureidopenicillin/ beta lactam inhibitor & Aminopenicillin/ beta lactam inhibitor	Moxifloxacin vs. Piperacillin/ Tazobactam & Amoxicillin/ Clavulanate	IV or oral vs. IV or oral	• Cured or improved condition of ulcer • Eradication of pathogens • Adverse events	7-21 days	Netherlands, UK, Germany, France, USA & Belgium Inpatient
Bradsher & Snow (1984)	Dual centre RCT	**Patient characteristics:** Hospitalised adults with suspected serious skin & soft tissue infections. **Evaluable total:** 84 patients (22 received cefazolin; 22 received ceftriaxone). 45% were being treated for a diabetic foot ulcer **Age:** Mean age 55 years	Cephalosporin vs. Cephalosporin	Ceftriaxone vs. Cefazolin	IV or IM[2] vs. IV	• Cured or improved condition of ulcer • Eradication of pathogens • Adverse events • Surgeries required	Not reported	USA Inpatient
Siami et al (2001)	Multi centre parallel group	**Patient characteristics:** Adult patients with a severe or limb-threatening	Quinolone vs. Ureidopenicillin/	Clinafloxacin vs. Piperacillin/	IV and oral vs. IV and oral	• Cured or improved condition of	14 days	Canada Inpatient

[3] A sub-set of patients enrolled in RELIEF trial

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Author (year)	Study type	Participants	Class of antibiotic	Drug comparisons	Route	Outcomes	Follow up	Location
	single blind RCT	skin & soft tissue infection[4]. **Evaluable total:** 409 patients (213 received clinafloxacin; 196 received Piperacillin/ Tazobactam **Age**: Mean age 58.4 years	beta lactam inhibitor	Tazobactam		ulcer • Eradication of pathogens		
Lipsky et al (1997)	Multi centre RCT	**Patient characteristics:** Hospitalised patients with diabetes mellitus & a foot infection **Evaluable total:** 88 patients (47 received Ofloxacin; 41 received amino-penicillins **Age:** Mean age 61.5 years	Quinolone vs. Aminopenicillin/ beta lactam inhibitor	Ofloxacin vs. Ampicillin/ Sulbactam & Amoxicillin Clavulanate	IV and oral vs. IV and oral	• Cured or improved condition of ulcer • Eradication of pathogens • Adverse events	7 days	USA Inpatient
Vick-Fragoso et al (2009)	Multi centre parallel group open label RCT	**Patient characteristics:** Adult patients with a complicated skin & soft tissue infection at 1 site only. **Evaluable total:** 427 patients (219 received moxifloxacin; 208 received amoxicillin/clavulanate **Age:** Mean age 52 years	Quinoonle vs. Aminopenicillin/ beta lactam inhibitor	Moxifloxacin vs. Amoxicillin/ Clavulanate	IV and oral vs. IV and oral	• Cure rates • Treatment duration • Eradication of pathogens • Adverse event	14-28 days	74 centres worldwide Inpatient
Lipsky et al (2007)	Multi centre double	**Patient characteristics:** Hospitalised patients with a cSSSI identified as a	Quinolone vs. Ureidopenicillin/	Moxifloxacin vs. Amoxicillin/	IV vs. IV or	• Cured rates • Eradication of pathogens	10-42 days	6 countries Inpatient

[4] Population included diagnosis of spontaneous infection or diabetic foot infections

Author (year)	Study type	Participants	Class of antibiotic	Drug comparisons	Route	Outcomes	Follow up	Location
	blind RCT	diabetic foot infection **Evaluable total:** 127 patients (63 received moxifloxacin; 64 received Piperacillin/Tazobactam **Age:** Mean age 57 years	beta lactam inhibitor	Clavulanate & Piperacillin/ Tazobactam	oral	• Adverse events • Withdrawals due to adverse event		
**Broad spectrum systemic vs. broad spectrum systemic + broad spectrum topical**
Lipsky et al (2012)	Multi centre open label RCT	**Patient characteristics:** Diabetic patients aged 18 to 80 years with a single moderately infected lower extremity ulcer **Evaluable total:** 33 patients (18 received gentamicin collagen sponge; 10 received Levofloxacin) **Age:** Mean age not 56.8	Quinolone & gentamicin sponge dressing vs. Quinolone & placebo sponge dressing	Levofloxacin & Gentamicin collagen sponge vs. Levofloxacin & placebo sponge	Oral and topical vs. oral	• Cured or improved condition of ulcer • Eradication of pathogens • Adverse events	14 days after treatment ceased	USA Outpatient
**Broad spectrum & Broad spectrum vs. Broad spectrum**
Clay et al (2004)	Open label RCT	**Patient characteristics:** Hospitalised adult male patients with diabetes mellitus & a lower extremity infection. **Evaluable total:** 70 patients (36 received metronidazole & ceftriaxone; 34 received ticarcillin/ clavulanate) **Age:** Mean age 63.8 years	Nitroimidazole & Cephalosporin vs. carboxypenicillin/ beta lactam inhibitor	Metronidazole & Ceftriaxone vs. Ticarcillin/ Clavulanate	IV vs. IV	• Cured or improved condition of ulcer • Mean duration of treatment	At least 4 days	USA Inpatient
**Narrow spectrum vs. Broad spectrum**
Lipsky et al (1990)	Double blind RCT	**Patient characteristics:** Outpatients with lower-	Lincosamide vs.	Clindamycin Hydrochloride	Oral vs.	• Cure or complete healing of ulcer	14 days	USA Outpatient

Author (year)	Study type	Participants	Class of antibiotic	Drug comparisons	Route	Outcomes	Follow up	Location
		extremity infections **Evaluable total:** 56 patients (29 received Cephalexin; 27 received clindamycin hydrochloride **Age:** Mean age 61 years	Cephalosporin	vs. Cephalexin	oral			
Lipsky et al (2004)	Multi centre open label RCT	**Patient characteristics:** Patients with diabetes mellitus & a foot infection **Evaluable total:** 361 patients (241 received Linezolid; 120 received aminopenicillin/ β lactamase inhibitors) **Age:** Mean age 62 years	Oxazolidinone vs. Penicillin/ beta lactam inhibitor & Aminopenicillin/ beta lactam inhibitor &	Linezolid vs. Ampicillin/ Sulbactam & Amoxicillin Clavulanate	IV or oral vs. IV or oral	• Cured or improved condition of ulcer • Eradication of pathogens • Adverse events • Withdrawals due to adverse event	15-21 days	8 countries Inpatient
Narrow spectrum & Broad spectrum vs. Broad spectrum								
File & Tan (1983)	Single blind open label trial	**Patient characteristics:** Hospitalised patients with clinical evidence of bacterial soft tissue infection. **Evaluable total:** 41 patients (20 received combination therapy; 21 received cefoxitin alone). 90% had infection of the leg or foot & 61% had diabetes. **Age:** Mean age 56 years	Penicillin plus Cephalosporin vs. Cephalosporin	Amdinocillin & Cefoxitin vs. Cefoxitin	IV vs. IV	• Cured or improved condition of ulcer • Patients needing amputations • Eradication of pathogens	Mean duration of therapy 14 days	USA Inpatient
Narrow spectrum & Narrow spectrum vs. Narrow spectrum & Narrow spectrum								
Lipsky & Stoutenbur	Multi centre single	**Patient characteristics:** Hospitalised patient with an complicated skin &	Lipopeptide & semi-synthetic	Daptomycin & semi synthetic penicillin	IV vs. IV	• Cured or improved	6-20 days	USA, Europe, South Africa,

Author (year)	Study type	Participants	Class of antibiotic	Drug comparisons	Route	Outcomes	Follow up	Location
gh (2005)	blind RCT	skin structure infection (with & without diabetes) **Evaluable total:** 103 patients (47 received daptomycin; 27 received semi-synthetic penicillin; 29 received vancomycin) **Age:** Mean age 62 years	penicillin vs. Glycoceptide & semi-synthetic penicillin	(nafcillin, oxacillin, cloxacillin or flucloxacillin) vs. Vancomycin & semi synthetic penicillin		condition of ulcer		Australia Israel Inpatient

4.11.3 Health economic evidence

A literature search was conducted for the question using standard health economics filters appplied to the clinical search strategies. No relevant cost-utility analyses were found. Health economic modelling was not prioritised for this review question

4.11.4 Evidence statements

Broad spectrum antibiotics versus broad spectrum antibiotics

Eleven RCTs of moderate to very low quality with 1824 participants reported no significant differences in the number of clinical cures, eradication of pathogens, the number of withdrawals due to adverse events, number of amputations and length of stay.

Two moderate to low quality RCTs with 307 participants found that the number of adverse events was significantly more for participants who received Imipenem/Cilastatin compared to participants who received Piperacillin/Clindamycin and for participants who received Moxifloxacin compared to participants who received Piperacillin/Tazobactam & Amoxicillin/Clavulanate.

One low quality RCT with 944 participants found that the number of study withdrawals due to adverse events was significantly lower for participants who had received ertapenem ± vancomycin compared to participants who had received tigecycline. The same trial found no significant difference between groups in terms of clinical cure or drug discontinuation due to adverse events.

Combination broad spectrum antibiotics versus single broad spectrum antibiotics

One low quality RCT with 70 participants reported no significant differences in the number of clinical cures or the mean duration of treatment between participants who received Metronidazole & Ceftriaxone and participants who received Ticarcillin/Clavulanate.

Narrow spectrum antibiotics versus broad spectrum antibiotics

One low quality RCT with 56 participants reported no significant differences in the number of clinical cures between participants who received Clindamycin hydrochloride and participants who received Cephalexin

However, another low quality RCT with 361 participants found that the number of adverse events was significantly more for participants that received Linezolid compared to participants who received Ampicillin/Sulbactam & Amoxicillin/Clavulanate.

Narrow spectrum & broad spectrum versus broad spectrum antibiotics

One low quality RCT with 41 participants reported no significant differences in the number of clinical cures, eradication of pathogens and the number of adverse events experienced between participants who received Amdinocillin & Cefoxitin and participants who received Cefoxitin alone.

Combination narrow spectrum versus combination narrow spectrum antibiotics

One low quality RCT with 103 participants reported no significant difference in the number of clinical cures between participants who received Daptomycin and semi-synthetic penicillin's or Vancomycin and semi-synthetic penicillin's.

4.11.5 Evidence to recommendations

Table 46: Linking Evidence to Recommendations Table

Relative value of different outcomes	The guideline development group (GDG) agreed that improving ulceration and re-ulceration rates was the critical outcome for this question and the guideline. The GDG argued that if these could be prevented then the subsequent likelihood of other outcomes such as infection, gangrene, amputation and death would be diminished.
	In this review all of the persons included will have already developed diabetic foot infection and it will be a case of treating active foot ulceration/infection. This will have long term impact in diminishing the likelihood of further complications from developing such as gangrene, amputation and death. Reducing the incidence of these complications will also result in reduced length of hospital admission with implications for better health-related quality of life.
Trade-off between benefits and harms	It was felt that the benefits of appropriate antibiotic therapy for people who have developed diabetic foot infections should include a clear improvement in the clinical outcomes listed above. At this stage we treat the infection with a view to helping to heal the underlying foot ulceration. If patients can have their foot infection heal quickly, underlying ulceration managed and reulceration prevented this can protect against the development of more severe complications such as gangrene and amputation. Secondly this therapy should be safe and do no harm.
	Potential harm as a result of offering the above treatment strategies includes any serious adverse effect found to worsen or slow the progress of healing. If a treatment has no effect, this too could lead to wasted resources and possible patient dissatisfaction if the patient sees that the diabetic foot problem is not responding to therapy. Adverse effects in themselves, even if not serious, may cause the patient to lose motivation for treatment and adhere poorly. This may, in turn, cause increased rates of gangrene, amputation, hospital admission with the resulting poor health-related quality of life if the disease is not properly controlled.
Economic considerations	Health economics were not considered as a priority for this review question. No economic studies were found.
	The GDG were careful to consider the resource implications of recommending one treatment over another.
Quality of evidence	The group agreed that the quality of evidence provided a good reflection of the interventions considered in the evidence review. However, the GDG chose to exclude the study by Lipsky et al (2008) as they believed the difference in microbiological methodology used in the study, could not be sufficiently reflected by the quality assessment and GRADE methodology. The group agreed it was not appropriate to consider the study as part of the evidence base.
Other considerations	The GDG had a discussion about the end-point of eradication of pathogens being of no clinical value (i.e. It is irrelevant whether following antibiotics the investigator continues to isolate an

organism or not as this has little or no bearing on the clinical response/wound healing.)

The group recognised that the recommendations needed to reflect all healthcare settings and discussed the relevance of studies undertaken in different geographical locations and being unable to extrapolate the results to a UK NHS setting because of differences in organism resistance prevalence. The recommendation was made that antibiotic treatment should reflect local guidelines and patterns of resistance.

The GDG acknowledged that it is very difficult to define broad and narrow spectrum antibiotics. Historically, pathogens change and population resistance also changes. For this reason, the group recognised that studies conducted several decades ago may not be relevant in the present day.

The group also discussed how to differentiate between mild, moderate and severe diabetic foot infections. The group agreed that the recommendations should reflect commonly used infection classification systems in the UK such as PEDIS and IDSA. In particular, the committee noted the utility of table 2 in the Infectious Diseases Society of America (IDSA) 2012 guidelines, which shows the PEDIS grades and ISDA infection severity classifications for diabetic foot infections.

The GDG heard the evidence presented from a randomised trial showing that tigecycline had failed a non-inferiority test against ertapenem +- vancomycin. They considered that this evidence may be sufficient to make a recommendation against the use of tigecycline in the treatment of diabetic foot infection.

The GDG also considered the need for antibiotics in people with diabetic foot infections and osteomyelitis. Although the evidence review did not specifically identify any findings for this sub-population, the group noted that people with osteomyelitis may require antibiotic therapy for a longer duration and therefore thought it was necessary to provide a specific recommendation to reflect this. That said, they also recognised that the treatment of osteomyelitis may be shortened by surgical intervention, therefore the wording "usually 6 weeks," was used.

4.11.6 Recommendations

43. **All hospital, primary care and community settings should have antibiotic guidelines covering the care pathway for managing diabetic foot infections that take into account local patterns of resistance.**

44. **Do not offer antibiotics to prevent diabetic foot infections.**

45. **Start antibiotic treatment for suspected diabetic foot infection as soon as possible. Take cultures and samples before, or as close as possible to, the start of antibiotic treatment.**

46. **Choose the antibiotic treatment based on the severity of the diabetic foot infection, the care setting, and the person's preferences, clinical situation and medical history and, if more than 1 regimen is appropriate, select the regimen with the lowest acquisition cost.**

47. **Decide the targeted antibiotic regimen for diabetic foot infections based on the clinical response to antibiotics and the results of the microbiological examination.**

48. **Do not offer tigecycline to treat diabetic foot infections unless other antibiotics are not suitable.**

49. **For mild diabetic foot infections, initially offer oral antibiotics with activity against gram-positive organisms.**

50. **Do not use prolonged antibiotic treatment (more than 14 days) for the treatment of mild soft tissue diabetic foot infections.**

51. **For moderate and severe diabetic foot infections, initially offer antibiotics with activity against gram-positive and gram-negative organisms, including anaerobic bacteria, as follows:**

    - Moderate infections: base the route of administration on the clinical situation and the choice of antibiotic.
    - Severe infections: start with intravenous antibiotics and then reassess, based on the clinical situation.

52. **Offer prolonged antibiotic treatment (usually 6 weeks) to people with diabetes and osteomyelitis, according to local protocols.**

4.11.7 Research recommendations

No research recommendations were drafted for this review question.

4.12 Adjunctive treatments for diabetic foot problems

4.12.1 Review Question

What is the clinical effectiveness of adjunctive treatments in treating diabetic foot problems?

4.12.2 Evidence Review

The aim of this review was to find the clinical and cost-effectiveness of the available adjunctive therapies for the management of diabetic foot ulcer. Adjunctive therapies can be understood as those treatments that can be added to the current standard of care in an effort to produce better outcomes for patients. These strategies include dermal or skin substitutes, growth factors, hyperbaric oxygen therapy, bio-debridement, topical negative pressure therapy, electrical stimulation and others. The review protocol for this question can be found in Appendix C (under review question 12)

Elements of this question were previously addressed by NICE clinical guideline 119 (CG119) and clinical guideline 10 (CG10). These areas were updated in this review in order to account for the amount of new evidence.

The original and rerun searches identified 1406 abstracts, 371 papers were identified. After ordering full paper copies, 308 papers were subsequently excluded because they did not fit the inclusion criteria (see Appendix B for a full list of excluded studies). Sixty two new papers from 58 original trials were included in the final review. One further study was found on citation check. (Edmonds, M. (2009), Abidia, A. (2003), Ma, L. (2013). Löndahl, M. (2010). Löndahl, M.(2011). Katarina, H. (2009). Faglia, E. (1996). Gentzkow, G. D. (1996). Veves, A. (2001). Veves,A.(1999). Sams,H.H. (2002), Marston, W. A. (2003). Hanft, J. R. (2002). Zelen, C. M. (2013). Caravaggi, C. (2003). Uccioli, L. (2011). Rajendra Prasad Agrawal, (2009). Robson, M. C. (2005). Smiell, J. M. (1999). Wieman, T. J. (1998). Robson,M.C. (2002). Steed, D. L. (2006). Hardikar, J. V. (2005). Jaiswal, S. S. (2010). Bhansali, A. (2009). Robson, M. C. (1999). Richard, J. L. (1995). Steed, D. L. (1992). Uchi, H. (2009). Hanft, J. R. (2008). Steed, D. L. (1995). Brigido, S. A. (2004). Brigido, S. A. (2006). Reyzelman, A. (2009). Akbari, A. (2007). Blume, P. (2011). Kaviani, A. (2011). Yingsakmongkol, N. (2011). Yingsakmongkol, N. (2013). Han, S. K. (2010). Tallis, A. (2013). Moretti, B. (2009). Lyons, T. E. (2007). Veves, A. (2002). You, H. J. (2012). Jeffcoate, W.J. (2009). Driver, V. R. (2006). Tom, W. L. (2005). Fife, C. (2007). Peters, E. J. (2001). Marfella, R. (2012). Gottrup, F. (2013). Alvarez, O. M. (2003). Larijani, B. (2008). Bahrami, A. (2008). Mulder, G. D. (1994). Bashmakov, Y. K. (2014). Siavash, M. (2013). Lavery, L. A. (2014). Gomez-Villa, R. (2014). Mueller, M. J. (2003). Blume, P. A. (2008). Armstrong DG (2005))

These papers were extracted for relevant information and were used to fill both the evidence tables and the GRADE profiles. The GRADE profiles for the included studies are included in Appendix I. The evidence tables are shown in Appendix G. Forest plots for the data discussed can be found in Appendix H.

Table 47 outlines the PICO framework used for this review question.

Table 47: PICO framework

Population	Children, young people and adults with type 1 or type 2 diabetes and foot ulcer (with or without soft tissue infection, osteomyelitis or gangrene)
Intervention	Adjunctive therapies, such as: dermal or skin substitutes skin grafts growth factors hyperbaric oxygen therapy hydro-debridement

	topical negative pressure therapy electrical stimulation ultrasonic simulation laser therapy surgical intervention (offloading / biomechanical healing) leucopatch
Comparator	The standard care of diabetic foot ulcer: Wound dressing Debridement Offloading Without adjunctive therapy
Outcomes	Cure rates of foot ulcer resulting from diabetes 1 Rates and extent of amputation (major or minor) 2 Length of stay 3 Health-related quality of life Adverse events
Include	Randomised controlled trials Crossover studies with a suitable washout period and carry over effects analysis Systematic reviews
Exclude	Non-randomised trials RCTs with < 10 study sample Crossover studies with no washout period and no carry over effects analysis Studies on adjunctive therapies for other conditions/diseases (other than diabetic foot problems).

After the development of the review protocol a further discussion was had with the Guideline Development Group in which it was agreed that a definition for standard care should be established in order to remove studies for which no direct comparison was possible due to a clear difference in standard of care when compared to UK practice. It was agreed that the baseline care of participants should include regular dressing changes, debridement and offloading. Studies that did not meet these standards were excluded. Studies that compared 2 or more adjunctive therapies without a placebo or standard care group were also excluded on the basis that these could not provide useful information by pairwise meta-analysis for the development of recommendations.

Therapies specifically for treatment of diabetic foot infection were already covered by other review questions (see sections 4.11 and 4.9), and were excluded from this review. Studies comparing different antibiotic regimens in patients with infected foot ulcers were felt to be better covered by another review question (Section 4.11), and were excluded from this review.

4.12.2.1 Summary of quality and methodological issues

In total, 57 trials were included that covered 36 different types of adjunctive therapy. These can be broadly grouped into 11 categories: Dermal or skin substitutes, Growth factor therapy, topical creams or ointments, immunomodulating topical or oral treatments, modern dressing product, hyperbaric oxygen therapy, low level laser therapy, electrical stimulation, external shock wave therapy, oral/topical/intravenous herbal therapies and non-contact normothermic wound therapy. Descriptions of these therapies can be found in the respective evidence tables in Appendix G.

Many included studies were downgraded for bias due to methodological issues such as:

- Unclear randomisation method

- Differences between groups at baseline

- Small sample size

- Large attrition rates

- Lack of blinding

- Evidence of sponsor influence (termination of trial early etc)

- Evidence of variance of care between groups

Additionally across outcomes, the majority of adjunctive therapies were found to have evidence of low or very low quality due to:

- Imprecision: if the confidence intervals for an outcome were found to cross one line of minimum important difference the study was downgraded once for quality. If the confidence intervals for a point estimate of effect were found to cross two lines of minimum important difference, the study was downgraded twice for quality.

- Inconsistency: only some of the outcomes were found to have papers with a high enough degree of heterogeneity (I^2) to downgrade for quality. If an outcome were found to have a 33-66% degree of heterogeneity between studies, the outcome was downgraded once for quality. If an outcome was found to have a 66% or higher degree of heterogeneity between studies, the outcome was downgraded twice for quality.

- Methodological bias: As described above.

In regards to indirectness of evidence, having taken measures to ensure that all included papers were comparable in terms of standard of care has meant that no outcomes were downgraded for indirectness of evidence.

A summary of the evidence for the outcomes of cure rate, amputation rate, length of hospital stay, rate of adverse events and rate of infection can be found below along with the relevant GRADE tables.

4.12.2.2 Rate of Cure of diabetic foot ulcers at 12 weeks

Cure rate at 12 weeks was chosen as the primary outcome for most studies, however the range of follow up after adjunctive therapy could vary from 4 weeks to 24 weeks. For two studies (Londahl et al 2010, Abidia et al 2003) which had a follow up of 1 year, results were presented for a year follow up for hyperbaric oxygen therapy. Regardless of this variance it was felt that the study data would still prove useful if pooled.

Forty eight studies (AGRAWAL 2009, Jaiswal 2010, Robson 2005, Hardikar 2005, Robson 1999, Richard 1995, Uchi 2009, Steed 1992, Blume 2011, Hanft 2008, marfella 2012, Driver 2006, Zelen 2013, Caravaggi 2003, Uccioli 2011, Veves 2001, Gentzkow 1996, Hanft 2002, Marston 2003, Brigido 2006, Reyzelman 2009, You 2012, Edmonds 2009, Lyons 2007, Moretti 2009, Fife 2007, Gottrup 2013, Veves 2002, Mulder 1994, Bahrami 2008, Bahrami 2008, Abidia 2003, Londahl 2010, Ma 2013, Jeffcoate 2009, Kaviani 2011, Peters 2001, Alvarez 2003, Tom 2005, Han 2010, Steed 1995, Blume 2008, Mueller 2003, Gomez-Villa 2014, Lavery 2014, Siavash 2013, Bashmakov 2014, Armstrong 2005) reported on the amount of complete ulcer cures within a certain time (12 weeks most commonly). This

outcome was generally defined as 100% epithelialisation as reported by an investigator. Forest plots can be found in Appendix H and GRADE profiles in appendix I.

4.12.2.3 Amputation at 12 weeks

Eleven studies (Veves 2001, Marfella 2012, Yingsakmongkol 2011, Abidia 2003, Faglia 1996, Londahl 2010, Jeffcoate 2009, Kaviani 2011, Peters 2001, Blume 2008, Lavery 2014, Armstrong 2005) reported on the amount of amputation events within a certain time (12 weeks most commonly). This outcome was generally defined as all amputations or separated for major or minor amputations. Forest plots can be found in Appendix H and GRADE profiles in appendix I.

4.12.2.4 Quality of life

Three studies (Abidia 2003, Londahl 2011, Jeffcoate 2009) reported quality of life outcomes for their participants. These outcomes included use SF-36 short forms, HADS and Cardiff Wound Impact Schedule (CWIS). Since not all of the papers produced comparative data, and results were mostly reported in P values with different quality of life measures used, available data was not suitable for producing Forest plots. GRADE profiles for these outcomes can be found in appendix I.

4.12.2.5 Length of hospital stay

One study (Flaglia 1996) reported length of hospital stay for participants receiving hyperbaric oxygen therapy. These outcomes were reported in mean days of hospital stay. Forest plots can be found in Appendix H and GRADE profiles in appendix I.

4.12.2.6 Adverse events

Thirty-nine studies (Bhansali 2009, Jaiswal 2010, Robson 2005, Robson 1999, Caravaggi 2003, Hanft 2002, Uchi 2009, Blume 2011, Hanft 2008, marfella 2012, Driver 2006, Zelen 2013, Caravaggi 2003, Uccioli 2011, Hanft 2002, Brigido 2004, Reyzelman 2009, You 2012, Edmonds 2009, Lyons 2007, Gottrup 2013, Veves 2002, Bahrami 2008, Bahrami 2008, Larijani 2008, Londahl 2010, Ma 2013, Jeffcoate 2009, Kaviani 2011, Peters 2001, Alvarez 2003, Han 2010, Akbari 2007, Steed 1995, Tallis 2013, Blume 2008, Gomez-Villa 2014, Lavery 2014, Hardikar 2005) reported on the amount of adverse events within a certain time (12 weeks most commonly). This outcome was generally defined as all adverse events or serious adverse events, data was pooled where possible. Forest plots can be found in Appendix H and GRADE profiles in appendix I.

4.12.2.7 Infection at 12 weeks

Twenty-one studies (AGRAWAL 2009, Jaiswal 2010, Robson 2005, Robson 1999, Richard 1995, Uchi 2009, Hanft 2008, Uccioli 2011, Veves 2001, Gentzkow 1996, Hanft 2002, Marston 2003, Brigido 2006, You 2012, Moretti 2009, Fife 2007, Gottrup 2013, Veves 2002, Mulder 1994, Jeffcoate 2009, Kaviani 2011, Peters 2001) reported on the amount of newly infected foot ulcers within a certain time (12 weeks most commonly). This outcome was generally defined as all infections clearly associated with the foot ulcer including cellulitis, osteomyelitis etc. data was pooled where possible. Forest plots can be found in Appendix H and GRADE profiles in appendix I.

Table 48: Summary table of included studies

Author (year)	Population	Comparisons	Outcomes of interest	Follow up	Study Location
Apligraf vs standard care					
Edmonds 2009	Randomised= 72 Treatment group= 33 Control group = 42 Inclusion: Aged 18-80 years Written informed consent Ulcer of primarily neuropathic origin, limited to plantar region, through the dermis without sinus tract, tendon capsule or bone exposure. Present at least 2 weeks at the date of screening. Surface area between 1 and 16 cm². Maximum of two ulcers on target foot. Not infected. Diminished sensation. Diabetic type 1 or type 2 Adequate vascular supply to target extremity Available to visit outpatient department for 6.5 months Can tolerate extensive debridement Can follow strict offloading requirements	Apligraf placed directly on the bed of the target ulcer. Then a primary, nonadherent dressing. Secondary dressing then applied to the site. Standard care was consistent with international treatment guidelines and comprised of sharp debridement, saline-moistened dressings and a non-weight bearing regimen. Versus Control group received the same primary and secondary dressings without the Apligraf. As well as standard care.	Cure rates of foot ulcer resulting from diabetes: Incidence to complete healing by 12 weeks: Number of non-fatal serious adverse events	3 months	United Kingdom, European Union, Australia
Hyperbaric oxygen therapy vs standard care					
Abidia (2003)	Randomised= 18 Treatment group= 9 Control group = 9 Inclusion:	Hyperbaric 100% oxygen given in a multi-place chamber via hood at a pressure of 2.4 atmospheres absolute for 90 minutes daily, 5 days per week, totalling 30	• Cure rates of foot ulcer resulting from diabetes: • Rates and extent of amputation: • Health related quality of	1 year	UK

The glossary has been updated to include a definifition of deformity.

Author (year)	Population	Comparisons	Outcomes of interest	Follow up	Study Location
	Ulcer 1–10 cm in maximum diameter. Non-healing despite optimum medical management for more than 6 weeks since presenting. Occlusive arterial disease confirmed by ankle brachial pressure index <0.8 (or great toe-brachial pressure index <0.7 if calf muscles were incompressible) HbA1c <8.5%	sessions. Versus Air given in a multi-place chamber via hood at a pressure of 2.4 atmospheres absolute for 90 minutes daily, 5 days per week, totalling 30 sessions. Wound care was standardised for all patients and included offloading, aggressive debridement and dressing which ensured that a moist wound environment was maintained. Antibiotic therapy was given if there were signs of infection.	life:		
Hyperbaric oxygen therapy versus standard care					
Ma (2013)	Randomised= 36 Treatment group= 18 Control group = 18 Inclusion: Diagnosis of diabetes mellitus At least one full thickness wound below the ankle (Wagner grade III or less) for > 3 months History of receiving standard care for >2 months Normal palpation of arterial pulses at lower extremities Normal lower limb Doppler scan results	Hyperbaric 100% oxygen given in a multi-place chamber via hood at a pressure of 2.4 atmospheres absolute, twice a day for 90 minutes, 5 days per week, for 2 weeks (20 treatment sessions). Versus Wound care standardised for all patients and included offloading, aggressive debridement and dressing	• Cure rates of foot ulcer resulting from diabetes: • Rates and extent of amputation: • Adverse events:	Length of follow up was 12 weeks	China

The glossary has been updated to include a definifition of deformity.

Author (year)	Population	Comparisons	Outcomes of interest	Follow up	Study Location
	TcPO2 > 30 mm Hg at the dorsum of the foot No abnormal Xray findings that may be indicative of chronic bone infection	which ensured that a moist wound environment was maintained. Antibiotic therapy was given if there were signs of infection.			
Hyperbaric Oxygen therapy vs standard care					
Londahl 2010	Randomised= 94 Treatment group= 49 Placebo group = 45 Inclusion: Diabetes At least one full thickness wound below the ankle for > 3 months Previously treated in a diabetes clinic for a period of no less than 2 months Adequate distal perfusion or nonreconstructable peripheral vascular disease Resolved acute phase infection of the foot	Hyperbaric 100% oxygen given in a multi-place chamber via hood at a pressure of 2.5 atmospheres absolute, daily for 85 minutes, 5 days per week, for 8 weeks (40 treatment sessions). Versus Air given in a multi-place chamber via hood at a pressure of 2.5 atmospheres absolute, daily for 85 minutes, 5 days per week, for 8 weeks (40 treatment sessions). Wound care was standardised for all patients and included revascularisation, offloading, aggressive debridement, regular dressing, metabolic control and regular attendance at the multidisciplinary diabetes foot clinic. Unclear wound dressing methods. Antibiotic therapy was also given if there were signs of infection	• Cure rates of foot ulcer resulting from diabetes: • Rates and extent of amputation: • Health related quality of life: • Adverse events:	1 year	Sweden

Author (year)	Population	Comparisons	Outcomes of interest	Follow up	Study Location
Hyperbaric oxygen therapy vs standard care					
Faglia (1996)	Randomised= 70 Treatment group= 36 Control group = 34 Inclusion: Only diabetic patients with full thickness gangrene (Wagner IV) or abscess (Wagner III). Subjects with less deep ulcers were also admitted if the ulcer was large and infected and showed defective healing in 30 days of outpatient therapy.	Patients breathed pure oxygen in a multiplace hyperbaric chamber, pressurised with air, with a soft helmet. Pressure was 2.5 absolute atmosphere in the first phase and 2.4-2.2 in the second phase, daily for 90 minutes. (8 sessions total) Versus Wound care was standardised for all patients and included orthopaedic devices for the feet, debridement and dressing up to twice a day. All patients received empirical antibiotic therapy	• Rates and extent of amputation: • Length of stay:	Length of follow up was variable, unclear if length was adequate	Italy
Dermagraft vs standard care					
Gentzkow (1996)	Randomised= 50 Group A: one piece of dermagraft applied weekly for a total of 8 pieces and eight applications, plus control treatment.= 12 Group B : two pieces of Dermagraft applied every 2 weeks for a total of eight pieces and four applications, plus control treatment= 14 Group C: one piece of dermagraft applied every 2 weeks for a total of four pieces and four applications, plus	Group A: one piece of dermagraft applied weekly for a total of 8 pieces and eight applications, plus control treatment.= 12 Group B : two pieces of Dermagraft applied every 2 weeks for a total of eight pieces and four applications, plus control treatment= 14 Group C: one piece of dermagraft applied every 2	• Cure rates of foot ulcer resulting from diabetes: • Adverse events:	12 weeks	USA

The glossary has been updated to include a definifition of deformity.

Author (year)	Population	Comparisons	Outcomes of interest	Follow up	Study Location
	control treatment= 11 Group D (control) conventional therapy and wound-dressing techniques.= 13 Inclusion: Type 1 or 2 diabetes Full thickness ulcer > 1cm² Free of necrotic tissue or infection at randomisation and suitable for skin graft Circulation adequate for healing Able to complete a 12 week course	weeks for a total of four pieces and four applications, plus control treatment= 11 Versus Group D (control) conventional therapy and wound-dressing techniques.= 13 Wound care was standardised for all patients and included sharp debridement, saline moistened gauze dressing and pressure relief. The study took place across 5 institutions however dressings were standardised.			
Graftskin vs standard therapy					
Veves 2001	Randomised= 277 Treatment group= 112 Control group= 96 Inclusion: Type 1 or 2 diabetes Age 18-80 years HbA1c between 6 and 12% Full thickness neuropathic ulcers ≥2 weeks duration Postdebridement ulcer size between 1 and 16 cm² Dorsalis pedis and posterior tibialis	Graftskin applied directly over the ulcer site. The site was then covered with a layer of saline moistened tegapore. The wound was then dressed at participants in the graftskin group could have Graftskin reapplied at study weeks 1–4 for a maximum of 5 applications if required. Versus Wound care was	• Cure rates of foot ulcer resulting from diabetes: • Adverse events:	3 months	USA

The glossary has been updated to include a definifition of deformity.

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Author (year)	Population	Comparisons	Outcomes of interest	Follow up	Study Location
	pulses audible by doppler	standardised for all patients and included debridement, regular dressing changes and offloading. Full dressing changes were performed at weeks 1,2,3 and 4. Secondary dressings were changed daily. Patients received customised sandals for offloading.			
Dermagraft vs standard care					
Marston 2003	Randomised= 245 Treatment group= 130 Control group= 115 Inclusion: Type 1 or 2 diabetes Age ≥18 years Ulcer present for a minimum of 2 weeks Patients foot ulcer is on the plantar surface of the forefoot or heel and ≥1.0 cm² at baseline Patients ulcer extends through the dermis and into subcutaneous tissue but without exposure of muscle, tendon, bone or joint capsule Patients wound is free of necrotic debris and appears to be healthy vascularised tissue Patient has adequate circulation to the foot as evidenced by a palpable pulse.	Dermagraft application and standard care Versus Wound care was standardised for all patients and included debridement, moist saline dressing and pressure relieving footwear, however patients were allowed to remain ambulatory.	• Cure rates of foot ulcer resulting from diabetes: • Adverse events:	12 weeks	USA
Dermagraft vs standard care					

The glossary has been updated to include a definifition of deformity.

Author (year)	Population	Comparisons	Outcomes of interest	Follow up	Study Location
Hanft (2002)	Randomised= 28 Treatment group= 14 Control group= 14 Inclusion: Type 1 or type 2 diabetes with a plantar foot ulcer on the heel or forefoot (including the toes) with a plantar foot ulcer on the heel or forefoot (including the toes) Ulcer: ≥1 cm² and ≤20 cm² and the ulcer had not decreased or increased in size by 50% or more during the 2 week screening period	Dermagraft application and standard care. Up to 7 additional applications could be given. Versus Standard therapy consisted of sharp debridement, offloading, and sailine moistened gauze. Unclear how regularly dressings were changed.	• Cure rates of foot ulcer resulting from diabetes: • Adverse events:	12 weeks	USA
Aminiotic membrane allograft versus standard therapy					
Zelen (2013)	Randomised= 25 Treatment group= 13 Control group= 12 Inclusion: Type 1 or 2 diabetes Age ≥18 years Ulcer size >1 cm and <25 cm² Ulcer duration of ≥4 weeks No clinical signs of infection Serum creatinine <3.0 mg/dl HbA1c <12% Adequate circulation, dorsum transcutaneous oxygen test ≥30 mmHg Ankle brachial index between 0.7 and 1.2 or triphasic or biphasic Doppler arterial waveforms at the ankle of the	Application of dehydrated amniotic membrane allograft (EpiFix) following surgical debridement of all necrotic tissue followed by moisture retentive dressing and compression dressing. Repeat applications were applied at 2, 4, 6, 8 and 10 weeks. Offloading was implemented Versus Wound care was standardised for control patients and included debridement, moist dressing and offloading footwear. Patients provided their own	• Cure rates of foot ulcer resulting from diabetes: • Adverse events:	12 weeks	USA

The glossary has been updated to include a definifition of deformity.

Author (year)	Population	Comparisons	Outcomes of interest	Follow up	Study Location
	effected leg	daily dressing changes after receiving instruction. Dressing changes in the treatment group took place weekly			
HYAFF 11 based autologous dermal and epidermal grafts versus standard therapy					
Caravaggi (2003)	Randomised= 82 Treatment group= 43 Control group= 36 Inclusion: Type 1 or 2 diabetes Ulcer ≥2 cm² on plantar surface or dorsum of the foot without signs of healing for 1 month Wagner score 1–2 TcPO2 ≥30 mmHg Ankle brachial pressure index ≥0.5	Autologous fibroblasts on Hyalograft3D, this was grafted onto the debrided and cleansed wound and covered with a nonadherent paraffin gauze and secondary dressing. Second graft could be applied as required. 7–10 days after hyalograft3D grafting the ulcer received autologous keratinocytes grown on Laserskin that was covered and dressed as before. A second keratinocyte graft was permitted where required. Versus Wound care was standardised for all patients and included debridement, paraffin dressing and offloading footwear or pressure relief. Patients provided their own daily dressing changes after receiving instruction. Dressing changes in the both groups took place twice daily.	• Cure rates of foot ulcer resulting from diabetes: • Adverse events:	11 weeks	Italy
Hyalograft-3D followed by Laserskin autograft versus standard therapy					

The glossary has been updated to include a definifition of deformity.

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Author (year)	Population	Comparisons	Outcomes of interest	Follow up	Study Location
Uccioli (2011)	Randomised= 180 Treatment group= 80 Control group = 80 Inclusion: type 1 or 2 diabetes ulcer greater or equal to 2cm on the plantar or plantar marginal surface or dorsum of foot with no signs of healing for 1 month Wagner score 1 or 2 transcutaneous partial pressure of oxygen greater than or equal to 20mmHg ankle brachial pressure index greater or equal to 0.5	At baseline visits patients received dermal tissue-engineered Hyalograft 3D autografts; the graft was covered with non-adherent paraffin gauze and a secondary bandage of sterile cotton pads and gauze. Approximately 2 weeks later, the ulcer received the epidermal tissue-engineered autograft Laserskin covered and dressed in an identical manner. based on clinician judgement a second autograft application was permitted. Versus Control group received covering with non-adherent paraffin gauze and a secondary bandage of sterile cotton pads and gauze. This could be changed daily depending upon the state of the wound bed. Both groups received standard care which included debridement and offloading	• Cure rates of foot ulcer resulting from diabetes: • Adverse events:	18 months	Italy
Platelet derived growth factor gel versus standard therapy					
Robson (2005), Smiell (1999), Wieman (1998), Steed (2006)	Randomised= 1071 Intent to treat= 1065 Standard therapy= 259	Becaplermin 100 µg/g gel plus adaptic dressing, once daily dressing changes	• Cure rates of foot ulcer resulting from diabetes: • Adverse events:	20 weeks	USA

The glossary has been updated to include a definifition of deformity.

Author (year)	Population	Comparisons	Outcomes of interest	Follow up	Study Location
	Vehicle gel group= 254 Becaplermin 30 µg/g group= 193 Becaplermin 100 µg/g group= 359 Inclusion: 18 years of age or older If female, practising birth control Have documented wound etiology resulting from complications of diabetes mellitus Non-healing cutaneous full thickness diabetic neuropathic foot ulcer between 1.7–12 cm² in area, 4–52 weeks duration, on the plantar aspect of the forefoot and free of necrotic and infected tissue post debridement. Supine TcPO2 >30 mmHg on the dorsum of the target foot ulcer organisms/g of tissue Have a ulcer tissue biopsy with <1 x 106 organisms/g of tissue and no beta haemolytic streptococci	Or Becaplermin 30 µg/g gel Versus Vehicle gel given as placebo in same manner as above gel Wound care was standardised for all patients and included daily moist dressing changes, appropriate debridement, effective offloading and appropriate infection control.			
Platelet derived growth factor vs standard therapy					
Jaiswal 2010	Randomised= 50 Treatment group= 25 Control group= 25 Inclusion: Type 1 or type 2 diabetes Chronic ulcers of at least 4 weeks duration IAET stage III and IV	Platelet derived growth factor gel (rhPDGF) (PLERMIN) 0.01% applied once daily Versus Wound care was standardised for all patients and included daily moist dressing changes, appropriate debridement, effective offloading and	• Cure rates of foot ulcer resulting from diabetes: • Adverse events:	10 weeks	India

The glossary has been updated to include a definifition of deformity.

Author (year)	Population	Comparisons	Outcomes of interest	Follow up	Study Location
		appropriate antibiotic prophylactic therapy.			
Platelet derived growth factor gel vs standard therapy					
Bhansali 2009	Randomised= 20 Treatment group= 10 Control group= 10 Inclusion: Type 1 or type 2 diabetes >20 years of age At least 1 neuropathic plantar ulcer Wagners grade ≥2 without Xray evidence of osteomyelitis Ankle brachial pressure index of >0.9	0.01% rh-platelet derived growth factor-BB (PLERMIN) Versus Wound care was standardised for all patients and included daily moist dressing changes, appropriate debridement, effective offloading and appropriate antibiotic prophylactic therapy.	• Cure rates of foot ulcer resulting from diabetes: • Adverse events:	150 days	India
Platelet derived growth factor gel vs standard therapy					
Hardikar 2005	Randomised= 113 rhPDGF-BB gel group= 55 Placebo gel= 58 Inclusion: 18 years of age or older but ≤80 years Type 1 or type 2 diabetes mellitus At least 1 but less than 3 full thickness chronic neuropathic ulcers of at least 4 weeks duration in the lower extremity Stage III or IV ulcers (as defined by Wound, Ostomy and Continence Nurses Society) Infection control as determined by a wound evaluation score Evidence of adequate perfusion	0.01% gel containing 100 µg/g of rhPDGF-BB gel. Wound covered with 1.5 mm of the gel and covered with moist saline gauze, applied daily with a maximum treatment period of 20 weeks. Versus Vehicle gel given as placebo in same manner as above gel	• Cure rates of foot ulcer resulting from diabetes: • Adverse events:	20 weeks	India

The glossary has been updated to include a definifition of deformity.

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Author (year)	Population	Comparisons	Outcomes of interest	Follow up	Study Location
Transforming Growth Factor ß2 vs standard therapy					
Robson (1999)	Randomised= 177 Standardised care group= 24 placebo group= 22 growth factor 0.05 µg/cm²= 43 growth factor 0.5 µg/cm²= 44 growth factor 5.00 µg/cm²= 44 Inclusion: ≥18 years of age Diabetes mellitus Neuropathic ulcer present for at least 8 weeks on the plantar surface of the forefoot, toes, metatarsals or dorsum of the foot. Between 1–20 cm² in area following debridement Full thickness without exposed bone or tendonankle brachial pressure index between 0.7 and 1.3 or a transcutaneous oxygen pressure measurement on the foot of 30 mm Hg or more	Transforming Growth Factor ß2 0.05 µg/cm² within collagen sponge Or Transforming Growth Factor ß2 0.05 µg/cm² within collagen sponge Or Transforming Growth Factor ß2 0.05 µg/cm² within collagen sponge Versus Placebo collagen sponge Wound care was standardised for all patients and included twice weekly dressing changes, appropriate debridement, and effective offloading although methods of offloading varied	• Cure rates of foot ulcer resulting from diabetes: • Adverse events:	3 months	USA
Topical human recombinant basic fibroblast growth factor (bFGF) vs standard care					
Richard (1995)	Randomised= 17 Treatment group= 9 Placebo group= 8	Topical human recombinant basic fibroblast growth factor 5 µg/ml spray delivery	• Cure rates of foot ulcer resulting from diabetes: • Adverse events:	18 weeks	France

The glossary has been updated to include a definifition of deformity.

Author (year)	Population	Comparisons	Outcomes of interest	Follow up	Study Location
	Inclusion: Diabetes mellitus Typical, chronic, non healing, neuropathic ulcer on the plantar surface Wagners grade I–III Largest diameter >0.5 cm following debridement Confirmed neuropathy	Versus Saline placebo spray delivery Wound care was standardised for all patients and included moist dressing, appropriate debridement, offloading i.e. the instruction to keep totally non-weight-bearing. The first 6 weeks were as inpatients with daily applications 12 weeks as outpatient follow up with twice weekly applications			
CT–102, homologous platelets containing multiple growth factors vs standard care					
Steed (1992)	Randomised= 13 Treatment group= 7 Placebo group= 6 Inclusion: Diabetes mellitus Neurotrophic ulcer of the lower extremity that had not healed after at least 8 weeks of standard treatment Platelet count of ≥100,000/mm³ Supine periwound TcPO2 >30 mmHg	CT-102 applied to cotton gauze sponge and placed on wound Versus Placebo applied to cotton gauze sponge and placed on wound Wound care was standardised for all patients within the same two clinics and moist dressing, aggressive debridement, offloading formed the basis of care. Wound dressings were changed every 12 hours.	• Cure rates of foot ulcer resulting from diabetes:	20 weeks	USA
Basic fibroblast growth factor versus standard therapy					

The glossary has been updated to include a definifition of deformity.

Author (year)	Population	Comparisons	Outcomes of interest	Follow up	Study Location
Uchi (2009)	Randomised= 150 0.001% bFGF group= 48 0.01% bFGF group= 49 Placebo group= 51 Inclusion: Diabetes mellitus Ulcers 900 mm² or less, not reaching the periosteum (Wagners stage 2) Pulsation of dorsalis pedis or posterior tibialis Ankle brachial pressure index >0.9	5 spray puffs of 0.001% bFGF once a day Or 5 spray puffs of 0.01% bFGF once a day Versus 5 spray puffs of placebo once a day (0.0005% benzalkonium chloride in saline Wound care was standardised for all patients and comprised moist dressing, regular debridement (but not surgical) and offloading of target ulcer.	• Cure rates of foot ulcer resulting from diabetes: • Adverse events:	8 weeks	Japan
Irremovable offloading devices versus control dressing					
Hanft (2008)	Randomised= 55 Treatment group= 29 Placebo group= 26 Inclusion: Aged 18–80 years Type 1 or type 2 diabetes HbA1c of ≤12% Grade 1A ulcer: University of Texas Diabetic Wound Classification- single full thickness wound below the	72 µg/cm² of topical telbermin in methylcellulose gel Versus Placebo (formulated bulk solution without telbermin) in methylcellulose gel Wound care was standardised for all patients	• Cure rates of foot ulcer resulting from diabetes: • Adverse events:	19 weeks	USA

The glossary has been updated to include a definifition of deformity.

Author (year)	Population	Comparisons	Outcomes of interest	Follow up	Study Location
	malleolus, extending through the epidermis and dermis but not involving bones, ligaments, muscles or tendons Chronic ulcer of four weeks or more but less than six months Ulcer area following debridement of 1–4 cm² Ankle brachial pressure index of 0.6–1.2 on the study foot Use of effective contraception in females of child bearing potential Charcot foot not involving study ulcer	which included debridement, offloading and dressing changes 3 times a week.			
Arginine-Glycine-Aspartic Acide (RGD) Peptide Matrix versus standard therapy					
Steed (1995)	Randomised= 65 Treatment group= 40 Placebo group= 25 Inclusion: 18 years or older Foot ulcers for at least 1 month Ulcer penetrates through the epidermis into the dermis without exposure of bone or tendon, measuring between 1 and 15 cm² in surface area HbA1c levels <10% Free of infection No osteomyelitis on X-ray Adequate arterial blood supply on Doppler and transcutaneous oxygen tension results	Arginine-Glycine-Aspartic Acide (RGD) Peptide Matrix applied topically to wound Versus Wound care was standardised for all patients which regular moist saline dressing changes twice a week, regular debridement, and offloading.	Complete wound healing by 10 weeks Adverse events:	10 weeks	USA
Acellular regenerative tissue matrix versus standard care					
Brigido (2004)	Randomised= 40	Acellular regenerative tissue	• Cure rates of foot ulcer	4 weeks	USA

The glossary has been updated to include a definifition of deformity.

Author (year)	Population	Comparisons	Outcomes of interest	Follow up	Study Location
	Treatment group= 20 Placebo group= 20 Inclusion: Full thickness wound to lower extremity secondary to type 1 or type 2 diabetes Chronic non-healing wounds present for at least 6 weeks without epidermal coverage Wounds >1cm² in size	matrix (GraftJacket tissue matrix). Change dressings at day 5, 10 and 15. Versus Conventional therapy with curasol wound gel, sharp debridement and offloading. Participants were evaluated weekly for 4 weeks	resulting from diabetes: • Adverse events:		
Acellular regenerative tissue matrix: Graftjacket versus standard therapy					
Brigido (2006)	Randomised= 28 Treatment group= 14 Control group= 14 Inclusion: Full thickness chronic wound for at least 6 weeks without epidermal coverage No evidence of active infection Palpable/audible pulse to the affected lower extremity	Acellular regenerative tissue matrix (GraftJacket tissue matrix). Change dressings at day 5, 10 and 15. Versus Conventional therapy with curasol wound gel, sharp debridement and offloading. Participants were evaluated weekly by a surgeon	• Cure rates of foot ulcer resulting from diabetes: • Adverse events:	16 weeks	USA
Acellular regenerative tissue matrix: Graftjacket versus standard therapy					
Reyzelman (2009)	Randomised= 86 Treatment group= 47 Standard of care group= 39 Inclusion: 18 years of age or older	Acellular regenerative tissue matrix (GraftJacket tissue matrix). Versus Conventional therapy with	• Cure rates of foot ulcer resulting from diabetes: • Adverse events:	Length of follow up was 12 weeks	USA

The glossary has been updated to include a definifition of deformity.

Author (year)	Population	Comparisons	Outcomes of interest	Follow up	Study Location
	Type 1 or type 2 diabetes University of Texas Grade 1 or Grade 2 diabetic ulcer Ranging in size from 1–25 cm² Absence of infection Adequate circulation based on transcutaneous oxygen measurement at the dorsum of the foot ≥30 mmHg, Ankle brachial pressure index from 0.7 to 1.2 or at least Doppler arterial waveforms at the posterior tibialis or dorsalis pedis arteries.	moist wound therapy, daily dressing changes, sharp debridement and offloading. Participants were evaluated weekly for 4 weeks Wound care was standardised for all participants. All participants were kept offloaded and debrided at similar intervals as per standard of care. Rate of dressing changes was daily.			
Formulated collagen gel with growth factor GAM501 vs standard therapy					
Blume (2011)	Randomised= 129 After exclusions and removing those who did not complete the study for the per protocol population= 116 Treatment with GAM501=72 FCG group= 33 Standard of care group= 19 Inclusion: Type 1 and Type 2 diabetes Aged 18 or older Wagner Classification Grade 1 present for at least 6 weeks Peripheral neuropathy (Sammmes-weinstein monofilament test) Adequate blood flow (TcpO2 >40 mmHg or toe pressure ≥40 mmHg)	GAM501 in formulated collagen gel, one application on day 1 OR GAM501 in formulated collagen gel, two application on day 1 and day 29 Versus Formulated collagen gel, one application on day 1 Formulated collagen gel, two application on day 1 and day 29 Wound care was standardised for all participants. Following qualification and informed consent, patients underwent	• Cure rates of foot ulcer resulting from diabetes: • Adverse events:	12 weeks	USA

The glossary has been updated to include a definifition of deformity.

Author (year)	Population	Comparisons	Outcomes of interest	Follow up	Study Location
		surgical debridement, offloading orthopaedic shoes fitted and daily dressing changes Wound care was standardised for all participants. Following qualification and informed consent, patients underwent surgical debridement, offloading orthopaedic shoes fitted and daily dressing changes			
Low level laser therapy versus standard therapy					
Keviani (2011)	Randomised= 23 Treatment group= 13 Placebo group= 10 Inclusion: Diabetic foot ulcer for a minimum of 12 weeks Wagner classification I or II	The low level laser therapy group received laser therapy 6 times a week for 2 weeks, then every other day until complete healing at a power density of 50 mW/cm² Versus Wound care may not have been standardised for all participants. During treatment participants were assigned individualised wound dressings and topical treatments. It is unclear how dressing care varied exactly.	• Cure rates of foot ulcer resulting from diabetes: • Adverse events:	20 weeks	Iran
WF10 (immunokine) versus placebo and standard therapy					
Yingsakmongkol (2011)	Randomised= 40 Treatment group= 20 Placebo group= 20	Infusions of the study treatment in randomised sequence at dosage of 0.5 mL/kg body weight diluted in	• Rates and extent of amputation: • Adverse events:	9 weeks	Thailand

The glossary has been updated to include a definifition of deformity.

Author (year)	Population	Comparisons	Outcomes of interest	Follow up	Study Location
	Inclusion: Aged 12-80 years Karnofsky Performance status greater than or equal to 60 Wound severity score greater than or equal to 8 HbA1c of 6-13%	500 mL of 0.9% normal saline. Administered over 6 hours once daily for 5 consecutive days. This cycle was repeated every 3 weeks for a total number of cycles of 3. Versus Placebo was given in the same manner as the treatment (0.9% saline) Wound care was standardised for all participants. Wound debridement, wound dressing, offloading and appropriate antibiotic drugs depending on infection severity.			
Uncultured, processed lipoaspirate cells versus placebo/control treatment with standard therapy					
Han (2010)	Randomised= 54 Treatment group= 26 Placebo group= 26 Inclusion: Tupe 1 or Type 2 diabetes Foot ulcer size >1.0 cm² that has not displayed signs of healing for 6 weeks Wagner grade 1 or 2 Transcutaneous oxygen pressure >30 mmHg	Processed Lipoaspirate cells suspended in 0.3-0.7 mL of fibrinogen and dispersed on the wound. The PLA cell autograft was then sealed using 0.2-1.0 mL of thrombin. Versus Placebo/control treatment with only fibrinogen and thrombin without cells applied	• Cure rates of foot ulcer resulting from diabetes: • Adverse events:	8 weeks	South Korea

The glossary has been updated to include a definifition of deformity.

Author (year)	Population	Comparisons	Outcomes of interest	Follow up	Study Location
	Ankle brachial pressure index >0.5	topically over the wounds. Wound care was standardised for all participants and involved moist dressing, pressure offloading and ongoing debridements. Wound dressing was changed every 3-7 days.			
Clostridial collagenase ointment for debridement versus standard therapy					
Tallis (2013)	Randomised= 48 Treatment group= 24 Placebo group= 24 Inclusion: Full thickness neuropathic foot ulcer, 0.5-10 cm² Ulcer duration of at least 1 month Willing and able to perform dressing changes daily Willing and able to use appropriate offloading device Adequate perfusion to target ulcer foot: transcutaneous oxygen pressure of >40 mm Hg or toe pressure >40 mm Hg Adequate nutrition (albumin greater or equal than 2.0 g/dL)	Clostridial collagenase ointment for debridement, applied once daily to the thickness of a nickel. Versus Selective sharp debridement and saline moistened gauze. After surgical sharp debridement participants were treated with daily dressing change and application of treatment daily and with weekly assessment for further debridement. All participants were offloaded.	• Adverse events:	12 weeks	USA
External shock wave therapy versus standard care					
Moretti (2009)	Randomised= 30 Treatment group= 15 Placebo group= 15	External shock wave therapy, three applications for 1-2 minutes every 72 hours up to 3 applications	• Cure rates of foot ulcer resulting from diabetes • Adverse events:	20 weeks	Italy

The glossary has been updated to include a definifition of deformity.

Author (year)	Population	Comparisons	Outcomes of interest	Follow up	Study Location
	Inclusion: Neuropathic foot plantar ulceration below the malleoli for a period of at least 6 months Area >1 cm² Age 30-70 years Diameter of the lesion between 0.5 and 5cm Type 1 diabetes mellitus with insulin therapy for at least 5 years prior Peripheral neuropathy Ankle brachial pressure index > 0.7	Versus Standard therapy: All patients were fitted with pressure relieving footwear, participants received debridement and silver cell dressing which was changed every 2-3 days, any infections were treated with antibiotics as required.			
talactoferrin alfa versus placebo and standard therapy					
Lyons (2007)	Randomised= 46 2.5% treatment group= 15 8.5% treatment group= 15 Placebo gel= 16 Inclusion: 18 years of age or older Diabetes mellitus HbA1c between 6% and 13% 1 or more diabetic neuropathic ulcers at or below the ankle that had not healed or decreased in size >30% within the 4 weeks prior study despite standard therapy Full thickness but not extending to the tendon, bone or joint capsule Post debridement size of 0.5 to 10 cm² Transcutaneous oxygen tension of	After sharp debridement of the target ulcer, talactoferrin alpha 2.5% was applied topically twice a day for 12 weeks with standard care. Or. After sharp debridement of the target ulcer, talactoferrin alpha 8.5% was applied topically twice a day for 12 weeks with standard care. Versus After sharp debridement of the target ulcer, placebo gel was applied topically twice a day for 12 weeks with	• Cure rates of foot ulcer resulting from diabetes: • Adverse events:	12 weeks, 4 months and 6 months	USA

Author (year)	Population	Comparisons	Outcomes of interest	Follow up	Study Location
	≥30 mm Hg Ankle brachial pressure index of ≥ 7	standard care. Standard therapy: initial and periodic (as required) sharp debridement; twice daily saline dressing changes and offloading using standardised devices was provided for all participants. As treatment took place in 7 different centres care may have varied.			
Promogran versus standard care					
Veves 2002	Randomised= 276 Promogran dressing group= 138 Standard wound care= 138 Inclusion: 18 years or older A diabetic foot ulcer of at least 30 days duration Wagner grade I or II ulcer and area of at least 1 cm² Adequate circulation Debrided of necrotic/nonviable tissue at enrollment	Promogran, collagen/oxidised regenerated cellulose dressing and standard care. Standard care: Moistened gauze and secondary dressing, Dressings were changed when clinically required. Debridement was performed on the wound initially and then on any follow up visits as required. Patients performed their own dressing changes as required, there were strict criteria to how often a wound should be changed depending upon its clinical state. All participants were offloaded and instructed to avoid weight bearing..	• Cure rates of foot ulcer resulting from diabetes: • Adverse events:	12 weeks	USA
Cultured allogenic keratinocyte sheets vs standard care					

The glossary has been updated to include a definifition of deformity.

Author (year)	Population	Comparisons	Outcomes of interest	Follow up	Study Location
You 2012	Randomised= 59 treatment group= 27 Standard wound care= 32 Inclusion: Type 1 or type 2 diabetes Foot ulcer >1.0 cm² with no signs of healing for 6 weeks Wagner grade I or II Transcutaneous oxygen pressure ≥ 40 mmHg	Weekly cultured allogenic keratinocyte sheets Versus Standard care: dressing changes weekly, secondary dressing changes up to as many as three times a week if required. Treatment group received the keratinocyte sheet as the primary dressing, control group received Vaseline gauze. Sharp debridement and offloading were performed.	• Cure rates of foot ulcer resulting from diabetes: • Adverse events:	12 weeks	South Korea
Aquacel versus two types of traditional dressing and standard care					
Jeffcoate (2009)	Randomised= 317 Inadine group= 108 Aquacel group= 103 N-A group= 106 Inclusion: Aged 18 or older Type 1 or type 2 diabetes Full thickness ulcer present for at least 6 weeks, not penetrating to the tendon, periosteum or bone, with a cross sectional area of 25-2500 mm²	Aquacel, a modern dressing product versus N-A, a non-adherent, knitted, viscose filament gauze Or Inadine, an iodine-impregnated dressing. Dressings could be changed by a district nurse or by an informed and willing participant. Dressings were	• Cure rates of foot ulcer resulting from diabetes: • Rates and extent of amputation: • Health related quality of life: • Adverse events:	24 weeks	UK

The glossary has been updated to include a definifition of deformity.

Author (year)	Population	Comparisons	Outcomes of interest	Follow up	Study Location
		changed daily, every other day or every third day depending upon need and clinical judgement. Frequency of dressing changes was documented as was frequency of visits.			
Autologous platelet rich plasma vs standard care					
Driver (2006)	Randomised= 72 treatment group= 40 Standard wound care= 32 Inclusion: Type 1 or type 2 diabetes Between the ages of 18 and 95 years An ulcer of at least 4 weeks duration HbA1c less than 12 Index foot ulcer located on the plantar, medial or lateral aspect of the foot Wound area between 0.5-20 cm² Clinically non-infected Full thickness without exposure of bone, tendon, muscle or ligament Charcot deformity free of acute changes	Platelet-rich Plasma gel applied topically and secured, changed twice weekly Versus Standard care: Control wounds were treated with a saline gel. Sharp debridement guidelines were provided as part of the protocol. Patients were required to use fixed-ankle-foot orthoses for offloading. Dressing changes were twice weekly.	• Cure rates of foot ulcer resulting from diabetes: • Adverse events:	24 weeks	USA
Topical tretinoin vs placebo and standard care					
Tom 2005	Randomised= 24 treatment group= 13 Standard wound care= 11 Excluded: Unable to give informed consent	Topical tretinoin, applied daily for 10 minutes, for 4 weeks Versus Saline placebo, coloured to	• Cure rates of foot ulcer resulting from diabetes: • Adverse events:	16 weeks	USA

The glossary has been updated to include a definifition of deformity.

Author (year)	Population	Comparisons	Outcomes of interest	Follow up	Study Location
	Had a known bleeding disorder Pregnant Infected ulcers or nearby tissues Lower extremity ulcers due to large artery disease	look the same. Applied topically for 10 minutes daily, for 4 weeks. Standard care included debridement when necessary and offloading of the wound. Cadexomer iodine gel was also applied to both groups and left on overnight, this was continued daily after treatment had finished.			
Chrysalin vs placebo and standard therapy					
Fife 2007	Intention to treat Randomised= 59 Placebo group= 21 1 µg Chrysalin group= 20 10 µg Chrysalin group= 18 Inclusion: Below the knee ulcers ranging from 0.9-38.5 cm², present for more than 8 weeks Wagner grade I, II and III	1 µg Chrysalin, amino acid peptide representing the natural sequence of Thrombin. Applied topically in a volume of 0.1 cm³ saline solution then after 1 minute covered with Cutinova foam and bandaged. Or 10 µg Chrysalin, amino acid peptide representing the natural sequence of Thrombin. Applied topically in a volume of 0.1 cm³ saline solution then after 1 minute covered with Cutinova foam and bandaged. Versus	• Cure rates of foot ulcer resulting from diabetes: • Adverse events:	20 weeks	USA

The glossary has been updated to include a definifition of deformity.

Author (year)	Population	Comparisons	Outcomes of interest	Follow up	Study Location
		Saline placebo applied topically in a volume of 0.1 cm³ saline solution then after 1 minute covered with Cutinova foam and bandaged. Standard therapy involved twice weekly visits for application of study treatment and dressing changes, debridement as needed to remove necrotic tissue and offloading of ulcer site.			
Electrical stimulation vs placebo and standard therapy					
Peters (2001)	Randomised= 40 Placebo group= 20 Electrical stimulation group= 20 Inclusion: University of Texas Diabetic Wound Classification grades 1A-2A Transcutaneous oxygen tension >30 mmHg	Micro-Z, a small electric stimulation device. Gives a treatment dose of 50V with 80 twin peak monophasic pulses per second, delivered for 10 minutes. Followed by 10 minutes of 8 pulses per second of current. Versus Placebo group used electric stimulation units that looked and acted identically to the treatment device but did not deliver current. Both groups received traditional wound care involving debridement, NU-GEL collagen wound gel and pressure reduction at the site	• Cure rates of foot ulcer resulting from diabetes: • Rates and extent of amputation: • Adverse events:	12 weeks	USA

The glossary has been updated to include a definifition of deformity.

Author (year)	Population	Comparisons	Outcomes of interest	Follow up	Study Location
		of the ulceration. Dressings were changed twice a day by the patient, their family members and, or home health care providers. Patients were seen every week to evaluate healing progress.			
Vildagliptin therapy vs standard therapy					
Marfella (2012)	Randomised= 106 Placebo group= 53 Treatment group= 53 Inclusion: Type 2 diabetic participants Chronic non-healing diabetic foot ulcers for more than 3 month duration Adequate distal perfusion (transcutaneous oxygen pressure >30 mmHg, ankle brachial pressure index >0.7 and <1.2)	Vildagliptin, a dipeptidyl peptidase 4 inhibitor. 50 mg, twice a day and standard care Versus Standard care: before randomisation and at each study visit study ulcers received sharp debridement and saline-moistened gauze dressings. The ulcers were debrided when considered necessary. Individualised topical treatment and dressings were used depending on the site and character of the ulcer. Offloading protective shoe wear with individually fitted in-soles were used.	• Cure rates of foot ulcer resulting from diabetes: • Rates and extent of amputation: • Adverse events:	12 weeks	Italy
Collagen/ORC/silver therapy vs standard therapy					
Gottrup 2013	Randomised= 39 Control group= 15 Treatment group= 24	Collagen/ORC/silver therapy applied directly onto the wound bed and standard care	• Cure rates of foot ulcer resulting from diabetes: • Adverse events:	14 weeks	Denmark

The glossary has been updated to include a definifition of deformity.

Author (year)	Population	Comparisons	Outcomes of interest	Follow up	Study Location
	Inclusion: Diabetic foot ulcer of at least 30 days duration	Versus Standard care: The same type of dressing was used in the test and control group and consisted of a foam dressing for moderately exuding wounds. The dressings were changed at least twice a week according to the condition of the wound. Patients in both groups were treated with standard wound treatment protocol including debridement and offloading			
Non-contact normothermic wound therapy vs standard therapy					
Alvarez (2003)	Randomised= 20 Control group= 10 Non-contact normothermic wound therapy group= 10 Inclusion: Diabetic neuropathic foot ulcers Plantar surface of the foot Type 1 or type 2 diabetes Secondary to peripheral neuropathy Adequate circulation (ankle brachial pressure index >0.7 and palpable pulses) Ulcer extends through the dermis and into subcutaneous tissue without involvement fo the bone, tendons, muscle or joint capsule	Non-contact normothermic wound therapy, maintains wound and surrounding skin surface temperature at 37 °C the wound cover was appled over the ulcer and served as the primary dressing. Warming treatments were performed 3 times daily for 1 hour. Wound cover was changed once daily. Otherwise standard care Versus Standard care: Weekly debridement and moist to moist saline gauze dressings (the gauze was not allowed to dry). Wound dressings were	• Cure rates of foot ulcer resulting from diabetes: • Adverse events:	12 weeks	USA

The glossary has been updated to include a definifition of deformity.

Author (year)	Population	Comparisons	Outcomes of interest	Follow up	Study Location
		changed once daily. All patients were fitted with a therapeutic healing sandal and instructed to avoid wound bearing.			
ANGIPARS versus standard therapy					
Larijani 2008	Randomised= 25 Control group= 9 Non-contact normothermic wound therapy group= 16 Inclusion: Chronic non-healing diabetic foot ulcer for several weeks-months Type 1 or type 2 On medication, either oral hypoglycaemic or insulin Ulcers which remained open without healing and had not shown improvement for more than 2 weeks	ANGIPARS, Semelil, a naïve herbal extract, intravenous administration 4cc daily for 28 days. Drug diluted in 50-100 cc normal saline and infused during 30-60 minutes and standard therapy Versus Standard care and placebo: Weekly debridement and moist to moist saline gauze dressings (the gauze was not allowed to dry). Wound dressings were changed once daily. All patients were fitted with a therapeutic healing sandal and instructed to avoid wound bearing.	Adverse events:	4 weeks	Iran
ANGIPARS versus standard therapy					
Bahrami (2008)	Randomised= 21 ANGIPARS oral= 6 ANGIPARS oral and gel= 6 Control group= 9 Inclusion: Adult 18-75 years	ANGIPARS, Semelil, a naïve herbal extract, oral therapy with 100 mg twice a day for 6 weeks in addition to conventional therapies Or	Cure rates of foot ulcer resulting from diabetes: Adverse events:	6 weeks	Iran

Author (year)	Population	Comparisons	Outcomes of interest	Follow up	Study Location
	Type 1 or type 2 diabetes One or more diabetic foot ulcers Open without healing and/or improvement for at least 2 weeks	ANGIPARS gel 3% added to the oral form of the same product besides conventional therapies for the same period of time Versus Standard care the comprised of wound debridement, irrigation with normal saline solution, antibiotic therapy, pressure offloading, wound dressing. Study visits scheduled for every 2 weeks. Unclear how often dressings were changed.			
Iamin-2% gel, or glycyl-l-histidyl-l-lysine: copper complex versus placebo and standard care					
Mulder 1994	Randomised= 181 (99 participants were included in a further trial testing delayed Iamin gel treatment for which no data of interest were reported) Iamin-2% gel group=40 Vehicle gel= 42 Inclusion: 20-90 years of age Adequately controlled diabetes as defined by a physician Minimum ulcer size 25 mm², maximum 2700 mm² General health confirmed by physical and laboratory examination	Iamin-2% gel, or glycyl-l-histidyl-l-lysine: copper complex, applied once a day for up to 8 weeks along with standard care. Versus A vehicle gel, applied once a day for up to 8 weeks along with standard care. Standard care involved: extensive sharp debridement at study entry; routine superficial debridement; daily dressing changes,	Cure rates of foot ulcer resulting from diabetes: Adverse events:	14 weeks	Iran

Author (year)	Population	Comparisons	Outcomes of interest	Follow up	Study Location
		standardised pressure-relieving foot wear; metered dosing of the gel; patient education; treatment of infection with systemica antibiotics and supportive care for limb oedema.			
Resvertrol verses placebo and standard care					
Bashmakov 2014	Randomised=24 (31 randomised but 7 dropped out for reason not related to study protocol) Resveratrol 14 Placebo 10 Inclusion: Documented history of type 2 diabetes Foot ulcer for over 4 weeks	Resveratrol - one capsule containing 50mg of active substance (t-RSV-L, Lycotec Ltd, UK) twice a day with noncarbonated water after a meal standard care comprising infection control, debridement and offloading Versus Placebo – capsule with inert substance and standard care comprising infection control, debridement and offloading	Cure rates of foot ulcer resulting from diabetes: defined as complete wound closure	60 days	Egypt
Topical royal jelly versus placebo and standard care					
Siavash 2013	Randomised by ulcer = 64 Royal Jelly = 32 Placebo = 32 Inclusion: People with type 2 diabetes with one or more foot ulcers	Royal Jelly 5% sterile gel was administered to the ulcer three times a week alongside standard care consisting of offloading, infection control, vascular improvement and debridement [if necessary] Versus	Cure rates of foot ulcer resulting from diabetes	3 months	Iran

The glossary has been updated to include a definifition of deformity.

Author (year)	Population	Comparisons	Outcomes of interest	Follow up	Study Location
		Placebo gel was administer to the ulcer three times a week alongside standard care consisting of offloading, infection control, vascular improvement and debridement (if necessary)			
Grafix versus standard care					
Lavery 2014	Randomised= 97 hVWM = 50 Standard care = 47 Inclusion: Adults between 18 and 80 with type 1 or type 2 diabetes with index wound present for between 4 and 52 weeks and wound located below the malleoli on plantar or dorsal surface of the foot and between 1cm2 and 15 cm2	hVWM alongside standard care of debridement (using scalpel, tissue nippers and/or curette), wound dressing (non-adherent dressing (Adaptic, Systagenix, UK) or saline-moistened gauze or Allevyn (Smith & Nephew, UK) followed by an outer dressing and offloading versus Standard care of debridement (using scalpel, tissue nippers and/or curette), wound dressing (non-adherent dressing (Adaptic, Systagenix, UK) or saline-moistened gauze or Allevyn (Smith & Nephew, UK) followed by an outer dressing and offloading (custom built or walking boots for wounds on the sole of the foot or post-op shoe if the wound was on the dorsum of the foot or the ankle)	Complete wound closure Time to wound closure Adverse events	12 weeks	USA

The glossary has been updated to include a definifition of deformity.

Author (year)	Population	Comparisons	Outcomes of interest	Follow up	Study Location
Recombinant human epidermal growth factor versus standard care and placebo					
Gomez-Villa 2014	Randomised=34 Standard care + rhEGF = 17 Standard care = 17 Inclusion: Patients over the age of 18, with a Grade A or B diabetic foot ulcer larger than 2cm2	rhEGF (75µg) was applied to the edge of the wound and to the wound bed by fine-needle injection thrice per week. Patients received a total fo 5mL in injections that were equally divided throughout the edges and wound bed evern Monday, Wednesday and Friday. Versus Placebo applied as rhEGF Standard care consisted of debridement of necrotic or infected tissue and an antimicrobial dressing with ionic silver. Dressing could be applied moist in wounds with low exudate and dry in wounds with high exudate. Patients were asked to stay of their feet using crutches.	Complete healing	8 weeks	Mexico
Total contact cast with Achilles lengthening versus total contact cast					
Mueller 2003	Total number of subjects=64 Achilles tendon lengthening= 31 Total Contact Casting= 33 Included: History of diabetes mellitus Loss of protective sensation Limitation of ankle dorsiflexion to ≤ 5	The treatment group had Achilles tendon lengthening. Ulcers were dressed, debrided and offloaded using a total contact cast until ulcer healing. Versus	Ulcer healing Quality of life	7 months and 7 months following healing	USA

The glossary has been updated to include a definifition of deformity.

Author (year)	Population	Comparisons	Outcomes of interest	Follow up	Study Location
	degrees A palpable ankle pulse A recurrent or non-healing ulcer on the forefoot	The control group had ulcers dressed, debrided and offloaded using a total contact cast until ulcer healing.			
Negative pressure wound therapy versus advanced moist wound therapy					
Blume 2008	Total= 342 Negative pressure wound therapy group= 169 Control group= 169 Included patients Diabetic adults ≥18 years with a stage 2 or 3 calcaneal, dorsal, or plantar foot ulcer ≥2 cm² in area after debridement Adequate blood circulation was assessed by a dorsum transcutaneous oxygen test ≥30 mm Hg Ankle brachial index values ≥0.7 and ≤1.2 with toe pressure ≥ 30 mmHg or Doppler arterial waveforms that were triphasic or biphasic at the ankle of the affected leg.	Vacuum assisted closure therapy Versus Moist wound dressing, debridement and offloading	Ulcer healing Amputation Infection	112 day follow up	USA
Armstrong 2005	Total= 162 Negative pressure wound therapy group= 77 Control group= 85 Included patients People aged 18 years or older, presence of a wound from a diabetic foot amputation to the transmetatarsal	Vacuum assisted closure therapy Versus Moist wound dressing, debridement and offloading	Ulcer healing Amputation Adverse events	112 day follow up	USA

The glossary has been updated to include a definifition of deformity.

Author (year)	Population	Comparisons	Outcomes of interest	Follow up	Study Location
	level of the foot, evidence of adequate perfusion, and wounds with University of Texas grade 2 or 3 in depth.				
Vacuum compression therapy vs standard therapy					
Akbari (2007)	Randomised= 18 Treatment group= 9 Standard of care group= 9 Inclusion: Diabetic foot ulcer corresponding to grade 2 of the University of Texas Diabetic Foot Wound Classification system	Vacuum compression therapy (1 hour a day, 4 times a week, for 10 sessions) Versus Wound care was standardised for all participants. Conventional therapy of debridement, blood glucose control agents, systemic antibiotics, wound cleaning with normal saline, offloading and daily wound dressings.	• Adverse events:	Length of follow up was 3 weeks	Iran

The glossary has been updated to include a definifition of deformity.

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4.12.3 Health economic evidence

A literature search was conducted to find any existing cost–utility analyses (CUAs) of prevention of diabetic foot problems (see appendix D for details of the search strategies). Two published CUAs matched the PICO for the question and were retrieved. In addition to these publications, the GDG reviewed the results of 2 exploratory cost–utility analyses that had been performed to support one of the guidelines that is being updated and replaced by this guideline (NICE clinical guideline 119, 2011). Because the GDG did not prioritise this question for original health economic analysis in the present update, no updates or revisions were made to the analyses from CG119; instead, they were treated as any other pre-existing health economic evidence, and subject to the same quality assessment. The appendix from CG119 detailing the methods and results of these analyses is reproduced in appendix J.4, as it has not been published elsewhere.

Hyperbaric oxygen therapy

Guo et al. (2003) report a CUA based on a hypothetical cohort of patients with diabetes, with costs considered from a USA health service and societal perspective. The model compared conventional wound care (without providing a clear definition) with conventional wound care plus hyperbaric oxygen therapy using a decision tree model. Depending on the healing rates and probability of amputation adopted (based on studies excluded from the clinical review for this question), the ICER ranged from $142,923, $27,310 to −$72,799 at year 1 in the worst/base/best scenarios. This sensitivity to input values, a lack of explicit detail on costs and and absence of comprehensive probabilistic sensitivity analysis are potentially serious limitations of this evidence.

An additional CUA (NICE, 2011) based on a UK, NHS and PSS payer perspective, compared hyperbaric oxygen therapy with standard care. The model used a decision tree structure for each of the interventions and noted that the analysis was 'highly exploratory' and 'utilises methods and data that might not usually be done in a full high quality review'. Data on clinical effectiveness was sourced from a meta-analysis of RCT evidence, but the derivation of parameter estimates was not reported. The ICER for hyperbaric oxygen therapy compared with standard care was £24,486/QALY. The authors noted that the cost was the key variable, but did not expand on this quantitatively.

Further details of these studies are provided in appendix J.3.

Platelet rich plasma gel

Dougherty's CUA (2008) was based on a hypothetical cohort of patients with diabetes, with costs considered from a USA health service and societal perspective. It used a decision tree framework to compare platelet rich plasma gel and standard wound care with a saline gel and standard wound care. Effectiveness estimates for platelet rich plasma were taken from a single RCT by Driver et al. (rated as very low quality in the clinical review for this question). The study reports that platelet rich plasma dominates (is cheaper and more effective) than saline gel and good wound care. The study does not present a fully incremental analysis, and uses indirect measurements of quality of life based on HAD scores which may not be applicable in a diabetic foot context. The sensitivity analysis was extremely limited, only varying the cost of platelet rich plasma gel according to a narrow range of likely prices, and this did not change the outcome.

Further details of this study are provided in appendix J.3.

Negative pressure wound therapy

One CUA (NICE, 2011) based on a UK, NHS and PSS payer perspective, compared negative pressure wound therapy with standard care. The model used the same structure as the hyperbaric oxygen therapy analysis summarised above, and was subject to the same limitations. The ICER for negative pressure wound therapy compared with standard care was £49,691/QALY. The authors noted that this result was critically dependent on the cost of the intervention, but did not expand on this quantitatively.

Further details of this study are provided in appendix J.3.

During the meeting at which this model was discussed, the GDG noted that the costs of the intervention have reduced considerably from those assumed in the 2011 analysis. Because the analysis derives from an undiscounted decision tree, it was possible to isolate the contribution to net costs made by the intervention itself and, therefore, the ICER could be easily recalculated with lower costs.

The 2011 analysis calculated the ICER for negative pressure wound therapy compared with standard care as follows:

$$\frac{Cost_{NPWT} - Cost_{standard}}{QALY_{NPWT} - QALY_{standard}} = \text{ICER}_{NPWT\,v\,standard}$$

$$\frac{5512 - 4542}{0.4953 - 0.474} = 49,691$$

Isolating the 2011 cost that was assumed for the intervention (£1680), the calculation may be rearranged to identify the intervention cost that would lead to an ICER of £20,000/QALY:

$$\frac{(x + [5512 - 1680]) - 4542}{0.4953 - 0.474} = 20,000$$

, which can be solved straightforwardly:

$$x = 20,000(0.4953 - 0.474) - (5512 - 1680) + 4542$$

$$x = 1100.$$

Therefore, this model suggests that negative pressure wound therapy would provide QALY gains at an ICER of less than £20,000 per QALY so long as the complete course cost less than £1100.

It is even simpler to identify the point at which the intervention would be cost-saving, as the QALY component of the calculation is no longer required:

$$x = 4542 - (5512 - 1680)$$

$$x = 710$$

Therefore, the model predicts NPWT negative pressure wound therapy be dominant (improving health and resulting in a reduction in net costs) if it cost less than £710.

4.12.4 Evidence Statements

Cure Rate

This review found an increase in cure rate at 12 weeks for the following adjunctive interventions when compared to standard care alone

- Amniotic memory wound graft (low quality evidence from one study including 25 participants)
- Dermagraft (moderate quality evidence from 3 studies including 341 participants)
- Cultured allogeneic keratinocyte sheet (low quality evidence from 1 study including 59 participants)
- Apligraft (low quality evidence from 1 study including 71 participants)
- Hyperbaric oxygen therapy (low quality evidence from 3 studies including 126 participants)
- Processed lipoaspirate cell therapy (low quality evidence from 1 study including 52 participants)
- RGD peptide matrix (low quality evidence from 1 study including 65 participants)
- Negative pressure wound therapy (very low quality evidence from 2 studies including 497 participants)
- Grafix therapy (high quality evidence from 1 study including 97 participants)

This review found no difference in cure rate at 12 weeks for the following adjunctive interventions when compared to standard care alone

- Topical platelet derived growth factors (very low quality evidence from four studies including 997 participants)
- Topical transforming growth factor (very low quality evidence from 1 study including 177 participants)
- Topical basic fibroblast growth factor (very low quality evidence from 2 studies including 111 participants)
- Topical growth factor CT-102 activated platelet supernatant (very low quality evidence from 1 study including 13 participants)
- Topical growth factor GAM501 (very low quality evidence form 1 study including 82 participants)
- Topical recombinant human vascular endothelial growth factor (moderate quality evidence from 1 study including 55 participants)
- Topical autologous platelet-rich plasma gel (very low quality evidence from 1 study including 72 participants)
- Oral incretine (low quality evidence from 1 study including 106 participants)
- Hyalograft-3D followed by Laserskin autograft (very low quality evidence from 2 studies including 221 participants)
- Graftskin (very low quality evidence from 1 study including 208 participants)
- Graftjacket (very low quality evidence from 2 studies including 113 participants)
- Talactoferrin (very low quality evidence from 1 study including 46 participants)
- External shock wave therapy (very low quality evidence from 1 study including 30 participants)
- Topical thrombin peptide chrysalin (very low quality evidence from 1 study including 59 participants)
- Topical promogran (very low quality evidence from 2 studies including 312 participants)

- Topical lamin copper complex gel (very low quality evidence from 1 study including 60 participants)
- Oral ANGIPARS herbal treatment (very low quality evidence from 1 study including 15 participants)
- AQUACEL dressing (very low quality evidence from 1`study including 209 participants)
- Low level laser therapy (very low quality evidence from 1 study including 20 participants)
- Electric stimulation therapy (moderate quality evidence from 1 study including 40 participants)
- Normothermic wound therapy (low quality evidence from 1 study including 20 participants)
- Topical tretinoin (low quality evidence from 1 study including 20 participants)
- Achilles tendon lengthening (low quality evidence from 1 study including 66 participants)
- Resveratrol (low quality evidence from 1 study including 24 participants)
- Royal jelly (moderate quality evidence from 1 study including 64 participants)
- recombinant human epidermal growth factor (low quality evidence from 1 study including 34 participants)

1 partly applicable CUA with very serious limitations, based on a decision tree structure, found that HBO2 therapy in the treatment of diabetic ulcers is cost-effective based on a long-term perspective. The analysis does not provide a clear breakdown of cost assumptions and this, along with its U.S setting, makes it difficult to translate into an NHS context.

1 partly applicable CUA with very serious limitations found that platelet rich plasma gels combined with good wound care dominated saline gels and good wound care. The lack of a fully incremental analysis, non-UK setting, and very limited quantification of uncertainty means the findings of this study should be interpreted with caution.

1 directly applicable CUA with potentially serious limitations from a UK, NHS and PSS perspective found that HBOT and NPWT were not cost effective at a QALY value of £20,000 and suggested that the costs of these interventions were the main driver of this finding

Amputation rate

This review found a reduction in amputation rate at 12 weeks for the following interventions when compared to standard care:
- Graftskin (low quality evidence from 1 study including 210 participants)
- Negative pressure wound therapy (very low quality evidence from 2 studies including 497 participants)

This review found no difference in amputation rate at 12 weeks for the following interventions when compared to standard care
- Incretine (low quality evidence from 1 study including 106 participants)
- Immunokine (WF10) (Low quality evidence from 1 study including 40 participants)
- Hyperbaric oxygen therapy (very low quality evidence from 4 studies including 100 participants)
- AQUACEL dressing (very low quality evidence from 1 study including 209 participants)
- low level laser therapy (very low quality evidence from 1 study including 22 participants)
- Achilles tendon lengthening (low quality evidence from 1 study including 66 participants)
- Grafix (low quality evidence from 1 study including 97 participants)

Length of hospital stay

Very low quality evidence from 1 study including 68 participants found no significant differences between those who were given hyperbaric oxygen therapy with standard therapy when compared to standard therapy alone.

Adverse events at 12 weeks

This review found fewer adverse events for the following interventions when compared to standard care:

- Incretin (low quality evidence from 1 study including 106 participants)
- Topical autologous platelet-rich plasma gel (moderate quality evidence from 1 study including 72 participants)
- Topical Promogran (very low quality evidence from 2 studies including 312 participants)

This review found no difference in adverse events for the following interventions when compared to standard care

- Topical platelet derived growth factors (very low quality evidence from 3 studies including 667 participants)
- Topical basic fibroblast growth factor (low quality evidence from 1 study including 139 participants)
- Topical GAM501 growth factor (low quality evidence from 1 study including 82 participants)
- Topical recombinant human vascular endothelial growth factor (low quality evidence from 1 study including 55 participants)
- Hyalograft-3D followed by Laserskin autograft (very low quality evidence from 2 studies including 250 participants)
- Dermagraft (very low quality evidence from 1 study including 46 participants)
- Graftjacke (very low quality evidence from 2 studies including 125 participants)
- cultured allogeneic keratinocyte sheet (very low quality evidence from 1 study including 46 participants)
- Apligraf (very low quality evidence from 1 study including 71 participants)
- Talactoferrin (low quality evidence from 1 study including 46 participants)
- ANGIPARS herbal (very low quality evidence from 1 study including 15 participants)
- ANGIPARS intravenous (very low quality evidence from 1 study including 25 participants)
- Hyperbaric oxygen therapy (very low quality evidence from 1 study including 16 participants)
- AQUACEL dressing (very low quality evidence from 1 study including 209 participants)
- low level laser therapy (very low quality evidence from 1 study including 23 participants)
- electric stimulation therapy (low quality evidence from 1 study including 40 participants)
- non-contact normothermic wound treatment (very low quality evidence from 1 study including 20 participants)
- topical processed lipoaspirate cells (very low quality evidence from 1 study including 52 participants)
- vacuum compression therapy (very low quality evidence from 1 study including 18 participants)
- RGD peptide matrix (very low quality evidence from 1 study including 65 participants)
- collagenase debridement treatment (very low quality evidence from 1 study including 48 participants)

- Grafix (moderate quality evidence from 1 study including 97 participants)
- recombinant human epidermal growth factor (low quality evidence from 1 study including 34 participants)
- negative pressure wound therapy (low quality evidence from 1 study including 162 participants)

Infection at 12 weeks

This review found a reduced infection rate for the following interventions when compared to standard care alone:

- Topical Promogran (very low quality evidence from 2 studies including 312 participants)
- Topical lamin copper complex gel (low quality evidence from 1 study including 82 participants)

This review found no difference in infection rates for the following interventions when compared to standard care alone

- Topical basic fibroblast growth factor (very low quality evidence from 2 studies including 156 participants)
- Topical recombinant human vascular endothelial growth factor (moderate quality evidence from 1 study including 55 participants)
- Hyalograft-3D followed by Laserskin autograft (very low quality evidence from 1 study including 171 participants)
- Graftskin (very low quality evidence from 1 study including 208 participants)
- Dermagraft (low quality evidence from 3 studies including 410 participants)
- Graftjacket (very low quality evidence from 2 studies including 27 participants)
- cultured allogeneic keratinocyte sheet treatment (very low quality evidence from 1 study including 46 participants)
- external shock wave therapy (very low quality evidence from 1 study including 30 participants)
- topical thrombin peptide chrysalin (very low quality evidence from 1 study including 59 participants)
- AQUACEL dressing (low quality evidence from 1 study including 209 participants)
- low level laser therapy (very low quality evidence from 1 study including 23 participants)
- electric stimulation therapy (low quality evidence from 1 study including 40 participants)
- negative pressure wound therapy (low quality evidence from 1 study including 342 participants)

Quality of life

Moderate quality evidence from 1 study including 18 participants found no significant difference between those who were given Hyperbaric oxygen therapy with standard therapy when compared to standard therapy alone in regards to the HAD depression score and the SF-36 score for health and vitality at 1 year follow up.

High quality evidence from 1 study including 33 participants found participants in the hyperbaric oxygen therapy group improved on two measures of SF-36 score for health and vitality from baseline to 1 year follow up: role limitation due to physical health and role limitation due to emotional health; there was no significant difference in any of the other measures. Participants in the placebo group didn't improve significantly in any areas from baseline.

Moderate quality evidence from 1 study including 209 participants found no significant difference between those who were given AQUACEL dressing with standard therapy when compared with standard therapy alone in regards to the Cardiff Wound Impact Schedule score and the SF-36 score for health and vitality at 12 and 24 weeks follow up.

Health economics

One partly applicable CUA with very serious limitations, based on a decision tree structure simulating a US population, reported a base-case finding that hyperbaric oxygen therapy is cost-effective in the treatment of diabetic ulcers, though noted that this result depended on the assumed effectiveness of the intervention and the time horizon adopted.

A second directly applicable CUA with very serious limitations found that, in a UK NHS context, hyperbaric oxygen therapy is associated with an ICER of around £25,000 per QALY gained compared with usual care.

One partly applicable CUA with very serious limitations found that platelet rich plasma gels combined with good wound care dominated saline gels and good wound care.

One directly applicable CUA with very serious limitations found that, in a UK NHS context, negative pressure wound therapy is associated with an ICER of around £50,000 per QALY gained compared with usual care. This CUA suggests that negative pressure wound therapy would be associated with an ICER of less than £20,000 per QALY gained if the costs of a complete course of treatment can be assumed to be £1110 or lower.

4.12.5 Evidence to Recommendations

Table 49: Linking evidence to recommendations table

Relative value of different outcomes	The guideline development group (GDG) agreed that improving ulceration and re-ulceration rates was the critical outcome for this guideline. The GDG argued that if these could be prevented then the likelihood of other outcomes such as infection, gangrene, amputation and death would be diminished. In the case of this review question all of the included persons will have already developed diabetic foot problems and it will be a case of trying to heal active foot ulceration and reduce the rate of reulceration. All of the persons should received a good standard of care (as outlined in section 4.10) for the healing of diabetic foot ulcers. This review will examine whether any adjunctive therapies have an additional benefit for ulcer healing when added to the standard management. Improving ulcer healing will have long term impact in diminishing the likelihood of further complications from developing such as infection, gangrene, amputation and death. Reducing the incidence of these complications will also result in reduced length of hospital admission with implications for health-related quality of life and resource use.
Trade-off between benefits and harms	The benefits of an adjunctive therapy for people who have developed diabetic foot ulcers include clear improvement in the clinical outcomes listed above. The main complication that we are eager to heal is ulceration. If patients can have their foot ulceration healed quickly and reulceration prevented this can protect from the development of further more severe complications such as infection, gangrene and amputation. Secondly this therapy should be safe and do no harm. Thirdly it should be available and implementable into practice in the UK

population.

Potential harm of offering the above treatment strategies could include a direct adverse effect as a result of using the therapy or if using the treatment is found to worsen or slow the progress of healing. If a treatment has no effect, this too could lead to wasted resources and possible patient dissatisfaction if the patient sees that the diabetic foot problem is not responding to therapy. A poorly motivated patient may allow their disease to go unmanaged or poorly controlled which could lead to an increased likelihood of the development of diabetic foot complications such as ulceration/reulceration. This may, in turn, cause increased rates of infection, gangrene, amputation, hospital admission with the resulting burden on health-related quality of life.

The GDG discussed the risk of advising adjunctive therapy for which there is poor evidence in the literature. None of the therapies were found to increase the risk of serious adverse events.

Economic considerations	The GDG discussed the low quality of the health economic evidence presented and agreed that translating the findings of the two CUA papers from the USA into an NHS setting was extremely challenging given the uncertainties around estimated costs and effects. The GDG agreed that it was difficult to link the health economic evidence back to the clinical evidence as several studies used to parameterise the CUA models presented were excluded from the clinical evidence review on grounds of quality and/or relevance. Therefore, the GDG concluded that it could not draw any robust inference from the published US CUAs.

In discussing the analysis of hyperbaric oxygen therapy performed for CG119 (2011), the GDG noted that the costs of the intervention were very likely to be substantially underestimated. This is because the capital costs of the facilities needed to provide this service did not appear to be included in the analysis. These would be very substantial and if, in the alternative, patients were to be transported to the small number of existing facilities, this would incur costs that had, equally, been omitted from analysis. For this reason, the GDG concluded that hyperbaric oxygen therapy is likely to provide worse value for money than estimated in the 2011 analysis which, in any case, found it was associated with an ICER of greater than £20,000 per QALY gained.

In discussing the analysis of negative pressure wound therapy performed for CG119 (2011), the GDG noted that costs of the intervention have reduced considerably from those assumed in the 2011 analysis. Because the analysis is an undiscounted decision tree with a 1-year time-horizon, it was possible to isolate the contribution to net costs made by the intervention itself and, therefore, the ICER could be easily recalculated with lower costs. Rearranging these calculations, it could be seen that negative pressure wound therapy would provide QALY gains at an ICER of less than £20,000 per QALY so long as the complete course cost less than £1100, and it would be dominant (improving health and resulting in a reduction in net costs) if it cost less than £710. The GDG was confident that, in their experience, current costs of negative pressure wound therapy

	are substantially lower than these figures. Therefore, although the GDG was aware of the significant limitations of the 2011 model, it was happy to see this analysis as an indication that negative pressure wound therapy is likely to provide good value for money in the current NHS.
Quality of evidence	The GDG discussed the very low quality of the evidence presented, most notably that for hyperbaric oxygen therapy: since cure rates for these papers were presented at 1 year follow up it was considered to be an unfair comparison with the other papers on different adjunctive therapies and did not provide a suitable measure of effect for this outcome. The largest trial researching hyperbaric oxygen therapy also found no statistical difference between groups up until the 1 year follow up point was reached.
	More over in some papers there were more participants with certain comorbidities included in the control groups and not all trials were placebo controlled. The possibility of selection bias was considered.
	The GDG felt that it was important that the included papers used the same definition of outcome i.e. 100% epithelialization of wounds although understood that a minority of papers may not have had such a clear definition. GDG also raised concerns about the 12 week length of follow up commonly seen within these studies although understood that it represented a mean length of time taken to complete ulcer healing and was such often used as a suitable comparison point between control and treatment groups. This, however, may not have been a long enough length of follow up to adequately capture a rate of amputation comparison between groups.
	The GDG had other wider concerns with the evidence including: the frequent exclusion of participants with peripheral vascular disease; the selective picking of participants with a certain grade/size of ulcer to participate in the trials; the lack of blinding in various trials.
	The significant findings on ANGIPARS herbal extract were found to be particularly flawed due to the very low participation rate. For this reason the results were deemed inconclusive and no recommendation was made regarding this product.
Other considerations	Many adjunctive therapies did not prove to have a significant effect in the treatment of diabetic foot ulceration and recommendations were made against the use of these treatments such as hormonal growth factors, electrical stimulation therapy, autologous platelet-rich plasma gel, regenerative wound matrices and dalteparin.
	Dermal or skin substitutes on the other hand did seem to show a significant benefit, the GDG noted however that these treatments can be expensive and thus should only be offered when good standard care is not working and upon the advice of the multidisciplinary foot care service. For negative pressure wound therapy two studies were found to be appropriate to our inclusion criteria and showed that negative pressure wound

therapy could be significantly effective in treating diabetic foot ulcer or post-operative wound when compared to standard care. The GDG noted that this treatment is usually applied after surgical debridement and therefore a recommendation was made reflecting this practice.

One study showed a possible preventive effect of Achilles tendon lengthening after treatment of diabetic foot ulcer however there was no significant difference found between groups in terms of time to healing or number of patients achieving complete healing. The GDG noted that this treatment would only be used in a very specific subpopulation anyway and therefore declined to make a recommendation on this inconclusive evidence.

For honey therapy or maggot debridement therapy no evidence was identified that adhered to the standard of care outlined in our inclusion criteria for the treatment of diabetic foot ulcers. The GDG however recognised that these treatments may be useful in other wound treatments and may simply require more evidence to prove clinical effectiveness in the diabetic foot ulcer population. Maggot debridement also has the added benefit that it can enable debridement in some situations when surgical debridement may not be possible.

4.12.6 Recommendations

53. Consider negative pressure wound therapy after surgical debridement for diabetic foot ulcers, on the advice of the multidisciplinary foot care service.

54. Consider dermal or skin substitutes as an adjunct to standard care when treating diabetic foot ulcers, only when healing has not progressed and on the advice of the multidisciplinary foot care service.

55. Do not offer the following to treat diabetic foot ulcers, unless as part of a clinical trial:

- Electrical stimulation therapy, autologous platelet-rich plasma gel, regenerative wound matrices and dalteparin.
- Growth factors (granulocyte colony-stimulating factor [G-CSF], platelet-derived growth factor [PDGF], epidermal growth factor [EGF] and transforming growth factor beta [TGF-β]).
- Hyperbaric oxygen therapy.

4.12.7 Research recommendations

What is the clinical effectiveness of negative pressure wound therapy in the treatment of diabetic foot ulcers?

Why this is important

The evidence reviewed for negative pressure wound therapy was limited and of low quality. It would be useful to have more evidence for this commonly used treatment. It is proposed that a randomised controlled trial is undertaken to explore this question. The proposed study would monitor and evaluate the cure rates of foot ulcer resulting from diabetes, rates and

extent of amputation (major or minor), health-related quality of life, adverse events and hospital admission rates and length of stay.

What is the clinical effectiveness of maggot debridement therapy in the debridement of diabetic foot ulcers?

Why this is important

The evidence surrounding maggot debridement therapy was limited. It would be useful to have more evidence for this commonly used treatment. It is proposed that a randomised controlled trial is undertaken to explore this question. The proposed study would monitor and evaluate the cure rates of foot ulcer resulting from diabetes, rates and extent of amputation (major or minor), health-related quality of life, adverse events and hospital admission rates and length of stay.

4.13 Signs and symptoms of suspected Charcot arthropathy

4.13.1 Review question

What signs and symptoms or risk factors should prompt healthcare professionals to suspect Charcot arthropathy?

4.13.2 Evidence review

The aim of this review was to identify signs and symptoms that may be suggestive of the development of Charcot arthropathy in people with diabetes. This clinical issue has briefly been considered, amongst other aspects of care, in the NICE Clinical Guidelines 10 and 119. The evidence identified in this review question will support the existing evidence identified in these previously published guidelines and will provide information on previously unidentified evidence related to the signs and symptoms of Charcot arthropathy. The review protocol for this question can be found in Appendix C (under review question 13).

The original and rerun searches identified 1087 abstracts, 66 papers were identified. 63 papers were subsequently excluded because they did not fit the inclusion criteria (See Appendix E for a full list of excluded studies). Three papers were included in this review. (Ross, A. J. (2013). Foltz, K. D. (2004). Stuck, R. M.. (2008))

Table 50 outlines the PICO framework used for this review question and Table 2 provides a summary of all studies included in the review. The GRADE profiles for these studies are shown in Appendix I. The evidence tables are shown in Appendix G.

Table 50: PICO framework

Population	Adults with type 1 or type 2 diabetes
Intervention	Signs and symptoms of Charcot arthropathy.
	Including: deformity, inflammation, loss of sensation, pain, redness, warmth and fractures
	Risk factors for the development of Charcot arthropathy.
Comparator	The confirmed diagnosis of Charcot foot
Outcomes	Accuracy metrics (sensitivity, specificity, positive/negative predictive values, likelihood ratios etc.)
	Predictive measures from adjusted regression model
	Rates of hospital admission for foot problems resulting from diabetes
	Rates and extent of amputation (major or minor)
Include	Systematic reviews
	Controlled trial test and treat
	Diagnostic cross-sectional studies
	If insufficient evidence available also include case control studies
Exclude	Development of Charcot foot problems in people without diabetes.
	Treatment or management of Charcot arthropathy and lower limb ischaemia.

Table 51: Summary table of included studies for the signs and symptoms of Charcot arthropathy

Study	Population	Intervention	Control	Follow-up	Conclusions
Participants with diabetic peripheral neuropathy with Charcot foot vs. Participants with diabetic peripheral neuropathy without Charcot foot					
Case Control Ross, A. 2013 USA	Total number included= 49 Acute Charcot neuroarthropathy= 20 No acute Charcot neuroarthropathy= 29 Included Available complete medical records for the variables of interest Documented diabetic peripheral neuropathy with or without diagnosis of Charcot foot Documented BMI or height and weight Excluded Documented history of non-diabetes related neuropathy Recent infection within 6 months before the date of chart review Recent trauma or surgery "that may have otherwise have incited an acute Charcot event" Baseline characteristics	Participants in the acute Charcot group were those with documented diabetic peripheral neuropathy with the diagnosis of Charcot foot. N= 20	Participants in the control group were those with documented diabetic peripheral neuropathy without the diagnosis of Charcot foot. N= 29	No follow up period as such. Unclear the length of retrospective observation Outcomes measured: Age, gender, peripheral vascular disease, type of diabetes and BMI[1].	In the present investigation, no statistically significant association was found between an elevated BMI[1] and the development of acute Charcot neuropathy of the foot. Of the individual predictors, only diabetes classification was found to be statistically significant with the odds of a patient with type 1 diabetes having Charcot foot being 3.90 times greater than that for type 2 diabetes mellitus.

The glossary has been updated to include a definifition of deformity.

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Study	Population	Intervention	Control	Follow-up	Conclusions
	Populations were similar for type of diabetes, peripheral vascular disease, gender, age and BMI[1].				
Participants with diabetes and Charcot foot vs. participants with diabetes without Charcot foot					
Case control Foltz, K. D. 2004 USA	Participants= 59 Charcot group= 18 Control group= 41 Inclusion: Diabetes Chronic, radiographically proven Charcot neuroarthropathy Radiographic evidence of bone and joint destruction, fragmentation and remodelling Control group: must have diabetes but no clinical or radiographich evidence of Charcot disease. Baseline characteristics: Populations were similar in regard to gender, age, weight, height, BMI[1], diabetes duration, diabetes type 2, oral agent use but differed in regard to	Participants= 18 Diabetes and Charcot neuroarthropathy	Participants= 41 Diabetes mellitus without Charcot neuroarthropathy	No follow up as such, data was collected during a routine clinical visit. Outcomes measured included: Vascular examination findings, superficial pain sensation examination, tuning fork examination, deep tendon reflex examination, Sammes-weinstein monofilament examination (fine touch).	The results indicate that simple neurologic testing combined with a thorough patient history were the most beneficial tools to determine diabetics with a higher probability of developing Charcot neuroarthropathy. Specifically, history of retinopathy (P<0.02), nephropathy (P<0.003), and previous foot ulcer (P<0.01) were found to be predictive. The neurologic findings of vibratory sensation (<0.001), deep tendon reflexes (p<0.05), and the 5.07 (10g) Semmes-Weinstein monofilament test (P<0.001) were also highly correlative for the development of Charcot foot deformity. Vascular examination were found to differentiate poorly between groups. The application of this data

The glossary has been updated to include a definifition of deformity.

Study	Population	Intervention	Control	Follow-up	Conclusions
	diabetes type 1, insulin use, retinopathy, nephropathy, history of ulcer and history of foot trauma				may provide for earlier detection of Charcot arthropathy based on the predictive capabilities.
Participants with diabetes who developed Charcot foot vs. participants with diabetes who did not develop Charcot foot					
Case Control Stuck, R. M. 2008 USA	Participants= 561,597 Number with Charcot foot= 652

Included
All veterans with diabetes mellitus using Veterans Affairs services in 2003
Patients with a BMI[1] value available

Baseline characteristics recorded included: age, gender, ethnicity, marital status, BMI[1], diabetes duration, HbA1c, obesity and peripheral neuropathy. | Patients with diabetes who developed Charcot foot in the study period | Patients with diabetes who did not develop Charcot foot | Observation period was from October 2002 and September 2003. As this was a case control study there was no follow up period, as such.

Outcomes recorded included:
All of the baseline characteristics as variables for the development of charcot with the addition of renal failure, rheumatoid arthritis and anaemia. | Obesity is significantly associated with an increased incidence of Charcot arthropathy independently of other risk factors, as is peripheral neuropathy alone. When obesity is combined with neuropathy, the Charcot arthropathy incidence rate increases multiplicatively. Prevention of Charcot arthropathy should take the interaction between obesity and neuropathy into consideration. Also at higher risk of developing Charcot arthropathy were those with renal failure and deficiency anaemia while those aged between 75–84 years and those of African American race were found to be at a lower risk of developing Charcot. |
| Abbreviations: | | | | | |

The glossary has been updated to include a definifition of deformity.

Study	Population	Intervention	Control	Follow-up	Conclusions
[1]BMI– body mass index					
[2]NCA- Neuropathic Charcot arthropathy					

The glossary has been updated to include a definifition of deformity.

4.13.3 Health economic evidence

A literature search was conducted for the question using standard health economics filters appplied to the clinical search strategies. No relevant cost-utility analyses were found. Health economic modelling was not prioritised for this review question

4.13.4 Evidence statements

This review found that the odds of developing Charcot foot were increased in those with the following variables:

- Age between 55 and 64 years compared with these aged less than 55 years (very low quality evidence from 1 study including 561,597 participants)
- Obesity (defined as BMI 30 kg/m² or more) compared to those with BMI < 30 kg/m^2. (very low quality evidence from 1 study including 561,597 participants)
- Type 1 diabetes compared to those with type 2 diabetes (very low quality evidence from 1 study including 49 participants)
- Duration of diabetes ≥ 6 years compared to those with diabetes < 6 years (very low quality evidence from 1 study including 561,597 participants)
- HbA1c > 7% compared to HbA1c < 7 (very low quality evidence from 1 study including 561,597 participants)
- Peripheral neuropathy compared to those without peripheral neuropathy. (very low quality evidence from 1 study including 561,597 participants)
- Comorbidities (specifically rheumatoid arthritis, renal failure and deficiency anaemia) compared to no comorbidity. (very low quality evidence from 1 study including 561,597 participants)

This review found that there was no association between Charcot foot and the following variables:

- Age as a continuous variable. (very low quality evidence from 1 study including 49 participants)
- BMI as a continuous variable (very low quality evidence from 1 study including 49 participants)

This review found that the odds of developing Charcot foot were decreased in those with the following variable:

- African-American ethnicity compated to Caucasian ethnicity. (very low quality evidence from 1 study including 561,597 participants)

Neurological examination results.

A very low quality case control study of 59 participants with diabetes found significantly lower measures of superficial pain sensation, vibrational (tuning fork) sensation, deep tendon reflex, and fine touch (Semmes-Weinstein monofilament) sensation in those with Charcot foot.

4.13.5 Evidence to recommendations

Table 52: Linking evidence to recommendations table

Relative value of different outcomes	The GDG considered the predictive accuracy of the different signs and symptoms identified in the review. The group felt that finding the strongest and most common risk factors for Charcot foot was important given the impact that acute Charcot

	arthropathy and subsequent complications can have on a person's life such as deformity, amputation and hospitalisation. The importance of identifying acute Charcot arthropathy and beginning early treatment was paramount in this question. The aim was to make sure that anyone in whom Charcot foot was suspected could receive immediate treatment and that this could help to prevent subsequent complications such as deformity, which could also lead to ulceration which could result in further infection, gangrene, amputation and increased mortality.
Trade-off between benefits and harms	Regarding strong suspicion of Charcot foot the GDG considered that in instances of identified Charcot foot, referral to appropriate services and appropriate care results in decreased risk of ulceration, deformity and both minor and major amputation and hospital admission (also see Section 4.3 and 4.14 protocols and MDS) In instances of being low risk for Charcot foot then reassurance and ongoing monitoring by appropriate health care professionals in the appropriate setting or service is appropriate or ongoing investigation and treatment of any other causes of the symptoms. (also see Section 4.3 and 4.14 protocols and MFS) The consequences of a missing someone at high risk include increased possibility of ulceration, deformity and both minor and major amputation as a result of an acute Charcot foot left untreated. The consequences of misdiagnosing someone with Charcot foot include increased assessment and discharge from one service to another. (also see Section 4.3 and 4.14 protocols and DFS and MFS) Because of the consequences outlined above, both for the patient and for the services provided, the GDG were mindful to consider that many patients may not present with an obvious acute Charcot episode. And also that a missed diagnosis could have potentially more severe consequences than investigation/treatment of Charcot.
Economic considerations	Health economics were not considered as a priority for this review question. No economic studies were found. The GDG were careful to consider the resource implications of any decisions made.
Quality of evidence	Overall the GDG agreed the evidence provided a good representation of the most important signs and risk factors of Charcot foot. Although initially included, the study by Sinacore et al (2008) compared people with diabetes, peripheral neuropathy and recent-onset Charcot foot to control patients with no diabetes, peripheral neuropathy or Charcot foot. This was felt to be an inappropriate comparison and as a result the study was excluded. Studies by Ross (2013) and Stuck (2008) both used multivariate analysis.

Other considerations	The GDG discussed the evidence and the relevance of the signs and symptoms discussed and agreed that the most important symptoms that may lead to a suggested diagnosis of Charcot foot were redness, warmth and swelling. The group agreed that these were the commonly seen signs and symptoms in the literature and in clinical experience. The group also discussed the various risk factors presented and agreed that peripheral neuropathy and renal failure were important risk factors for Charcot arthropathy. This was as they were more common risk factors. Charcot foot always occurs in the presence of peripheral neuropathy and this was acknowledged as a pre-requisite. The group recognised rheumatoid arthritis as a potential risk factor but felt this should be classed lower down in importance as a risk factor. This was because rheumatoid arthritis was a less common risk factor. The group noted that deformity could also be a relevant sign of Charcot even in the absence of other signs or risk factors The group agreed that a person presenting with signs of Charcot should always be referred to specialist foot care teams. The group noted that deformity was representative of a late stage Charcot. They wanted to raise awareness that Charcot could be suspected even in the absence of deformity or other signs and therefore felt it was important to note this within the recommendations. Since fractures usually precede Charcot foot deformity the GDG wished to write a recommendation to make aware that diabetic foot fractures may progress to Charcot arthropathy. Evidence presented in a later CDUK study (see section 4.16) helped to support this view. The recommendation was made on consensus. The GDG also noted that people can present with signs of Charcot at different stages of development. The group agreed that unrecognised chronic Charcot still needs recognition as well as people presenting with acute signs of Charcot.

4.13.6 Recommendations

56. **Be aware that if a person with diabetes fractures their foot or ankle, it may progress to Charcot arthropathy.**

57. **Suspect acute Charcot arthropathy if there is redness, warmth, swelling or deformity (in particular, when the skin is intact), especially in the presence of peripheral neuropathy or renal failure. Think about acute Charcot arthropathy even when deformity is not present or pain is not reported.**

58. **To confirm the diagnosis of acute Charcot arthropathy, refer the person within 1 working day to the multidisciplinary foot care service for triage within 1 further working day. Offer non-weight-bearing treatment until definitive treatment can be started by the multidisciplinary foot care service.**

4.13.7   Research recommendations

Which risk stratification tools could be used to predict the likelihood of Charcot arthropathy?

Why this is important

The evidence surrounding Charcot arthropathy was limited and of low quality. It is proposed that a test and treat randomised control trial, or cohort study is undertaken to explore this question. The proposed study would monitor and evaluate the rates of Charcot arthropathy resulting from diabetes, rates of amputation (major and minor), rates of defomity resulting from Charcot foot and resource use and costs as a result of the use of a Charcot arthropathy risk stratification tool.

4.14 Indicators for referral to specialist services

4.14.1 Review Question

What are the indicators for referral to specialist services?

4.14.2 Evidence Review

The aim of this review was to establish the situations when it is 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. The review protocol for this question can be found in Appendix C (under review question 14).

From 18307 citations identified in the original and re-run searches a total of 168 abstracts were identified as potentially relevant to this question were requested for full text. Following the examination of full text papers 18 observational studies were found to be relevant to the review question and were included in the final review. (Mills, J. L. (1991). Alexandrescu, V. (2008). Edmonds, M. E. (1986). Weck, M. (2013). Rerkasem, K. (2008). Larsson, J. (1995). Armstrong, D. G. (2012). Yesil, S. (2009). Faglia, E. (1998). Trautner, C. (2007). Nather, A. (2010). Hedetoft, C.. (2009). Chiu, C. C. (2011). Cahn, A. (2014). Williams, D. T. (2012). Setacci, C. (2013). Elgzyri, T. (2014). Rubio, J. A. (2014)).

The papers were extracted for useful information which was used to fill the evidence tables (see Appendix G) and the GRADE profiles (see Appendix I).

Table 53 outlines the PICO framework used for this review question.

Table 53: PICO framework

Population	Children, young people and adults with type 1 or type 2 diabetes.
Intervention	Varying criteria for referral of people with diabetes to specialist services such as investigative or interventional radiology, orthopaedic or vascular services, specialist pain management and specialist orthotics.
Comparator	Not applicable
Outcomes	Rates (and recurrent rates) of foot ulceration, infection and gangrene resulting from diabetes.
	Rates of hospital admission for foot problems resulting from diabetes.
	Rates and extent of amputation (major or minor)
	Health-related quality of life
Include	Unrestricted search including all types of evidence
	Published papers only
Exclude	Examination of service arrangements of specialist services.
	Examination of configurations of team members of specialist services.

Summary of quality and methodological issues

Discussion was had with the GDG group regarding the purpose of the question and which types of studies we would be interested in. Since we were not able to find studies discussing whether referral to a specialist at a certain point in time or a certain stage in disease process had better outcomes than those who were referred at different stages or time points the decision was made to extract data from studies which compared specialist care to non-specialist care (or specialist teams to lack of specialist teams) and use the populations, protocols and services described in these studies to guide discussion and recommendations.

After the review was conducted 18 observational studies were found. Details of the skills, task of or professionals involved in the multi-disciplinary teams in each of the included studies is outlined in Table 44. A modified GRADE approach was used to quality assess this evidence.

Since there was substantial overlap between section 4.3 and section 4.14, and as both questions had similar methodological issues and required similar types of evidence, both reviews were presented together and recommendations were written in the same meeting.

Table 54: Included studies and details of skills, task or professionals involved in multi-disciplinary teams

Study	Detail of team involved
Alexandrescu 2008	A multidisciplinary diabetic foot clinic employing 2 diabetologists, vascular surgeons, 3 orthopaedic surgeons, 2 podiatrists 2 radiologists, 1 plastic surgeon, 2 psychologists and 1 infectionist. These were joined to specialised nurse and orthotist staff.
Armstrong 2012	Intergrated podiatric surgery with a vascular surgical limb-salvage service.
Cahn 2014	Multidisciplinary team lead by an endocrinologist and orthopaedic foot surgeon to target appropriate patients. An ambulatory day care unit was opened up to enable better follow up post discharge.
Chiu 2011	Surveillance and care by experienced specialists (endocrinologists, vascular surgeons and plastic surgeons with decision algorithm
Edmonds 1986	Specialised foot clinic for people with diabetes employing a chiropodist, shoe-fitter, nurse, physician and surgeon established
Faglia 1998	A diabetological unit for foot ulcer, single centre. Comprehensive protocol combined with a multidisciplinary approach in a dedicated centre.
Hedetoft 2009	Establishment of a multidisciplinary team in the clinic employing diabetes specialist, orthopaedic surgeon, podiatrist and nurse reviewing the patients simultaneously.
Larsson 1995	A comprehensive medical and orthopaedic programme for the prevention and treatment of diabetic foot ulcers. Team consisting of a dialectologist and an orthopaedic surgeon assisted by a diabetes nurse, a podiatrist, and an orthotist and working in close cooperation with the department of vascular surgery and the department of infectious diseases.
Mills 1991	A single vascular surgical service.
Nather 2010	Multidisciplinary Diabetic Foot Team combined with a clinical pathway. The team was composed of an orthopaedic surgeon an endocrinologist, an infectious disease specialist, a vascular surgeon, podiatrists, nurses specialised in wound care, foot care, foot screening and a case manager.
Rerkasem 2008	Multidisciplinary team and flow sheets based on foot protection algorithms
Trautner 2007	An interdisciplinary ward for inpatient treatment including preoperative and post-operative care
Weck 2013	Organisation of structured healthcare system based on integrated outpatient treatment, acute inpatient care and rehabilitative treatment. All participating medical institutions shared a common set of diagnostic and

Study	Detail of team involved
	therapeutic algorithms.
Williams 2012	The provision of rapid access referral pathways for severe diabetic foot disease, facilitating early assessment by a vascular team with an interest in wound healing 2) weekly podiatry, orthotic and vascular clinics running concurrently, optimising multidisciplinary communication and management 3) Co-ordinated fortnightly vascular or podiatry clinical reviews for patients requiring intensive outpatient management 4) all patients with diabetic foot disease requiring inpatient management admitted where possible to the vascular ward
Yesil 2009	A diabetic foot care team consisting of endocrinologists, orthopaedist, plastic and vascular surgeons, infectious disease specialists, radiologists, rehabilitation specialists, diabetes education and wound-care nurses and footwear technician
Setacci 2013	Application of new interdisciplinary shared protocol in a vascular and endovascular department.
Elgzyri 2014	Patients were treated with a standardised preset protocol in and out of hospital until healing. Team consisted of a diabetologist, an orthopaedic surgeon, an orthotist, a podiatrist and a registered nurse educated in diabetes.
Rubio 2014	A multidisciplinary diabetic foot unit, team for the diagnosis and treatment of diabetic foot disease. Coordinated by an endocrinologist and a podiatrist

Statements of the evidence findings for all outcomes can be found below.

4.14.3 Health Economic Evidence

A literature search was conducted for the question using standard health economics filters appplied to the clinical search strategies. No relevant cost-utility analyses were found. Health economic modelling was not prioritised for this review question

4.14.4 Evidence Statements

Rates (and recurrent rates) of foot ulceration, infection and gangrene resulting for diabetes

Evidence from 3 observational studies including 1,415 participants found that the multidisciplinary team had a significant reduction on the severity of foot ulcers at discharge, reduced rates of ulceration and gangrene per year and improved ulcer healing. No evidence was identified for infection rates. The quality of the evidence was very low.

Resource use and costs

Evidence from 1 observational study including 939 participants found that the introduction of multidisciplinary team had a non-significant impact on the mean hospitalisation cost per patient although mean hospitalisation cost per patient fell per year after the establishment of the team. The quality of the evidence was very low.

Rates of hospital admission for foot problems resulting from diabetes

Evidence from 2 observational studies with 10,267 participants found that the introduction of a multidisciplinary team did not have a significant effect on the number of patients admitted but admission rates did fall after implementation of the multidisciplinary team care. The quality of the evidence was very low.

Length of hospital stay

Evidence from 4 observational studies including 11,440 participants found that the introduction of a multidisciplinary team led to a reduction in the length of inpatient stay but the evidence was conflicting between the studies. The quality of the evidence was very low.

Rate and extent of amputation

Evidence from 16 observational studies including 15,105 participants found that the introduction of a multidisciplinary team led to a reduction in both the rate of and extent of amputation but the evidence was conflicting between the studies. The quality of the evidence was very low.

Evidence from 2 observational studies including 530 participants found that prompt vascular opinion and treatment was associated with improved outcomes for the rate of and extent of amputation. The quality of the evidence was very low.

Health-related quality of life

Evidence from 2 observational studies including 867 participants found that the introduction of a multidisciplinary team led to an increase in the health-related quality of life. The quality of the evidence was very low.

4.14.5 Evidence to Recommendations

Table 55: Linking evidence to recommendations table

Relative value of different outcomes	The guideline development group (GDG) agreed that reducing ulceration and re-ulceration rates was the critical outcome for this question and the guideline. The GDG argued that if these could be prevented then the subsequent likelihood of other outcomes such as infection, gangrene, amputation and death would be diminished. In the case of this question many of the patients will have already developed diabetic foot problems and it will be a case of trying to cure active foot ulceration and reduce the rate of reulceration. This will have long term impact in diminishing the likelihood of further complications from developing such as infection, gangrene, amputation and a reduced health-related quality of life. Reducing the incidence of these complications will also result in reduced rates of hospital admission.
Trade-off between benefits and harms	The benefits of appropriate referral to specialist services within the multidisciplinary foot care service for the appropriate diabetic population includes the following desired outcomes: A patient with active disease will receive the best available care at the earliest stage possible and this can prevent a complication such as ulceration from developing into further complications such as infection, gangrene, amputation and death. The patient would experience less delay in care in being referred between services as there will be a defined referral pathway. This will result in improved patient satisfaction. On the other hand an inappropriate referral to specialist services within the multidisciplinary foot care service could result in wasted NHS resources, wasted time for the referred person and dissatisfaction with the service. This could result in the person presenting late or not presenting at all next time they develop a

	problem which could cause an increase in the incidence of diabetic foot problems such as ulceration, which could lead to an increase in infection, gangrene and amputation outcomes.
Economic considerations	The GDG considered the substantial resource implications inherent in setting up multi-disciplinary services but found that the evidence of long term benefit suggests that there would likely be future cost-savings in return for any initial outlay. All evidence presented suggested that in terms of cost effectiveness the hospital multidisciplinary team service was a good investment in resources.
Quality of evidence	This review was initially designed to be a prognostic question looking for evidence to determine the relative risk of referring a person at different stages of their diabetic foot disease process. We were not able to find any such prognostic papers. The protocol was subsequently broadened to include studies that show the effect of establishing a multidisciplinary or integrated care pathway in the context of a hospital based multidisciplinary foot care service.
	Such studies would give an idea of the benefit of establishing multidisciplinary team in terms of rates and recurrent rates of foot ulceration, infection and gangrene, resource use and cost, hospital admission rates, length of hospital stay, rates and extent of amputation and health-related quality of life. While this would not directly answer the question of who should receive specialist referral and multidisciplinary care we were able to look at the types of populations included in these studies and extrapolate the stages at which it would be preferable and cost effective for patients to receive the multidisciplinary foot care service.
	The quality of the evidence was especially poor since we were unable to identify the prognostic type of evidence that we initially set out to find. Interventional type evidence was presented that only answered the question of who would benefit from referral to a hospital multidisciplinary foot care service in an indirect way. Since the purpose of the evidence presented was to prove benefit from the implementation of pathways, protocols and interdisciplinary care in different healthcare settings, and since all studies were of the observational type with a high risk of bias, all presented evidence was rated as very low quality.
	The GDG also discussed the difficulty in finding the source of the beneficial effect within a "before and after" study showing benefit from establishing multidisciplinary care. For example we could not prove that a particular referral pathway within a service protocol (e.g. pathways for vascular intervention) was effective since the study only showed the benefit of the implementation of a multidisciplinary service and protocol as a whole.
	The GDG decided a study by Sloan et al should be excluded on the basis that it held no useful information regarding when a patient should be referred to specialist services.
Other considerations	Across all settings the evidence seemed to show that having a hospital multidisciplinary foot team service was not only beneficial in terms of patient outcomes such as rates and recurrent rates of foot ulceration, infection and gangrene,

hospital admission rates, length of hospital stay, rates and extent of amputation and health-related quality of life but also that such a strategy could significantly be more cost effective in the long term. One study showed a decreasing mean hospitalisation cost per patient after the implementation of a multidisciplinary diabetic foot team combined with a clinical pathway.

As a result of the largely very consistent evidence about the benefits of multidisciplinary care the GDG decided that a recommendation should be made to ensure that there exists a hospital multidisciplinary team service for the prevention of diabetic foot problems and the treatment and management of complex diabetic foot disease.

More detailed evidence was found in certain studies that showed the benefit of a clear protocol and pathways that span the care of people with diabetes who are at low risk for developing diabetic foot complications to those patients who have developed active complications. The GDG as a result made recommendations that multidisciplinary foot protection services should not stand alone but rather should have integrated care pathways shared between the hospital and the community (also see section 4.3). Implementation of such protocols, according to the evidence identified, should be based upon the risk assessment of the patient and the severity of any current disease. Such assessments should be standardised across inpatient multidisciplinary foot care services and outpatient foot protection services as covered in other review questions (see section 4.4).

Such complex treatment initiatives would require constant and regular review. For this reason the GDG decided to make a consensus recommendation that patient and treatment outcomes should be regularly audited in line with the National Diabetes Foot Care Audit (see section 4.3).

Based on the management received by the patients in the evidence reviewed (where a detailed protocol was recorded), the GDG was able to extrapolate the types of services that they would want providing such levels of care for patients at different risk stratifications or stages of disease.

The GDG recognised that those who had developed active diabetic foot problems could be referred to the foot protection service or hospital multidisciplinary foot team depending on disease severity and the sophistication of the foot protection service available. The diabetic foot protection service may be able to provide triage for the hospital multidisciplinary team and treat simple active problems. However such service organisation would depend upon local protocols, resources and practice (also see section 4.3).

In order to define a reasonable standard for care providers to achieve, the GDG produced a consensus recommendation on the timeframe in which all people with diabetes who had developed active foot complications should be referred to the foot protection or multidisciplinary team service (within 1 working day) and triaged (1 further working day). This would help to

direct timely assessment of patients who had developed complications.

The GDG gave examples of life and limb threatening emergency problems (people who would not be able to safely wait a maximum of 72 hours to be seen and treated) in recommendation 58. The GDG felt that it had to make clear that these patients should be referred immediately to acute services or the multidisciplinary foot care service, according to local protocols (since the MDS may not always be available, for instance, when out of hours).

The GDG were eager that no patients should "fall out of the system." The main area of concern was for those patients who bypass the foot protection service and present in emergency care. There was potential for such patients to have treatment delayed if it was felt that the care of diabetic foot was not the responsibility of the health care provider to which the patient presents. For this reason both in emergency care and general practice it was recommended that each trust should have available a shared protocol for the treatment of a diabetic foot complications. This protocol should be integrated across the multidisciplinary hospital team, the foot protection service and emergency and general practice services. (see section 4.3)

The GDG discussed the need for an admitting team to provide immediate assessment and treatment in persons referred to secondary care with a diabetic foot problem. The aim of this recommendation (see section 4.1) was to ensure that the person did not receive delayed care in hospital settings. Active management should continue up until the multidisciplinary foot care service may choose to take over care.

There was substantial overlap between section 4.3 and section 4.14, and as both questions had similar methodological issues and required similar types of evidence, both reviews were presented together. This section refers to indications for referral to specialist services, and since the multidisciplinary foot care service consists of many different specialists the decision was made to write the recommendations specific to the multidisciplinary foot care service within this section.

4.14.6   Recommendations

59. **If a person has a limb-threatening or life-threatening diabetic foot problem, refer them immediately to acute services and inform the multidisciplinary foot care service (according to local protocols and pathways; also see recommendation 8), so they can be assessed and an individualised treatment plan put in place. Examples of limb-threatening and life-threatening diabetic foot problems include the following:**

- Ulceration with fever or any signs of sepsis.
- Ulceration with limb ischaemia (see the NICE guideline on lower limb peripheral arterial disease).

- Clinical concern that there is a deep-seated soft tissue or bone infection (with or without ulceration).
- Gangrene (with or without ulceration).

60. For all other active diabetic foot problems, refer the person within 1 working day to the multidisciplinary foot care service or foot protection service (according to local protocols and pathways; also see recommendation 8) for triage within 1 further working day.

4.14.7 Research recommendations

Within the hospital based MDT, when it is 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?

Why this is important

The evidence surrounding different referral criteria for those who have developed diabetic foot problems within the multidisciplinary foot care service to other specialist services was limited. It is proposed that a cohort study is undertaken to explore this question. The proposed study would monitor and evaluate the rates (and recurrent rates) of foot ulceration, infection and gangrene resulting from diabetes, resource use and costs, rates and extent of amputation, rates of hospital admission for foot problems resulting from diabetes, length of hospital stay, and the health-related quality of life as a result of different referral criteria to these teams.

4.15 Tools for assessing and diagnosis Charcot arthropathy

4.15.1 Review Question

What are the clinical utilities and accuracy of tools for assessment and diagnosis of Charcot arthropathy in people with diabetes?

4.15.2 Evidence Review

The aim of this review was to find the clinical use and diagnostic accuracy of the available tools for the assessment and diagnosis of Charcot neuroarthropathy in all its clinical stages in the diabetic population. Tools for assessment and diagnosis may include radiographic interventions, bedside tests or basic clinical suspicion. The review protocol for this question can be found in Appendix C (under review question 15).

This was a new review question that had not previously been undertaken in any previous systematic reviews such as clinical guideline 119 (CG119) or clinical guideline 10 (CG10). These review questions were created to include any new evidence on the diagnosis of Charcot foot.

The original and rerun searches identified 928 abstracts 52 papers were identified. After ordering full paper copies, 45 papers were subsequently excluded because they did not fit the exclusion criteria (see Appendix F for a full list of excluded studies). Seven new papers were included in the final review. Chantelau, E. A. (2013). Chantelau, E. (2006). Chantelau, E. (2005). Basu, S. (2007). Moura-Neto, A. (2012). Höpfner, S. (2004). Beltran, J. (1990).

These papers were extracted for relevant outcomes and were used to fill both the evidence tables and the GRADE profiles. The GRADE profiles for the included studies are included in Appendix I. The evidence tables are shown in Appendix G.

Table 56 outlines the PICO framework used for this review question.

Table 56: PICO framework

Population	Children, young people and adults with type 1 or type 2 diabetes
Intervention	Diagnostic interventions, such as: Magnetic resonance imaging (MRI) Bone scans (e.g. with neuropathy and primary fracture) Clinical suspicion and deformity Temperature difference in the foot
Comparator	X-ray, or as above
Outcomes	Clinical utility or diagnostic test accuracy (if available) including: • Test validity such as face validity, content validity, construct validity, concurrent validity, criterion validity; • Test reliability such as internal reliability/consistency, test-retest reliability, inter-rater reliability. • Sensitivity, specificity, positive predictive value, negative predictive value, likelihood ratios, diagnostic odds ratio and area under the ROC analyses.
Include	Systematic review Test and treat RCT Cross-sectional study If insufficient evidence is available progress to:

	Case control study
Exclude	People without diabetes

Following the agreement of the review protocol a further discussion was had with some members of the Guideline Development Group in which it was agreed that studies would not have to be comparative studies or be compared with X-ray to be included. Studies should, however, have some measure of clinical utility or diagnostic accuracy.

Summary of quality and methodological issues

In total, 7 studies were included that covered use of MRI, plain radiograph, PET scan and temperature difference often compared to clinical follow up or surgical findings. Descriptions of these studies and the therapies used can be found in the respective evidence tables in Appendix G

Many included studies were downgraded for bias due to methodological issues such as:

- Unclear if groups comparable at baseline
- Data taken retrospectively
- No attempt to balance groups for confounders
- Lack of blinding to other investigations
- No pre-specified threshold
- Results of reference standard were not interpreted without knowledge of index test
- Unclear inclusion criteria

Additionally many studies did not provide the accuracy measures stated in the protocol, however if a potentially useful measure of assessment was reported such papers could be included.

A summary of evidence for all outcomes can be found below along with the relevant GRADE tables in Appendix I.

Table 57: Summary table of included studies for tools for assessing and diagnosis of Charcot arthropathy

Study	Population	Intervention	Control	Follow-up	Conclusions
Magnetic resonance imaging vs X-ray as primary method of investigation with MRI follow up vs X-ray with no MRI follow up for diagnosis of Charcot foot					
Retrospective Cohort Chantelau, 2013 Germany	Total= 71 cases, 59 participants Cases diagnosed as Charcot disease stage 0= 27 Cases diagnosed as Charcot disease stage 1= 44

Included Cases treated and followed up by the diabetic foot clinic until complete healing of the acute Charcot foot

Excluded Coexisting plantar ulceration Possible skeletal septic pathology

Baseline characteristics Unclear if groups were comparable at baseline, since characteristics were not compared between those who received Xray instead of MRI as primary investigation | Standard care involved complete offloading and immobilisation of the affected foot immediately (wheelchair or hospital bed), Patients were then provided with a bivalve removable total contact cast, although a small minority received a prefabricated polypropylene ankle-foot orthosis

Magnetic resonance imaging, MRI n=50 | Standard care involved complete offloading and immobilisation of the affected foot immediately (wheelchair or hospital bed), Patients were then provided with a bivalve removable total contact cast, although a small minority received a prefabricated polypropylene ankle-foot orthosis

X-ray as primary method of investigation followed by magnetic resonance imaging n=21

X-ray alone (not followed by magnetic resonance imaging) (n=13) | Length of follow up was variable

Outcomes measured: Median time from symptom onset to treatment Detection of stage 0 Charcot foot Median time from symptom onset to treatment for stage 0 Charcot foot | The time from onset of symptoms until institution of total contact casting was not found to be significantly affected by stage of disease process. However it was found to be significantly affected by choice of investigation: Those who received MRI or X-ray cross checked by MRI received treatment for charcot arthropathy sooner than those investigated with X-ray alone. |
| Plain Radiography vs Magnetic resonance imaging for the diagnosis of Charcot foot | | | | | |

The glossary has been updated to include a definifition of deformity.

Study	Population	Intervention	Control	Follow-up	Conclusions
Retrospective case series Chantelau 2006 Germany	Number of patients included: 20 participants, 26 Charcot feet Inclusion: retrospective case series of the charts of participants with diabetic charcot neuroarthropathy Baseline characteristics: Mean age: 59 years (median) Males/females: 11 men, 9 women (charcot group)	(1) Plain Radiography Test: a board qualified radiologist blinded to the clinical findings qualitatively and quantitvely analysed all the X-rays. Number unable to participate in the index test and reasons given: Not stated (2) Magnetic resonance imaging Test: a board qualified radiologist blinded to the clinical findings qualitatively and quantitvely analysed all the MRIs. Number unable to participate on the index test and reasons given: Not stated	Reference standard: The reference standard was based on clinical and radiological findings, undefined. Details: Unclear Number unable to participate in the reference test : Nil	No follow up as such, data was collected retrospectively from charts Outcomes: Number of affected bones disclosed by investigations.	MRI was able to disclose a greater number of affected bones and joints among those participants with stage 0 Charcot disease although similar findings were found for stage 1-3 Charcot foot.
Early diagnosis and treatment of Charcot vs later diagnosis and treatment of Charcot foot (overt Charcot foot)					
Retrospective case series Chantelau 2005 Germany	Number of patients included: 24 participants Included the charts of participants with diabetic charcot neuroarthropathy seen in one university hospital	(1) Early diagnosis: The outcomes of those with earlier diagnosis and treatment of Charcot foot before fractures appeared on plain radiograph (established on the basis of clinical symptoms plus bone abnormalities on X-ray e.g. osteoarthritis, MRI (bone oedema), CT	Reference standard: The reference standard was the outcomes of those with later diagnosis and treatment of Charcot foot after fractures appeared on plain radiograph (Overt Charcot foot) (n=13) Details: treatment with total contact cast and offloading	Follow up period unclear as results were taken from retrospective charts Outcomes: Number misdiagnosed prior to treatment Time from onset of symptoms until application of total	A greater proportion of participants who had been caught in early stages of Charcot foot had received an MRI, technetium scan or CT scan

Study	Population	Intervention	Control	Follow-up	Conclusions
	Baseline characteristics Mean age: In the early treatment group= 61 years median, in delayed treatment group= 52 years median Males/females: In the early treatment group= 5/6, in delayed treatment group= 8/5	(hidden line fractures), or bone technetium scan (e.g. increased isotope uptake). Incipient Charcot foot (n=11) Test: further details unclear, treatment with total contact cast and offloading Number unable to participate in the index test and reasons given: Not stated	Number unable to participate in the reference test : Not stated	contact casting Time from application of total contact casting to healing Progression to definite fractures of either the tarsometatarsal joints or of the talonavicular joint Progression to gross foot deformity Proportion of participants with MRI, technetium scan, or CT scan	
FDG PET vs Magnetic resonance imaging for the diagnosis of Charcot foot					
Retrospective review of the results from a prospective trial designed to investigate the usefulness of FDG PET Basu 2007 USA	Number of patients included: 63 participants were included. These were split into 4 groups. Groups A) 17 participants with a clinical diagnosis of Charcot's neuroarthropathy B) 21 participants with uncomplicated diabetic foot C) 5 participants with a proven osteomyelitis secondary to complicated diabetic foot D) 20 non-diabetic participants with normal lower extremities. Included data was only reported	(1) FDG PET image acquisition and analysis Test: experienced nuclear physicians blinded to the radiological data and final diagnosis qualitatively and quantitvely analysed all PET images (n=17) (2) Magnetic resonance imaging Test: Interpreted by experienced radiologists of the institute for structural abnormalities of the feet blinded to final diagnosis and FDG	Reference standard: Surgical and histological findings, or the results of long term follow up (undefined) Details: All specimens including debrided tissue and bone fragments from surgery were examined by standard staining techniques and microbiological examination results	Follow up period unclear as results were taken from retrospective data Outcome: Sensitivity and specificity	In a population with osteomyelitis or Charcot foot FDG PET showed a greater sensitivity for the diagnosis of Charcot foot than MRI. There was no difference in specificity between the two investigations.

The glossary has been updated to include a definifition of deformity.

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Study	Population	Intervention	Control	Follow-up	Conclusions
	for those with a final diagnosis of osteomyelitis and charcot foot Baseline characteristics Mean age: 59.4 ± 8.6 years (charcot group) Males/females: 11 men, six women (charcot group)	PET results (n=17)			
Infrared skin thermometer for the diagnosis of Charcot foot					
Case series Moura-Neto 2012 Brazil	Number of patients included: 28 Included unclear Baseline characteristics Mean age: 58.8 years Males/females: 14 males, 14 females	(1) Infrared skin thermometer (Minitemp, Raytec) Test: skin temperature taken at the same spot on affected and non-affected feet. Temperature difference calculated.	Reference standard: The results of long term follow up (1 year) Details: All participants had monthly follow up visits for a year in order to catch any feet presenting with relapse Number unable to participate in the reference test : Not stated	Follow up period= 1 year Outcomes recorded: Number who progressed to consolidation/remission by 1 year Following withdrawal of immobilisation based on temperature difference, frequency of relapse after 1 year follow up	Infrared skin thermometer may be an effective method of diagnosing acute Charcot foot going into remission.
Ring PET vs Hybrid PET vs Magnetic resonance imaging for the diagnosis of Charcot foot					
Case series Hopfner 2004 Germany	Number of patients included: 16 participants Included Participants with Charcot foot conditions requiring surgical intervention hospital	(1) Ring PET Test: two experienced examiners blinded to the results of the other tests Siemans ECAT EXACT HR	Reference standard: Surgical findings Details: Not provided	Follow up period unclear Outcomes: Sensitivity for diagnosis of Charcot foot	Results indicate both ring PET and MRI are effective in the preoperative detection of small, inflammatory, non-infectious Charcot lesions. The most important limitation of MRI is its restricted

The glossary has been updated to include a definifition of deformity.

Study	Population	Intervention	Control	Follow-up	Conclusions
	Baseline characteristics: Mean age: 60.1 ± 10 years Males/females: 9 men, 7 women	(2) Hybrid PET Test: two experienced examiners blinded to the results of the other tests Marconi AXIS y-PET² scanner (3) Magnetic resonance imaging Test: two experienced examiners blinded to the results of the other tests Siemans Harmony scanner (1.0 Tesla field strength)			efficacy in patients with metal implants.
Plain radiograph vs Magnetic resonance imaging for the diagnosis of Charcot foot					
Retrospective case series Beltran 1990 USA	Number of patients included: 14 participants Included participants with suspected foot infection and/or neuropathic joint Baseline characteristics: Mean age: not stated Males/females: not stated	(1) Plain radiograph Test: two experienced examiners blinded to the results of the other tests and clinical findings No further details provided (2) Magnetic resonance imaging Test: two experienced examiners blinded to the results of the other tests and clinical findings 1.5 Tesla magnet	Reference standard: long term follow up and development of disease Details: Not provided	Follow up period unclear. Retrospective. Outcomes: Sensitivity and specificity for diagnosis of Charcot foot	MRI was found to be accurate in detecting and differentiating between neuroarthropathy and osteomyelitis and superior to plain radiography in the detection of Charcot foot.

The glossary has been updated to include a definifition of deformity.

Study	Population	Intervention	Control	Follow-up	Conclusions

Abbreviations:

The glossary has been updated to include a definifition of deformity.

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4.15.3 Health economic evidence

A literature search was conducted for the question using standard health economics filters appplied to the clinical search strategies. No relevant cost-utility analyses were found. Health economic modelling was not prioritised for this review question

4.15.4 Evidence statements

Magnetic resonance imaging vs X-ray cross checked by MRI or X-ray alone in the diagnosis of stage 0 Charcot foot

Very low quality evidence from 2 studies including 78 participants found MRI and plain radiograph or MRI alone to have greater sensitivity than plain radiograph in the detection of Eichenholtz stage 0 Charcot foot.

Magnetic resonance imaging vs X-ray in the diagnosis of acute Charcot foot in participants with suspected foot infection and/or Charcot foot

Very low quality evidence from 1 study including 14 participants found MRI to have a greater sensitivity than plain radiograph in the diagnosis of Charcot foot in participants with suspected foot infection and/or Charcot foot.

Magnetic resonance imaging vs X-ray cross checked by MRI or X-ray alone in the diagnosis of stage I and II Charcot foot

Very low quality evidence from 1 study including 14 participants showed no significant difference between the sensitivity of MRI and plain radiograph in the detection of Eichenholtz stage I and stage II Charcot foot.

FDG PET vs MRI for the diagnosis of Charcot foot

Very low quality evidence from 1 study found that in a population with osteomyelitis or Charcot foot including 22 participants FDG PET showed a greater sensitivity for the diagnosis of Charcot foot than MRI. There was no difference in specificity between the two investigations.

Ring PET or hybrid PET vs MRI in the preoperative assessment of Charcot foot

Very low quality evidence from 1 study including 16 participants found ring PET to have a greater sensitivity for Charcot lesions than MRI or hybrid PET. MRI was found to have a greater sensitivity for Charcot lesions than hybrid PET in the preoperative assessment of participants with Charcot foot.

Foot skin temperature in the assessment remission of Charcot foot

Very low quality evidence from 1 study including 25 participants found that following use of skin temperature difference for the diagnosis of acute Charcot foot remission no participants experienced relapse in the one year follow up.

Early vs delayed diagnosis and treatment of Charcot foot

Very low quality evidence from 1 study found that participants with delayed diagnosis of Charcot foot showed significant difference in progression to definite fractures and progression to gross foot deformity to those with early diagnosis following symptoms. Results were in favour of the early diagnosis group.

Very low quality evidence from 1 study found that participants with delayed diagnosis of Charcot foot showed significant difference to those with early diagnosis in the amount that had received MRI, technetium scan or CT scan previously. Fewer participants with delayed diagnosis had received MRI, technetium scan or CT scan.

4.15.5 Evidence to recommendations

Table 58: Linking evidence to recommendation table

Relative value of different outcomes	The GDG considered the predictive accuracy of the different diagnostic tools and tests identified in this review. The group agreed that they would be prepared to accept lower specificity in exchange for higher sensitivity in order to ensure all patients with active disease receive the treatment they require. The group felt that false positives were preferable to false negatives given the impact that acute Charcot arthropathy and subsequent consequences can have on a person's life such as deformity, amputation, and hospitalisation.
	The importance of identifying acute Charcot arthropathy and beginning immediate treatment was paramount in this question. The aim was to make sure that anyone in whom Charcot was suspected could receive immediate treatment and that this could help to prevent subsequent complications such as deformity, which could also lead to ulceration which could result in further infection, gangrene, amputation and increased mortality.
Trade-off between benefits and harms	Regarding accuracy outcomes the GDG considered that in instances of a true positive, referral to appropriate services, and receipt of treatment therein, results in decreased risk of ulceration, deformity and both minor and major amputation and hospital admission (see Section 4.3 Protocols and MDS).
	In instances of true negatives then reassurance and ongoing monitoring by appropriate health care professionals in the appropriate setting or service is sufficient with ongoing investigation and treatment of the true cause of the symptoms. (see Section 4.3 Protocols and MFS)
	The consequences of a false negative include increased likelihood of ulceration, deformity and amputation as a result of an acute Charcot foot left untreated. The consequences of a false positive include increased assessment and discharge from one service to another (see Section 4.3 Protocols and DFS and MFS).
	Because of the consequences outlined above, both for the patient and for the healthcare services, the GDG were mindful to consider that many patients may not present with an obvious acute Charcot episode. And also that a false negative could have potentially more severe consequences than a false positive finding.
Economic considerations	Health economics were not considered as a priority for this review question. No economic studies were found.
	The GDG considered the relative cost and effectiveness of each of the diagnostic tests presented and made recommendations

	with consideration of these factors
Quality of evidence	Evidence was scarce and the quality of evidence was generally very low. Many of the studies were not designed in a manner in which to best answer the questions of interest. No studies reported test validity and test reliability findings. The GDG felt that sensitivity and specificity values calculated from studies that did not reflect the populations seen in practice (e.g. those with no overlying foot infection or stage 0 Charcot) could be misleading if taken at face value. Outcomes measured were not always of interest for example the number of preoperative lesions detected. Also problematic was the lack of commonality between the reference standards used in each of the included studies (e.g. X-ray, clinical diagnosis, MRI). This can make comparisons between studies difficult.
Other considerations	The GDG recognised the scarcity of evidence for this review question and the poor quality of the published papers. The GDG were satisfied that evidence seemed to show a strong benefit of early diagnosis and treatment of Charcot foot for the clinical outcomes of disease progression and deformity. The GDG discussed the risk of appearing to recommend MRI for all patients with Charcot foot. It was agreed that diagnosis should remain primarily from clinical findings with a plain radiograph and MRI performed only in the absence of any radiographic findings where suspicion remains. It was felt strongly that although MRI can detect pathological changes to the Charcot joint at earlier stages than plain radiograph, it is still a highly unspecific test especially in populations with osteomyelitis or infection. It will therefore not always add benefit to clinical decision making in cases that can be detected by plain radiograph. As a result the decision was made that diagnosis should be made on the basis of X-ray cross checked by MRI if clinical suspicion remains. The comparison of MRI to plain radiograph in the stage 0 Charcot foot population was considered not a helpful comparison since, by definition, participants with stage 0 Charcot foot will not show changes on plain radiograph. Similarly it was felt that there was not enough evidence to show that a PET scan would add significant benefit in terms of clinical utility and patient important outcomes. The use of PET scanning in preoperative assessment was not felt to add anything above MRI in terms of clinical usefulness to the surgeon. The evidence presented showed that monitoring skin temperature difference between feet could be used to accurately diagnose an acute Charcot foot which had gone into remission. This could be useful in clinical practice for unilateral acute Charcot foot. Therefore a further recommendation was made on monitoring the Charcot foot using both temperature difference and serial X-rays.

4.15.6 Recommendations

61. If acute Charcot arthropathy is suspected, arrange a weight-bearing X-ray of the affected foot and ankle. Consider an MRI if the X-ray is normal but Charcot arthropathy is still suspected.

62. Monitor the treatment of acute Charcot arthropathy using clinical assessment. This should include measuring foot–skin temperature difference and taking serial X-rays until the acute Charcot arthropathy resolves. Acute Charcot arthropathy is likely to resolve when there is a sustained temperature difference of less than 2 degrees between both feet and when X-ray changes show no further progression.

4.15.7 Research recommendations

When is it safe to stop contact casting in the treatment of acute Charcot arthropathy?

Why this is important

The evidence surrounding Charcot arthropathy was limited and of low quality. It is proposed that a test and treat randomised control trial, cross-sectional study or case control study is undertaken to explore this question. The proposed study would monitor and evaluate the test validity, test reliability, sensitivity, specificity, positive predictive value, negative predictive value, diagnostic odds ratios and likelihood ratios as a result of different tests for acute Charcot arthropathy remission. Alternatively the study could examine the rates of Charcot recurrence, deformity, amputation and ulceration following the stopping of contact casting in the treatment of acute Charcot arthropathy.

4.16 Management strategies for Charcot arthropathy

4.16.1 Review Question

What is the clinical effectiveness of surgical interventions, adjunctive treatment, offloading or orthoses for managing Charcot arthropathy?

4.16.2 Evidence Review

The aim of this review was to determine the most effective methods of surgical interventions, adjunctive treatment, offloading and orthoses for managing Charcot arthropathy in all its clinical stages in the diabetic population. Treatment options available include total contact casting, removable boot devices, bisphosphonates and the various types of surgical arthrodesis, amputation and offloading. The review protocol for this question can be found in Appendix C (under review question 16).

This was a new review question that had not previously been undertaken in any previous systematic reviews such as clinical guideline 119 (CG119) or clinical guideline 10 (CG10). These review questions were created to include any new evidence on the management of Charcot foot.

The original and rerun searches identified 924 abstracts, 32 papers were identified. After ordering full paper copies, 24 papers were subsequently excluded because they did not fit the exclusion criteria (see Appendix E for a full list of excluded studies). Eight new papers were included in the final review. (Pakarinen, T. K., (2011). Chantelau, E. (1997). Hanft, J. R. (1998). Shah, N. S. (2011). Bharath, R., Bal, A. (2013). Game, F. L., (2012). Pakarinen, T. K. (2002). Clohisy, D. R. (1988).

These papers were extracted for relevant outcomes and were used to fill both the evidence tables and the GRADE profiles. The GRADE profiles for the included studies are included in Appendix I. The evidence tables are shown in Appendix G.

Table 59 outlines the PICO framework used for this review question.

Table 59: PICO framework

Population	People with diabetes and diagnosed Charcot arthropathy
Intervention	surgical interventions adjunctive treatment offloading orthoses
Comparator	Surgical gold standard Non-surgical gold standard
Outcomes	Amputation Mortality Ulceration Time to remission Rates and extent of amputation Deformity
Include	Systematic review Randomised controlled trials If insufficient evidence is available progress to: Non-randomised controlled trials Cohort study
Exclude	People without diabetes

Summary of quality and methodological issues

In total 8 studies were included that covered use of bisphosphonates, combined magnetic field bone growth stimulation, palliative radiotherapy, external fixation, retrograde intramedullary nail fixation, weight bearing treatment, removable offloading and non-removable offloading. Descriptions of these studies and the therapies used can be found in the respective evidence tables in Appendix H.

Many included studies were downgraded for bias due to methodological issues such as:

- Unclear method of randomisation/no randomisation
- Unclear if groups were comparable at baseline
- Lack of blinding
- Evidence of variance in care between groups apart from treatment under study
- Imprecise definition of outcome/unreliable method of determining outcome
- Lack of measure of compliance or treatment completion
- Retrospective

Additionally many studies did not provide the outcome measures stated in the protocol, however if a potentially useful measure of effectiveness was reported such papers could be included.

A summary of evidence for all outcomes can be found below along with the relevant GRADE tables in Appendix G and Appendix I respectively.

Table 60: Summary table of included studies for management strategies for Charcot arthropathy

Study	Population	Intervention	Control	Follow-up	Conclusions
IV zoledronic acid vs placebo for the treatment of Charcot foot					
Randomised controlled trial Pakarinen 2011 Finland	Randomised= 39 (4 subsequently excluded) Treatment group= 18 Placebo group = 17 Included Included: Acute midfoot Charcot neuroarthropathy, based on clinical examination and radiological findings. Warm, swollen foot with erythema over the warmest area of the foot. Increase of ≥2°C on infrared thermometer compared with the same site on the contralateral foot. MRI: periarticular focal bone marrow oedema, absent sinus tracts or soft tissue fluid collections and preservation of periarticular subcutaneous fat. Excluded Renal insufficiency (serum creatinine >400	4mg of IV zoledronic acid (bisphosphonate), 3 times with 1 month intervals. Standard care.	Placebo. Standard care included initial non-weight bearing below the knee contact cast. When the temperature difference between the feet was 1-2°C and no other clinical signs of active Charcot processes were present, partial weight bearing was allowed and a fixed ankle-foot orthosis was applied. Full weight bearing permitted when feet reached <1°C temperature difference with no evidence of erythema or oedema.	Length of follow up was 1 year Outcomes measured: Median time for total immobilization Relapse of Charcot neuropathy	This study showed a significant difference between zoledronic acid and placebo in the median time for total immobilisation. Results were in favour of the placebo group.There was no significant difference between groups for the outcome of relapse of Charcot arthropathy.

The glossary has been updated to include a definifition of deformity.

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Study	Population	Intervention	Control	Follow-up	Conclusions
	μmol/L) Previous bisphosphonate treatment Baseline characteristics Groups were similar at baseline.				
Palliative radiotherapy vs standard care and placebo for acute Charcot foot					
Randomised control trial Chantelau 1997 Germany	Randomised= 12 Treatment group= 6 Placebo group = 6 Inclusion: Acute diabetic osteoarthropathy of known duration less than 2 months Defined by clinical criteria: redness, swelling and hyperthermia Xray findings: fracture, osteolysis	Radiotherapy was performed three times weekly to a total dose of 2.45 Gy. Standard therapy.	Sham radiotherapy included 6 sessions with 0 Gy. Standard therapy included complete relief of pressure from affected foot by bed rest or wheel chair, systematic treatment with oral antibiotics to prevent infection, low dose heparin as an anti-thrombotic agent.	Variable length of follow up Outcomes included time to remission and patient compliance	This study found no significant difference between radiotherapy and sham radiotherapy treated groups for the outcome of overall healing time (time to remission.
Combined magnetic bone growth stimulator vs standard care for the treatment of acute neurogenic osteoarthropathy					
Randomised control trial Hanft 1998 USA	Randomised= 31 Treatment group= 21 Placebo group = 10 Inclusion: Peripheral neuropathy secondary to diabetes mellitus Clinical, thermographic,	Combined magnetic bone growth stimulator device used for ½ an hour every day. Standard care	Participant could be treated with total contact cast or fixed ankle walker depending on contraindications.	Length of follow up was variable Outcomes: Mean time to consolidation	This study found significant difference between treatment and control groups for the outcome of median time to consolidation. Results were in favour of the treatment group.

The glossary has been updated to include a definifition of deformity.

Study	Population	Intervention	Control	Follow-up	Conclusions
	and radiographic evidence of acute Charcot joint Exclusion: Presence of open ulceration or wound on the limb being studied Active skin or bone infection Previous history of a Charcot episode on the limb being studied Renal failure Inability to comply with treatment Treatment used for 75% of allotted time Baseline characteristics: Unclear if groups were similar at baseline.				
Uniplanar external fixation vs intramedullary interlocked nailing for the purpose of tibio-talar arthrodesis					
Retrospective cohort Shah 2011 India	Total= 11 Uniplanar external fixator group= 6 Retrograde intramedullary nailing group= 5 Included Patients with tibio-talar arthrodesis for Charcot's neuroarthropathy	Tibio-talar arthrodesis for Charcot's neuroarthropathy treated by uniplanar external fixation assisted by external immobilisation Standard care included open reduction, debridement, synovectomy, compression of	Tibio-talar arthrodesis for Charcot's neuroarthropathy treated by uniplanar external fixation assisted by retrograde intramedullary interlocked nailing Standard care included open reduction, debridement, synovectomy,	Length of follow up was variable. Average 3.2 years Outcomes: Amputation Time to remission	This study showed a significant difference between uniplanar external fixator vs retrograde intramedullary nailing for ankle arthrodesis for the outcomes of amputation, delayed union and non-union. Results were in favour of the retrograde intramedullary nailing

The glossary has been updated to include a definifition of deformity.

Study	Population	Intervention	Control	Follow-up	Conclusions
		cancellous tibio-talar bony surfaces	compression of cancellous tibio-talar bony surfaces		treatment group.
	Exclusion: For participants treated with external fixator: Ulceration over potential external fixator pin sites For participants treated with retrograde nail: Normal subtalar joint Significant tibial deformity with malunion, greater than 10 degrees in any plane Marked loss of calcaneal body height Active infections of foot or ankle Baseline characteristics It is unclear if groups were comparable at baseline including all major confounding factors especially since each groups seemed to have differing exclusion criteria. Many baseline characteristics were not reported. Exclusion criteria for the retrograde nail group seemed to rule out more participants with increasingly severe disease this would be highly confounding.				

The glossary has been updated to include a definifition of deformity.

Study	Population	Intervention	Control	Follow-up	Conclusions
Zoledronic acid vs alendronate for the treatment of Charcot foot					
Randomised control trial Bharath 2013 India	Randomised= 45 (15 subsequently excluded) Zoledronic acid group= 16 Alendronate group = 14 Included data was only reported for those with a final diagnosis of osteomyelitis and charcot foot Inclusion: Participants with the presence of hot swollen foot with or without redness of the overlying skin after the exclusion of conditions resembling Charcot foot. Exclusion: Fever Elevated leucocyte counts Serum creatinine ≥3 mg/dL Clinical or radiological features of Osteomyelitis of foot bone Clinical or radiological features of peripheral vascular occlusive disease	Zoledronic acid injection 5 mg, as an intravenous infusion (diluted in 100ml, normal saline infused over 30 minutes, after hospital admission with total contact casting	Alendronate 70 mg, once a week, till the complete resolution of acute Charcot foot along with total contact casting. Feet were strictly offloaded with the help of a walker.	Length of observation was 1 year Outcome: Time to remission	This study found no significant difference between zoledronic acid and alendronate treated groups for the outcome of median time to complete resolution of clinical symptoms.

The glossary has been updated to include a definifition of deformity.

Study	Population	Intervention	Control	Follow-up	Conclusions
	Presence of foot ulcer Hypocalcaemia Planned dental procedure Previously treated for Charcot foot On bisphosphonate treatment for any other reason Surgical procedure of affected foot in the past Rheumatoid arthritis or gout in the past Baseline characteristics: Groups were similar at baseline for all reported factors				
Initial therapy with non-removable offloading vs removable offloading, therapy with bisphosphonates vs no bisphosphonates for the treatment of Charcot foot					
Retrospective Cohort Game 2012 UK and Ireland	Total= 288 Initial non-removable offloading group= 88 Initial removable offloading group= 123 Inclusion: New cases of acute Charcot foot at centres in the UK and Ireland over a period of 20 months Exclusion: None given	1) Initial therapy with non-removable offloading device 2) Therapy with bisphosphonates Standard care may vary between centres	1) Initial therapy with removable offloading device 2) No therapy with bisphosphonates Standard care may vary between centres	Computerised prompts were used to request follow up information at intervals of 3 months up to 18 months after registration, therefore follow up may vary between participants. Outcomes recorded: Time to remission	This study showed a significant difference between removable offloading and non-removable offloading for the outcome of time to remission. Results were in favour of the non-removable offloading treatment group. This study showed a significant difference between those treated with bisphosphonates and those who were not for the outcome of time

The glossary has been updated to include a definifition of deformity.

Study	Population	Intervention	Control	Follow-up	Conclusions
	Baseline characteristics No baseline characteristics provided between treatment groups				to remission. Results were in favour of the group who did not receive bisphosphonates.
Cast and total non-weight-bearing at initial presentation vs not treated with cast and total non-weight-bearing at initial presentation for Charcot foot					
Retrospective cohort Pakarinen 2002 Finland	Total= 36 feet, 32 participants Treated with cast and total non-weight-bearing at initial presentation= 18 Not treated with cast and total non-weight-bearing at initial presentation= 18 Included All feet diagnosed as Charcot neuroarthropathy at Tampere University Hospital Baseline characteristics: It is unclear if groups were comparable at baseline including all major confounding factors as such data was not provided per group. Participants varied in stage of Charcot at presentation, type of surgery and immobilisation and location of Charcot	Cast and total non-weight-bearing at initial presentation Standard care may have varied	No cast and total non-weight-bearing at initial presentation Standard care may have varied	Follow up: Average 21 months (range 1-81 months) Outcomes: Amputation	This study showed a significant difference between those treated with cast and total non-weight-bearing at initial presentation vs those who were not for the outcome of number requiring eventual surgical intervention. Results were in favour of the group who did receive cast and total non-weight-bearing at initial presentation.

The glossary has been updated to include a definifition of deformity.

Study	Population	Intervention	Control	Follow-up	Conclusions
	disease.				
Non-weight-bearing protective devices vs permitted weight bearing for the treatment of Charcot foot					
Retrospective cohort Clohisy 1988 USA	Total= 18 participants Treated with non-weight-bearing protective devices within 2 months of treatment= 7 allowed weight-bearing within 2 months of treatment= 11 Included Juvenile onset diabetes All people with diabetes who had a radiograph of the foot or ankle made at one university hospital between 1974 and 1984 Exclusion: Osteomyelitis Treated elsewhere (unreachable) Baseline characteristics: It is unclear if groups were comparable at baseline including all major confounding factors as such data was not provided per group. The paper states that groups were not statistically different for	Treated with non-weight-bearing protective devices within 2 months of treatment Standard care may have varied	Allowed weight-bearing within 2 months of treatment Standard care may have varied	Median follow up 5 years (range 9 months-9 years) Outcomes: Number undergoing amputation Number who could not walk	This study showed a difference between those treated with total non-weight-bearing device within 2 months of symptoms and those given other treatment within 2 months of symptoms for the outcome of number walking on follow up and number of amputations. Results were in favour of the group who did receive total non-weight-bearing within 2 months of symptoms of fracture.

The glossary has been updated to include a definifition of deformity.

Study	Population	Intervention	Control	Follow-up	Conclusions
	number with bilateral fractures however. Participants varied in stage of Charcot at presentation, severity of trauma, age, comorbidities, time from symptoms to diagnosis of fracture and location of Charcot disease and it is unclear how these were distributed between groups.				

The glossary has been updated to include a definifition of deformity.

4.16.3 Health economic evidence

A literature search was conducted for the question using standard health economics filters applied to the clinical search strategies. No relevant cost-utility analyses were found. Health economic modelling was not prioritised for this review question

4.16.4 Evidence statements

Zoledronic acid vs placebo as adjunctive therapy for the treatment of Charcot neuroarthropathy

Very low quality evidence from 1 study including 35 participants showed a significant difference between zoledronic acid and placebo in the median time for total immobilisation. Results were in favour of the placebo group.

The same study found there to be no significant difference between groups for the outcome of relapse of Charcot arthropathy.

Zoledronic acid vs Alendronate as adjunctive therapy for the treatment of Charcot neuroarthropathy

Very low quality evidence from 1 study including 30 participants found no significant difference between zoledronic acid and alendronate treated groups for the outcome of median time to complete resolution of clinical symptoms.

Combined magnetic field bone growth stimulation as adjunctive therapy for the treatment of Charcot neuroarthropathy

Very low quality evidence from 1 study including 31 participants found significant difference between treatment and control groups for the outcome of median time to consolidation. Results were in favour of the treatment group.

Palliative radiotherapy as adjunctive therapy for the treatment of Charcot neuroarthropathy

Low quality evidence from 1 study including 12 participants showed no significant difference between Palliative radiotherapy and placebo in the median time to healing.

Uniplanar external fixator vs retrograde intramedullary nailing for ankle arthrodesis in Charcot neuroarthropathy

Very low quality evidence from 1 study including 11 participants showed a significant difference between uniplanar external fixator vs retrograde intramedullary nailing for ankle arthrodesis for the outcomes of amputation, delayed union and non-union. Results were in favour of the retrograde intramedullary nailing treatment group.

Removable offloading vs non-removable offloading in the treatment of Charcot neuroarthropathy

Very low quality evidence from 1 study including 210 participants showed a significant difference between removable offloading and non-removable offloading for the outcome of time to remission. Results were in favour of the non-removable offloading treatment group.

Treatment with intravenous/oral bisphosphonates vs no treatment with bisphosphonates in the treatment of Charcot neuroarthropathy

Very low quality evidence from 1 study including 210 participants showed a significant difference between those treated with bisphosphonates and those who were not for the outcome of time to remission. Results were in favour of the group who did not receive bisphosphonates.

Treatment with cast and total non-weight-bearing at initial presentation vs no cast and total non-weight-bearing at initial presentation in the treatment of Charcot neuroarthropathy

Very low quality evidence from 1 study including 36 participants showed a significant difference between those treated with cast and total non-weight-bearing at initial presentation vs those who were not for the outcome of number requiring eventual surgical intervention. Results were in favour of the group who did receive cast and total non-weight-bearing at initial presentation.

Treatment with total non-weight-bearing device within 2 months of symptoms vs weight-bearing or walking with short cast within 2 months of symptoms in the treatment of participants with juvenile onset diabetes, neuropathic arthropathy and fracture.

Very low quality evidence from 1 study including 18 participants showed a difference between those treated with total non-weight-bearing device within 2 months of symptoms and those given other treatment within 2 months of symptoms for the outcome of number walking on follow up and number of amputations. Results were in favour of the group who did receive total non-weight-bearing within 2 months of symptoms of fracture.

4.16.5 Evidence to recommendations

Table 61: Linking evidence to recommendations table

Relative value of different outcomes	The guideline development group (GDG) agreed that improving ulceration and re-ulceration rates was the critical outcome for this question and the guideline. The GDG argued that if these could be prevented then the subsequent likelihood of other outcomes such as infection, gangrene, amputation and death would be diminished. In this review all of the included patients will have already developed Charcot arthropathy and it will be a case of primarily trying to manage acute cases of Charcot in order to prevent the disease from progressing to deformity which may raise the risk of ulceration in the future. Treating at an early stage could have long term impact in diminishing the likelihood of further complications from developing such as infection, gangrene, amputation and mortality rate. Reducing the incidence of these complications will also result in reduced rates of hospital admission with implications for better health-related quality of life.
Trade-off between benefits and harms	The benefits of good treatment and management of acute Charcot are most profound when it is caught early. Early treatment could lead to the prevention of deformity developing and a decreased future risk of ulceration. Preventing ulceration could then reduce the likelihood of subsequent infection, gangrene, amputation and death.

	The potential harm of giving treatment could be from a direct adverse event, or an ineffective treatment regime that leads to patient dissatisfaction and disengagement with future care. The above may lead to worsening of the current diabetic foot problem or an increase in future complication rate. Since the harmful effects of bisphosphonates could not be ruled out it was agreed to make a do not recommendation against the use of bisphosphonates in people with Charcot foot except in research settings. GDG also considered palliative radiotherapy to be potentially harmful when used as treatment.
Economic considerations	Health economics were not considered as a priority for this review question. No economic studies were found. The GDG considered the relative cost and effectiveness of each of the interventions presented and made recommendations with consideration of these factors
Quality of evidence	GDG discussed the general poor quality of evidence. Specific evidence on many interventions was scarce. Many of the randomised controlled trials had methodological flaws and it was common for there to be differences in the standard treatment of participants between comparison groups especially amongst the less robust observational studies. The GDG discussed the difficulty in producing randomised trials for surgical techniques since few people are eligible and blinding is often impossible.
Other considerations	Outcomes of rates of amputation, time to remission and deformity were presented. Two papers discussed bisphosphonates. Both found that bisphosphonates may prolong the length of treatment over placebo or no treatment. The GDG discussed the exclusion of one paper by Jude et al that reported surrogate outcomes showing a possible benefit of bisphosphonate treatment using temperature of feet and bone turnover markers as outcomes. After seeing the paper it was felt that the prior exclusion was justified. Despite the poor quality of evidence, since the harmful effects of bisphosphonates could not be ruled out it was agreed to make a do not recommendation against the use of bisphosphonates in people with Charcot foot except in research settings. Outcomes for palliative radiotherapy were non-significant and would not be UK practice. The quality of the study that suggested that combined magnetic field growth stimulation may be beneficial was found to be too low to make any strong recommendations on especially since combined magnetic field growth stimulation would not be widely available in the UK population. One study comparing two types of surgical arthrodesis amongst late stage Charcot foot used what was felt to be an unfair comparison between intramedullary nail fixation and uniplanar external fixation. Uniplanar external fixation is not commonly used in the UK. Multiplanar external fixation is more commonly used. For this reason the GDG chose not to make a recommendation of internal fixation over external fixation

devices. The positive results reported in this study for the outcomes of amputation did however help the GDG to agree that the referral of participants with unstable, hind foot Charcot arthropathy to a surgical specialist was important; however this should be done under the decision making within the multidisciplinary foot care service (see section 4.16).

Evidence was considered in favour of early non-removable offloading. The GDG discussed the importance of offloading the suspected Charcot foot, even when diagnosis has not yet been confirmed. This was based on multiple studies that showed worse outcomes for those participants who had not received early offloading after onset of symptoms.

4.16.6 Recommendations

63. **If the multidisciplinary foot care service suspects acute Charcot arthropathy, offer treatment with a non-removable offloading device. If a non-removable device is not advisable because of the clinical, or the person's, circumstances, consider treatment with a removable offloading device.**

64. **Do not offer bisphosphonates to treat acute Charcot arthropathy, unless as part of a clinical trial.**

65. **People who have a foot deformity that may be the result of a previous Charcot arthropathy are at high risk of ulceration and should be cared for by the foot protection service.**

4.16.7 Research recommendations

What strategies may be useful in the prevention of Charcot arthropathy?

Why this is important

The evidence surrounding Charcot arthropathy was limited and of low quality. It is proposed that a prospective cohort study is undertaken to explore this question. The proposed study would monitor and evaluate the rates of Charcot arthropathy resulting from diabetes, rates and extent of amputation (major or minor), rates and extent of deformity, health-related quality of life, and hospital admission rates following strategies for the prevention of Charcot arthropathy or its sequelae.

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5.1 Review question 1 included studies

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5.2 Review question 2 included studies

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5.3 Review question 3 included studies

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5.4 Review question 4 included studies

5.4.1 Examination tools

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5.10 Review question 10 included studies

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6 Glossary and Abbreviations

6.1 Glossary

Bias

Influences on a study that can lead to invalid conclusions about a treatment or intervention. Bias in research can make a treatment look better or worse than it really is. Bias can even make it look as if the treatment works when it actually does not. Bias can occur by chance or as a result of systematic errors in the design and execution of a study. Bias can occur at various stages in the research process, such as in the collection, analysis, interpretation, publication or review of research data.

Biomechanics

The study of the action of external and internal forces on the living body, especially on the skeletal system. A specialist will have knowledge of the development of prostheses and offloading devices.

Case–control study

A study that starts with the identification of a group of individuals sharing the same characteristics (for example people with a particular disease) and a suitable comparison (control) group (such as people without the disease). All subjects are then assessed with respect to things that happened to them in the past, for example things that might be related to getting the disease under investigation. Such studies are also called retrospective as they look back in time from the outcome to the possible causes.

Cohort study

An observational study that takes a group (cohort) of patients and follows their progress over time in order to measure outcomes such as disease or mortality rates and make comparisons according to the treatments or interventions that patients received. Thus, within the study group, subgroups of patients are identified (from information collected about patients) and these groups are compared with respect to outcome, for example comparing mortality between one group that received a specific treatment and one group that did not (or between two groups that received different levels of treatment). Cohorts can be assembled in the present and followed into the future (a 'concurrent' or 'prospective' cohort study) or identified from past records and followed forward from that time up to the present (a 'historical' or 'retrospective' cohort study). Because patients are not randomly allocated to subgroups, these subgroups may be quite different in their characteristics and some adjustment must be made when analysing the results to ensure that the comparison between groups is as fair as possible.

Comorbidity

Two or more diseases or conditions occurring at the same time, such as depression and anxiety.

Confidence interval (CI)

A way of expressing certainty about the findings from a study or group of studies, using statistical techniques. A confidence interval describes a range of possible effects (of a treatment or intervention) that are consistent with the results of a study or group of studies. A

wide confidence interval indicates a lack of certainty or precision about the true size of the clinical effect and is seen in studies with too few patients. Where confidence intervals are narrow they indicate more precise estimates of effects and a larger sample of patients studied. It is usual to interpret a '95% confidence interval' as the range of effects within which we are 95% confident that the true effect lies.

Cost-effectiveness analysis (CEA)

Cost-effectiveness analysis assesses the cost of achieving a benefit by different means. The benefits are expressed in non-monetary terms related to health, such as symptom-free days, heart attacks avoided, deaths avoided or life years gained (that is, the number of years by which life is extended as a result of the intervention).

Cross-sectional study

The observation of a defined set of people at a single point in time or time period – a snapshot. (This type of study contrasts with a longitudinal study, which follows a set of people over a period of time.)

Deformity

A change in foot shape that results in difficulty in fitting standard shoes and is subjectively assessed by the practitioner

Diabetic foot ulcer

A localised injury to the skin and/or underlying tissue, below the ankle, in a person with diabetes.

Double-blind/masked study

A study in which neither the subject (patient) nor the observer (investigator/clinician) is aware of which treatment or intervention the subject is receiving. The purpose of blinding is to protect against bias.

Economic evaluation

Technique developed to assess both costs and consequences of alternative health strategies and to provide a decision-making framework.

Effect (as in effect measure, treatment effect, estimate of effect, effect size)

The observed association between interventions and outcomes, or a statistic to summarise the strength of the observed association.

Evidence statement

A brief summary of one finding from a review of evidence that a clinical guideline is based on.

Evidence table

A table summarising the results of a collection of studies which, taken together, represent the evidence supporting a particular recommendation or series of recommendations in a guideline.

Follow up

Observation over a period of time of a person, group or initially defined population whose appropriate characteristics have been assessed in order to observe changes in health status or health-related variables.

Foot protection service

A service for preventing diabetic foot problems, and for treating and managing diabetic foot problems in the community.

Guideline Development Group (GDG)

A group of healthcare professionals, patients, carers and members of the Internal Clinical Guidelines Technical Team who develop the recommendations for a clinical guideline. The group writes draft guidance, and then revises it after a consultation with organisations registered as stakeholders. This group is also known as a guideline committee.

Generalisability

The degree to which the results of a study or systematic review can be extrapolated to other circumstances, particularly routine healthcare situations in the NHS in England and Wales.

Heterogeneity

A term used to illustrate the variability or differences between studies in the estimates of effects.

Incidence

A measure of the number of new cases of a disease, divided by the total population at risk of getting the disease, during a certain time period.

Incremental cost-effectiveness analysis

The analysis of additional costs and additional clinical outcomes that are associated with different interventions.

Incremental cost-effectiveness ratio (ICER)

The difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest.

Index test

The test being evaluated in a study to compare it with the best available test (the reference standard).

Multidisciplinary foot care service

A service for managing diabetic foot problems in hospital and in the community that cannot be managed by the foot protection service

Offloading

A method of redistributing or reducing pressure, in this case pressure is reduced across the foot to prevent the development of diabetic foot ulcers

Odds ratio (OR)

Odds are a way of representing probability, especially familiar for betting. In recent years, odds ratios have become widely used in reports of clinical studies. They provide an estimate (usually with a confidence interval) for the effect of a treatment. Odds are used to convey the idea of 'risk', so an odds ratio of 1 between two treatment groups would imply that the risks of an adverse outcome were the same in each group. For rare events the odds ratio and the relative risk (which uses actual risks and not odds) will be very similar.

Prevalence

The proportion of people in a population with a particular characteristic. For example, smoking prevalence is the proportion of smokers in the population. Prevalence may be expressed by age, sex, socio-economic group, ethnic group, etc. See also Incidence.

Prospective study

A study in which people are entered into the research and then followed up over a period of time, with future events recorded as they happen. This contrasts with studies that are retrospective.

Quality-adjusted life year (QALY)

A measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life. One QALY is equal to 1 year of life in perfect health.

Randomised controlled trial

A form of clinical trial to assess the effectiveness of medicines or procedures. Considered reliable because it tends not to be biased.

Reference standard

An agreed standard, for example for a test or treatment, against which other interventions can be compared.

Relative risk (RR)

A summary measure that represents the ratio of the risk of a given event or outcome (such as an adverse reaction to the drug being tested) in one group of subjects compared with another group. When the 'risk' of the event is the same in the two groups the relative risk is 1. In a study comparing two treatments, a relative risk of 2 would indicate that patients receiving one of the treatments had twice the risk of an undesirable outcome than those receiving the other treatment. Relative risk is sometimes used as a synonym for risk ratio.

Retrospective study

A type of study that deals with past events and does not involve studying future events. This contrasts with prospective studies.

Sensitivity

In diagnostic testing, this refers to the chance of having a positive test result if you have the disease. Sensitivity of 100% means that all people with the disease will test positive. However, a person could have a positive test result but not have the disease – this is called a

'false positive'. The sensitivity of a test is also related to its 'negative predictive value' (true negatives) – a test with a sensitivity of 100% means that all people who have a negative test result do not have the disease. To fully judge the accuracy of a test, its specificity must also be considered.

Sensitivity analysis

A means of representing uncertainty in the results of economic evaluations. Uncertainty may arise from missing data, imprecise estimates or methodological controversy. Sensitivity analysis also allows exploration of the generalisability of results to other settings. The analysis is repeated using different assumptions to examine the effect on the results.

Specificity

In diagnostic testing, this refers to the chance of having a negative test result given that you do not have the disease. Specificity of 100% means that all people without the disease will test negative. However, a person could have a negative test result yet still have the disease – this is called a 'false negative'. The specificity of a test is also related to its 'positive predictive value' (true positives) – a test with a specificity of 100% means that all people who have a positive test result definitely have the disease. To fully judge the accuracy of a test, its sensitivity must also be considered.

Standard deviation

A measure of the spread, scatter or variability of a set of measurements. Usually used with the mean (average) to describe numerical data.

Systematic review

Research that summarises the evidence on a clearly formulated question according to a pre-defined protocol using systematic and explicit methods to identify, select and appraise relevant studies, and to extract, collate and report their findings. It may or may not use statistical meta-analysis.

6.2 Abbreviations

Table 62: Abbreviations

Abbreviation	Term
ABPI	ankle brachial pressure index
ADA	American Diabetes Association
BMI	body mass index
CEA	cost effectiveness analysis
CI	confidence interval
CRP	c-reactive protein
CSI	composite severity index
CT	computed tomography
CUA	cost-utility analysis
DFS	diabetic foot service
DUSS	diabetic ulcer severity score
ED	emergency department
ESR	erythrocyte sedimentation rate

Abbreviation	Term
GDG	guideline development group, also known as guideline committee
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HbA1c	glycated haemoglobin
ICER	incremental cost-effectiveness ratio
IDSA	Infectious Diseases Society of America
ITT	intention-to-treat
IWGDF	International Working Group on Diabetic Foot
LEA	lower extremity amputation
MDS	multidisciplinary foot care service, may also be known as an interdisciplinary foot care service
MID	minimal important difference
MRI	magnetic resonance imaging
NDS	neuropathy disability score
NSS	neuropathy symptoms score
OR	odds ratio
PAD	peripheral arterial disease
PCT	procalcitonin
QALY	quality-adjusted life year
RCT	randomised controlled trial
RR	relative risk
SD	standard deviation
SE	standard error
SIGN	Scottish Intercollegiate Guidelines Network
UT	University of Texas
VPT	vibration perception threshold
WCC	white cell count
WTP	willingness to pay (threshold)

The glossary has been updated to include a definifition of deformity.