Internal Clinical Guidelines team

Draft for consultation

Diabetic foot problems

Prevention and management of foot problems in people with diabetes

Clinical Guideline XXX <update>

Methods, evidence and recommendations

[Month] 2015

Draft for Consultation

Commissioned by the National Institute for Health and Care Excellence

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

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1 Overview

1.1 Introduction

Diabetes is one 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).

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.

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. 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 the prevention and management of diabetic foot problems, there is variation in practice across different NHS settings, and amputation rates still vary up to fourfold.

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. Variability can be found based 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.

Furthermore, the implementation of foot care screening programmes is still inconsistent 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 Medicines

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

1.9 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. 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 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.

You are invited to comment all sections of this guideline except recommendations which end 2011 highlighted by an orange text box and any sections of the guideline highlighted with an orange text box (see below).

2011

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.

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2.12 GDG membership, Peer reviewers, ICG technical team

2.1.13 GDG membership

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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
		The Diabetes & Endocrine Centre and Diabetes Foot Clinic & Research Unit, Ipswich
Stella Vig	Vascular Surgeon	Vascular and General Surgical Consultant, Croydon University Hospital

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2.1.2 Technical Team

Stephen Duffield (from April 2014)

Technical Analyst

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Nicole Elliott (until June 2014)

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Michael Heath (until October 2014)

Programme Manager

Vicky Gillis (from November 2013 to June 2014)

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Hugh McGuire (from March 2014)

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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 GDG members chose their 10 highest ranking recommendations for implementation and a weighted average of their responses was calculated. 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 healthcare settings

Commissioners and service providers should ensure that the following are in place:

- A diabetic 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).
- Robust protocols and clear local pathways for the continued and integrated care of people across all healthcare 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, at least annually thereafter (see recommendation 18), if problems arise, and on any admission to hospital.

When examining a person's feet, remove their shoes, socks, bandages and dressings, and examine both feet for evidence of the following:

- Neuropathy (use a 10 g monofilament to test foot sensation).
- Limb ischaemia (also see the NICE guideline on lower limb peripheral arterial disease).
- Ulceration.
- Callus.
- Infection and/or inflammation.
- Deformity.
- Gangrene.
- Charcot arthropathy

Assess the person's risk of developing a diabetic foot problem using the following risk stratification:

- Low risk: no risk factors present, for example, no signs of neuropathy, no signs of peripheral arterial disease, and no other risk factors.
- Moderate risk: 1 risk factor present, for example, signs of neuropathy or signs of peripheral arterial disease, but without callus or deformity. Disabled adults who cannot see their feet are also at moderate risk.
- High risk: previous ulceration or amputation, or on renal replacement therapy, or more than 1 risk factor present, for example, signs of neuropathy or signs of peripheral arterial disease, with callus or deformity.
- Active diabetic foot problem: ulceration, spreading infection, critical ischaemia, gangrene, suspicion of an acute Charcot arthropathy, or an unexplained hot, red, swollen foot with or without pain.

Assessing the risk of developing a diabetic foot problem

Refer people with an active diabetic foot problem to the foot protection service or multidisciplinary foot care service within 24 hours for appropriate triage according to local protocols.

If any of the following active diabetic foot problems are present, refer the person to the multidisciplinary foot care service within 24 hours so they can be assessed and an individualised treatment plan put in place according to local protocols:

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

Diabetic foot infection

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

- Off-loading.
- Control of foot infection.
- Control of ischaemia.
- Wound debridement.
- Moist wound dressings if appropriate.

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.

Refer the person urgently (within 24 hours) to the multidisciplinary foot care service to confirm the diagnosis, and offer non-weight-bearing treatment until definitive treatment can be started.

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 team 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 team 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 team. (recommendation 4)

2. Care across all healthcare settings

Commissioners and service providers should ensure that the following are in place:

- A diabetic 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).
- Robust protocols and clear local pathways for the continued and integrated care of people across all healthcare 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 7)

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.
- Tissue viability. (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:

- Diabetology.
- Podiatry.
- Diabetes specialist nursing.
- Vascular surgery.
- Microbiology.
- Orthopaedic surgery.
- Orthotics and/or biomechanics.
- Interventional radiology.
- Casting.
- Tissue viability. (recommendation 6)

Healthcare professionals may need to discuss, agree and make special arrangements 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. (recommendation 10)

3. Assessing the risk of developing a diabetic foot problem

3.1. Frequency of assessments for diabetic foot problems

For children with diabetes who are younger than 12 years, give them, and their parents or carers (as appropriate), basic foot care advice. Children younger than 12 should not need an annual assessment of their feet unless a diabetic foot problem is found or suspected. (recommendation 15)

For young people with diabetes who are 12–17 years, the paediatric care team or the transitional care team should carry out an annual assessment of their feet and provide education about foot care. If a diabetic foot problem is found or suspected, the paediatric care team or the transitional care team should refer them to the appropriate specialist. (recommendation 16)

For adults with diabetes, assess their risk of developing a diabetic foot problem at the following times: when diabetes is diagnosed, at least annually thereafter (see recommendation 18), if problems arise, and on any admission to hospital. (recommendation 17)

3.2. Assessing the risk of developing a diabetic foot problem

When examining a person's feet, remove their shoes, socks, bandages and dressings, and examine both feet for evidence of the following:

- Neuropathy. (use a 10 g monofilament to test foot sensation)
- Limb ischaemia. (also see the NICE guideline on lower limb peripheral arterial disease)
- Ulceration.
- Callus.
- Infection and/or inflammation.
- Deformity.
- Gangrene.
- Charcot arthropathy. (recommendation 11)

Interpret ankle brachial pressure index results carefully because calcified arteries may falsely elevate results. (recommendation 12)

Assess the person's risk of developing a diabetic foot problem using the following risk stratification:

- Low risk: no risk factors present, for example, no signs of neuropathy, no signs of peripheral arterial disease, and no other risk factors.
- Moderate risk: 1 risk factor present, for example, signs of neuropathy or signs of peripheral arterial disease, but without callus or deformity. Disabled adults who cannot see their feet are also at moderate risk.
- High risk: previous ulceration or amputation, or on renal replacement therapy, or more than 1 risk factor present, for example, signs of neuropathy or signs of peripheral arterial disease, with callus or deformity.
- Active diabetic foot problem: ulceration, spreading infection, critical ischaemia, gangrene, suspicion of an acute Charcot arthropathy, or an unexplained hot, red, swollen foot with or without pain. (recommendation 13)
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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 (also see recommendation 18) (recommendation 14)

Refer people who are at moderate or high risk of developing a diabetic foot problem to the foot protection service (also see recommendations 5 and 18) (recommendation 8)

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 orthotics.
- 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 events. (recommendation 19)

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 9)

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 to 6 months) for people who are at moderate risk.
- More frequently (for example, every 1 to 2 months) for people who are at high risk, if there is no immediate concern.
- Very frequently (for example, every 1 to 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. (recommendation 18)

3.4. Information and support for people at risk of developing a diabetic foot problem

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

- Basic foot care advice and the importance of foot care.
- Foot emergencies and who to contact.
- Footwear advice.
- The person's individual risk of developing a foot problem.
- Information about diabetes and the importance of blood glucose control. (recommendation 20)

4. Diabetic foot problems

4.1. Referral for people with an active diabetic foot problem

Refer people with an active diabetic foot problem to the foot protection service or multidisciplinary foot care service within 24 hours for appropriate triage according to local protocols. (recommendation 54)

If any of the following active diabetic foot problems are present, refer the person to the multidisciplinary foot care service within 24 hours so they can be assessed and an individualised treatment plan put in place according to local protocols:

- Ulceration with fever or any signs of sepsis.
- Clinical concern that there is a deep-seated soft tissue or bone infection (with or without ulceration).
- Ulceration with limb ischaemia (also see the NICE guideline on lower limb peripheral arterial disease.)
- Gangrene (with or without ulceration).
- Suspicion of acute Charcot arthropathy. (recommendation 55)

4.2. Patient information and support for people with a diabetic foot problem

Provide consistent, relevant information and clear explanations as part of the individualised treatment plan for people with a diabetic foot problem. Information should 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. (recommendation 31)

If people present 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. (recommendation 32)

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 21)

Use a standardised system to document the severity of the foot ulcer, such as the SINBAD (Site, Ischaemia, Neuropathy, Bacterial Infection and Depth) or the University of Texas classification system. (recommendation 22)

Do not use the Wagner classification system to assess the severity of a foot ulcer. (recommendation 23)

5.2. Treatment

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

- Off-loading.
- Control of foot infection.
- Control of ischaemia.
- Wound debridement.
- Moist wound dressings if appropriate. (recommendation 33)

Offer non-removable casting to off-load plantar neuropathic, non-ischaemic, uninfected forefoot and midfoot ulcers. (recommendation 34)

In line with the NICE guideline on pressure ulcers, use a pressure-redistributing device and strategies to minimise the risk of pressure ulcers developing. (recommendation 35)

Debridement in hospital should only be done by healthcare professionals from the multidisciplinary foot care team, 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 36)

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 37)

Consider negative pressure wound therapy after debridement, on the advice of the multidisciplinary foot care service. (recommendation 49)

When deciding about wound dressings and off-loading, 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 38)

Consider dermal or skin substitutes as an adjunct to standard care only when healing has not progressed and on the advice of the multidisciplinary foot care service. (recommendation 50)

Do not offer the following treatments, 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 51)

When deciding the frequency of follow-up as part of the treatment plan, take into account the overall health of the person, how healing has progressed, and any deterioration. (recommendation 29)

Ensure that the frequency of monitoring set out in the person's individualised treatment plan is maintained whether the person is being treated in hospital or in the community. (recommendation 30)

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 superficial swab because it may provide useful information on the choice of antibiotic therapy. (recommendation 24)

Consider an X-ray of the person's affected foot (or feet) to determine the extent of the foot problem. (recommendation 25)

Think about osteomyelitis if the person has a local infection, a deep foot wound or a chronic foot wound. (recommendation 26)

Be aware that osteomyelitis may be present despite normal inflammatory markers, X-rays or probe-to-bone testing. (recommendation 27)

If osteomyelitis is suspected but is not confirmed by initial X-ray, consider MRI to confirm the diagnosis. (recommendation 28)

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 39)

Do not offer antibiotics to prevent foot infections. (recommendation 40)

Start antibiotic treatment for suspected foot infection as soon as possible. Take cultures and samples before, or as close as possible to, the start of antibiotic therapy. (recommendation 41)

Choose the antibiotic therapy based on the severity of the foot infection, the care setting, and the person's preferences, clinical situation and medical history and, if more than one regimen is appropriate, select the one with the lowest acquisition cost. (recommendation 42)

Use the clinical response to antibiotics and the results of the microbiological examination to decide the targeted antibiotic regimen. (recommendation 43)

Do not offer tigecycline unless other antibiotics are not suitable. (recommendation 44)

For mild foot infections, offer oral antibiotics with activity against gram-positive organisms. (recommendation 45)

Do not use prolonged antibiotic therapy for mild soft tissue infections. (recommendation 46)

For moderate and severe foot infections, 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[a]. (recommendation 47)

Offer prolonged antibiotic treatment (usually 6 weeks) to all people with diabetes and osteomyelitis, according to local protocols. (recommendation 48)

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 52)

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 53)

Refer the person urgently (within 24 hours) to the multidisciplinary foot care service to confirm the diagnosis, and offer non-weight-bearing treatment until definitive treatment can be started. (recommendation 54)

If acute Charcot arthropathy is suspected, X-ray the affected foot. Consider an MRI if the X-ray is normal but clinical suspicion still remains. (recommendation 57)

7.2. Treatment

If the multidisciplinary foot care service suspects acute Charcot arthropathy, offer treatment with a non-removable off-loading device. Only consider treatment with a removable off-loading device if a non-removable device is not advisable because of the clinical or the person's circumstances. (recommendation 59)

Do not offer bisphosphonates to treat acute Charcot arthropathy, unless as part of a clinical trial. (recommendation 60)

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 58)

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 61)

2.4 Research recommendations

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

[a] See table 2 in the Infectious Diseases Society of America (IDSA) guidelines, which shows the PEDIS grades and ISDA infection severity classifications for diabetic foot infections.

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.

What is the clinical effectiveness of different dressing types (for example honey-based dressings) 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.

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

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 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.

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.

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

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.

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 team 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.

What measures 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 measures for the prevention of Charcot arthropathy or its sequelae.

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.

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.

What is the role of education 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 a randomised control trial 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, 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 new educational measures to these patients.

What is the effectiveness of different footwear 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 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.

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

- Pressure ulcers (update). NICE clinical guideline 179 (2014).
- Lipid modification (update). NICE clinical guideline 181 (2014).
- Exercise referral schemes. NICE public health guidance 54 (2014).
- Neuropathic pain – pharmacological management (update). NICE clinical guideline 173. (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).
- Hypertension. NICE clinical guideline 127 (2011).
- Preventing type 2 diabetes: population and community interventions. NICE public health guidance 35 (2011).
- Venous thromboembolism: reducing the risk. NICE clinical guideline 92 (2010).
- Depression with a chronic physical health problem. NICE clinical guideline 91 (2009).
- 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).

- Diabetes in children and young people. NICE clinical guideline. Publication expected August 2015.
- Diabetes in pregnancy. NICE clinical guideline. Publication expected February 2015.
- Type 1 diabetes. NICE clinical guideline. Publication expected August 2015.
- Type 2 diabetes. NICE clinical guideline. Publication expected August 2015.

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

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 orthotics, 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

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

2 Actual number unknown, not reported.

4.1.43 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)

4.1.58 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 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 team 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 team 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 team.**

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 team and the multidisciplinary foot care team?

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 teams providing care for people at risk of foot problems and multidisciplinary foot care teams 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
	Diabetologist	81.3	18.2	0.5

Study	Results			
	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 • district nurses.			

Study	Results
	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.

1

4.2.32 Health Economic Evidence

3 A literature search was conducted for the question using standard health economics filters
4 applied to the clinical search strategies. No relevant cost-utility analyses were found. Health
5 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 paramount as the critical outcome for this question and indeed 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 clincial benefits and harms	The benefits of establishing the appropriate composition of the foot protection service or multidisciplinary foot service include the following desired outcomes: A patient would 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 would result in faster treatment, fewer mistakes and a better informed and satisfied patient. The patient 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 team 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 patient alongside general dissatisfaction with the service. Poor levels of patient satification may reduce future engagement with the service and potentially 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 initially the implementation of clear local pathways and clear lines of communication across services.
Trade-off between net health benefits and resource use	The GDG considered the substantial resource implications inherent in setting up multi-disciplinary 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 were 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 report 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 was 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 team 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 services be present in person to support every patient referred to the multidisciplinary team. The group agreed that a distinction between the two 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 specialist core health 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 one exception to this was that a podiatrist was named specifically for leadership of the foot protection service as, 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.
    - Tissue viability.

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.
    - Orthotics and/or biomechanics.
    - Interventional radiology.
    - Casting.
    - Tissue viability.

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 team or the multidisciplinary foot care team?

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 teams or multidisciplinary foot care teams. 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 teams
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 teams or multidisciplinary foot care teams 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 teams and multidisciplinary foot care teams 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 team 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 teams to lack of foot protection teams) 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.

4.3.36 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.

4.3.40 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 paramount importance. In this review some of the patients included will have already developed diabetic foot problems and the primary aim will 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 will 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 team for persons with diabetes at the appropriate stage of disease will have the following desired outcomes: A person will be caught at as early a stage as possible and their risk of developing a foot problem would be

	defined at as early a stage as possible resulting in better control of a person's risk factors and reduction in the likelihood of future development of ulceration or other foot problems. Appropriate referral to the multidisciplinary foot care team 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, gangrene, amputation and death. On the other hand inappropriate referral to either the foot protection service or to the multidisciplinary foot care team 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 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 multi-disciplinary services but found that the evidence of long term benefit suggests that they 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 were 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 to patients and to 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 could only answer the question of who would benefit from referral to a foot protection service in an indirect way. The purpose of the evidence review was to identify those individuals with diabetes who would benefit from referral to either the foot protection servcie or multidisciplinary foot care service. Instead the evidence reviewed identified that the wider diabetes population would benefit from the implementation of pathways, protocols and interdisciplinary care across 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 study showing benefit from implementation of multidisciplinary care. For example, it is impossibe 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 would 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 extrapolate the stages at which it would be most likely be effective for patients to receive foot protection and multidisciplinary care.
Other considerations	The GDG considered the aim of an integrated model of management/care pathway (incorporating a foot protection service and a multidisciplinary footcare service) for people with diabetic foot that starts at the point of diagnosis of diabetes and continues 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 appeared 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 rate of bilateral amputations amongst unilateral amputated persons after the implementation of a multidisciplinary focused foot protection program. Even if this very low quality evidence was reliable it would be hard to discount all the other evidence that multidisciplinary care is beneficial for all other patient groups and it would not make sense to offer such high risk patients 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 ensure that a foot protection service for the prevention of diabetic foot problems and the treatment and management of simple diabetic foot problems is established. Evidence was found that showed the benefit of clear protocols and pathways spanning the care of people with diabetes who are at low risk for developing diabetic foot complications to those people who have developed active complications. The GDG wanted to make recommendations that multidisciplinary 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 outpatient foot protection services as covered in other review questions.

	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. Based on the evidence presented and the types of treatments received by the patients for which a detailed protocol was given the GDG was able to extrapolate the types of services that they would want providing 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 this was consistent with the evidence and in 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. The standard of treatment that patients should receive based on risk stratification was reviewed in section 4.4. The GDG therefore stated that the foot protection service should provide the required management as previously stated for those at high and medium risk of developing diabetic foot complications. The GDG also referred to these studies when deliberating on the timeframes by which patients should be referred from primary care to either of the teams. By considering the risk assessment (see section 4.4), the GDG considered the frequency of monitoring that each risk category would necessitate. In order to define a reasonable standard for care providers to achieve, the GDG produced a consensus recommendation on the timeframe in which all newly referred people with diabetes should be seen by the service. This would help to direct timely assessment of newly referred medium and high risk patients The GDG debated on 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 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 defined in section 4.4, the GDG were mindful of the need for prompt care in these situations and thus agreed that those newly referred at high risk should be assessed at between 2 and 4 week intervals, The GDG also agreed that the multidisciplinary foot care service should treat and manage

	diabetic foot care problems that the diabetic foot protection service are unable to manage. The GDG allowed for the fact that some foot protection services may be 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 were mindful that having clear protocols/pathways would be of benefit in this. The GDG agreed that clear communication between the services was also essential for integrated care to be effective. 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 footcare service, the foot protection service, accident and emergency servcies and general practice services. Lastly while considering the best service structure for the populations described the GDG agreed that special arrangements would likely be required 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.

4.3.6 Recommendations

Across all settings

7. Commissioners and service providers should ensure that the following are in place:

- A diabetic 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).
- Robust protocols and clear local pathways for the continued and integrated care of people across all healthcare 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.

8. Refer people who are at moderate or high risk of developing a diabetic foot problem to the foot protection service (also see recommendations 5 and 18).

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.

10. **Healthcare professionals may need to discuss, agree and make special arrangements 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.**

4.3.7 Research recommendations

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

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.

4.41 Classifying and stratifying risk of foot problems

4.4.12 Review Question

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

4.4.25 Evidence Review

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

13 For development purposes this review was treated as two questions:

14 • What are the clinical utilities of stratification systems for classifying the risk of foot
15 problems for people with diabetes?

16 • What are the clinical utilities of assessment tests for examining the feet of people with
17 diabetes?

4.4.1218.1 Risk stratification systems

19 In assessing risk stratification systems, papers were considered for inclusion if they reported
20 systematic review, test and treat RCT, cohort studies or case control studies. Papers
21 reporting cross-sectional studies or case series were excluded. The original and rerun
22 searches identified 9,738 abstracts, 37 full-text articles were examined. 32 papers were
23 excluded: 5 papers describing 4 primary studies met the inclusion criteria for the review of
24 stratification systems. (Leese,G.P. (2006), Monteiro-Soares,M. (2012), Monteiro-Soares,M.
25 (2011), Monteiro-Soares,M. (2010), Peters,E.J. (2001). The protocol for this review question
26 can be found in Appendix C (see review question 4). The evidence tables for the included
27 studies can be found in Appendix F. The list of excluded studies can be found in Appendix E.

28 1 paper was a systematic review (Monteiro-Soares, 2011) examining three of the identified
29 primary studies and therefore has not been included in the summary tables or GRADE
30 profiles. GRADE profiles for the included studies can be found in Appendix I.

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

33 **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

1

2 **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	

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

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.

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

4.4.2.21 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 94 studies were subsequently excluded. 13 papers describing 13 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), Sriyani, K. A. (2013), 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

1 **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.
Sriyani (2013) Cross sectional, case control. Sri Lanka	88 subjects with leg and foot ulcers and 80 non ulcer controls taken from a population of patients with type 2 diabetes.	128-Hz vibrated tuning fork 10g Semmes-Weinstein monofilament	Retrospective, unclear	Authors concluded incidental diagnosis of DM, wearing covered shoes and normal monofilament test on 1st metatarsal head were found to be protective of ulceration while education of grade 6 and below, income less than US$ 140, impaired vibration sense, abnormal monofilament test on 1st, 3rd and 5th toe were found to be associated with increased risk of ulceration.

4.4.31 Health Economic Evidence

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

4.4.45 Evidence Statements

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

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

4.4.512 Evidence to Recommendations

13 **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 at 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 Protocols and DTS and MDS) In instances of true negatives then reassurance and ongoing monitoring by appropriate health care professionals in the appropriate setting or service would be considered appropriate. (see Section 4.3 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 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 were mindful to consider that all patients, and not just those at high risk, were to 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 were mindful 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 were 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 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 then on admission to reduce their risk of heel ulceration by a variety of means. The group discussed the limited evidence available on the ability of the various tests of sensation loss to predict foot ulceration. There was limited evidence available from multi-variate analysis on the ability of tests in predicting foot ulcer occurrence. More evidence was available for use of the 10g monofilament in testing for lack of sensation 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. It was highlighted however that equipment should be maintained to a good standard.

	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 was not available to recommend changing this practice. The group also felt it important to specify a specific type of risk assessment system in order to ensure uniformity of practice across the NHS. The group discussed the other tests used in examining the feet of people with diabetes. The group felt it important that the guideline cross-referenced 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.

4.4.61 Recommendations

11. When examining a person's feet, remove their shoes, socks, bandages and dressings, and examine both feet for evidence of the following:

- Neuropathy (use a 10 g monofilament to test foot sensation).
- Limb ischaemia (also see the NICE guideline on lower limb peripheral arterial disease).
- Ulceration.
- Callus.
- Infection and/or inflammation.
- Deformity.
- Gangrene.
- Charcot arthropathy.

12. Interpret ankle brachial pressure index results carefully because calcified arteries may falsely elevate results.

13. Assess the person's risk of developing a diabetic foot problem using the following risk stratification:

- Low risk: no risk factors present, for example, no signs of neuropathy, no signs of peripheral arterial disease, and no other risk factors.
- Moderate risk: 1 risk factor present, for example, signs of neuropathy or signs of peripheral arterial disease, but without callus or deformity. Disabled adults who cannot see their feet are also at moderate risk.
- High risk: previous ulceration or amputation, or on renal replacement therapy, or more than 1 risk factor present, for example, signs of

neuropathy or signs of peripheral arterial disease, with callus or deformity.

- Active diabetic foot problem: ulceration, spreading infection, critical ischaemia, gangrene, suspicion of an acute Charcot arthropathy, or an unexplained hot, red, swollen foot with or without pain.

14. **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 (also see recommendation 18).**

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 aimed to assess 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 are preventable secondary outcomes of having an ulcer.
Trade-off between benefits and harms	The GDG considered that the major benefit accruing from increasing frequencies of monitoring is to be found in those at moderate or high risk of developing diabetic foot problems (see Section 4.3 on protocols). They subsequently considered that the benefits of increasing the frequency of monitoring should increase with each level of risk. For the patient, the major 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 footcare problems can help avoid un-necessary 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 the 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.
Trade-off between net health benefits and resource use	At the outset of guideline development, the GDG had been keen to review original economic evidence on the frequency of follow-up. However, having explored the available evidence, it was 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 considering its recommendations. For the NHS, the prevention and early treatment of developing footcare problems can help avoid un-necessary hospitalisation and longer term management of complication such as infection, gangrene and amputations. This will help avoid unnecessary resource use also. 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 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 is 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 two different frequencies of review, rather comparing monthly chiropodist appointments to no intervention at all. The control group were 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 felt it was important that some recommendations should be made based on the identified risk of the patient (see section 4.4). As a result the recommendation was made to provide a structure for foot review frequency in patients with diabetes. It was important to outline this rec for the reasons outlined above and so that high risk patients should be reviewed most frequently and low risk least frequently. No evidence was identified for children and young people and a subsequent 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

15. For children with diabetes who are younger than 12 years, give them, and their parents or carers (as appropriate), basic foot care advice. Children younger than 12 should not need an annual assessment of their feet unless a diabetic foot problem is found or suspected.

16. For young people with diabetes who are 12–17 years, the paediatric care team or the transitional care team should carry out an annual assessment of their feet and provide education about foot care. If a diabetic foot problem is found or suspected, the paediatric care team or the transitional care team should refer them to the appropriate specialist.

17. For adults with diabetes, assess their risk of developing a diabetic foot problem at the following times: when diabetes is diagnosed, at least annually thereafter (see recommendation 18), if problems arise, and on any admission to hospital.

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

4.5.7 Research recommendations

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

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 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 off-loading 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 off-loading 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.			

1

2

4.6.31 Health Economic Evidence

4.6.3.12 Systematic review of published cost–utililty analyses

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

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

26 These studies are summarised in the evidence tables in appendix F

4.6.3.27 Original health economic analysis– methods

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

39 A full description of the model is given in Appendix J, a summary is presented here. The
40 model was developed in line with the NICE reference case (National Institute for Health and
41 Care Excellence 2013). A Markov model was developed that runs on a monthly cycle length
42 for the remaining life expectancy of a cohort of patients with a mean age of 60 years. A life
43 expectancy time horizon was chosen because the patients receiving orthotic shoes and
44 inserts will require a new set each year for the rest of their lifetime, and will therefore accrue
45 costs and benefits for that time. A monthly cycle was considered appropriately short to
46 capture the important pathological changes in diabetic feet whilst remaining computationally
47 manageable, and was selected following consultation with the GDG. Costs associated with
48 the provision of orthotic shoes and inserts are attached to the intervention arms as per the
49 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.

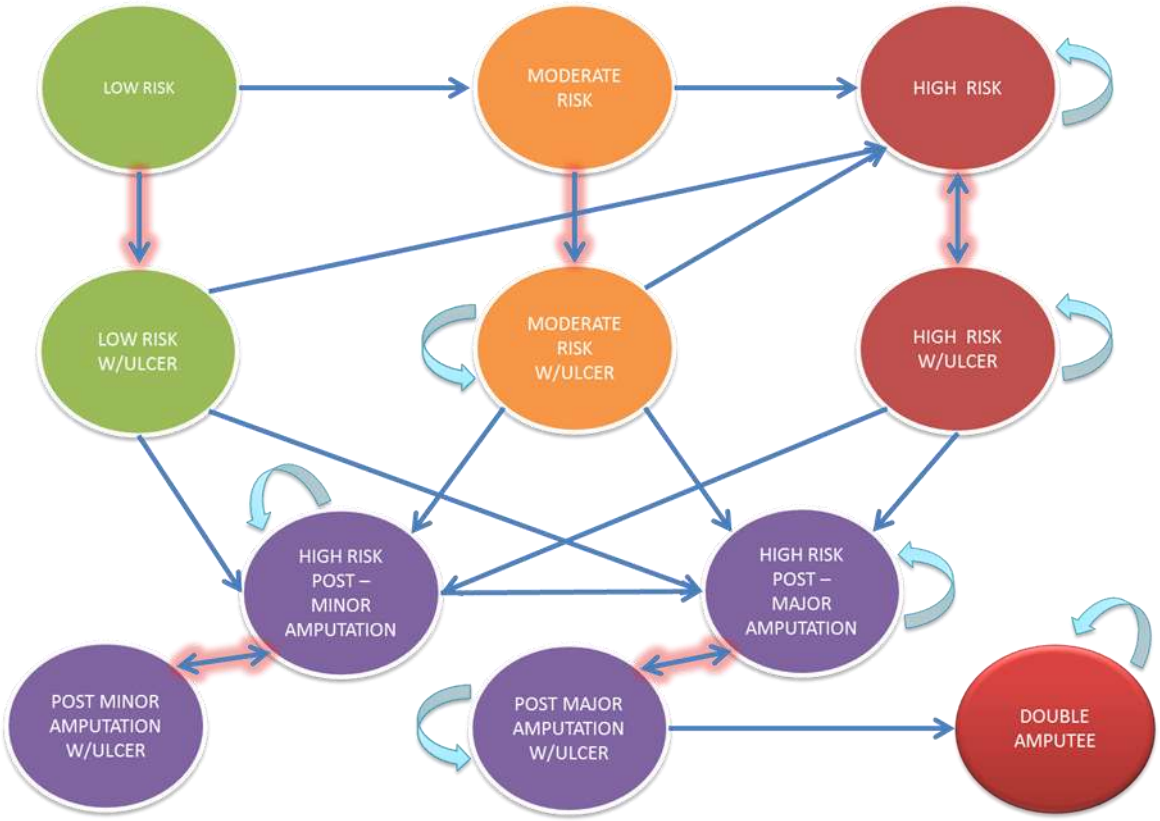

Figure 1 Simplified diagram of the de-novo Markov model- highlighted arrows indicate transitions affected by the intervention

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 orthotics, insoles and education. We also modelled another scenario where less effective "off-the-shelf" orthotics 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.

4.6.3.31 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 orthotics	£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 orthotics 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 orthotics 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 Orthotics	£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

4.6.41 Evidence Statements

2 Ulceration

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

5 • infrared temperature monitoring at home (moderate quality evidence from 2 studies
6 including 398 participants)

7 • pressure customised footwear for patients with previous ulceration and neuropathy (low
8 quality evidence from 1 study including 130 participants)

9 • therapeutic shoes with a custom mould insert (very low quality evidence from 1 study
10 including 69 participants)

11 • custom made orthoses and therapeutic shoes (low quality evidence from 1 study including
12 334 participants).

13 • orthotic silicone padding (low quality evidence from 1 study including 167 participants).

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

16 • education (very low to low quality evidence from 3 studies including 1052 participants)

17 • augmented foot examination (very low quality evidence from 2 studies including 184
18 participants).

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

20 • education combined with protective footwear (very low quality evidence from 1 study
21 including 53 participants)

22 • footwear and a customised cork insert (very low quality evidence from 1 study including
23 400 participants)

24 • pressure customised footwear for patients with previous ulceration and neuropathy. (very
25 low quality evidence from 1 study including 171 participants)

26 • footwear and customised cork insert or footwear and polyurethane insert (Low quality
27 evidence from 1 study including 400 participants)

28 • shear reducing insole (low quality evidence from 1 study including 299 participants)

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

33 Amputation

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

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

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

42 • Infrared temperature monitoring at home (very low quality evidence from 1 study including
43 85 participants)

44 • physician and participant education (very low quality evidence from 1 study including 396
45 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, orthotics 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 orthotics 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 orthotics 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 aimed to assess the 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 are preventable secondary outcomes of having developed an ulcer. It was recognised 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 however the extent of amputation was not always reported.
Trade-off between benefits and harms	It was felt that the benefits of a good preventative treatment therapy should be that firstly it achieves what it was designed to

	do. i.e. that through the use of the therapy the patient is protected from developing the diabetic foot problem that they would have been at high risk of developing. As mentioned above, the main complication that we are eager should be prevented is ulceration. If patients can have their foot ulceration prevented this can protect the development of further 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 easy and simple to implement into practice in the real world. Potential harms as a result of offering preventative therapy could be as simple as having a direct adverse effect as a result of using the therapy. Negative impact of these therapies, however, may be on a wider level if NHS resources are used inappropriately to give preventive therapy to populations who were at low risk for developing foot problems anyway. Giving preventative treatment to low risk patients may infact result in the opposite effect if the patient feels that they are being treated for no good reason, this 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, cause increased rates of infection, gangrene, amputation, hospital admission with the 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 were 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 were convinced by the finding that it is likely to be cost-saving to provide bespoke orthotic footwear to people who are categorised as at high risk of ulceration, but had more hesitation 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 where 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 which 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 two papers on podiatry and chiropody care; there were quality issues with both of the evidence papers. Notably one of the studies only included participants that would normally not require podiatry care which resulted in extremely low event rates in both the intervention and control group 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 anyway. 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, from their experience in clincial practice, would expect to see was not clear in the evidence presented. 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 recieved even if 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 two recommendations were made to cover 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 orthotics the GDG felt that foot wear 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 there are good insoles and poor insoles and that the evidence summaries should not therefore be too simplified. It was noted that the use of orthotic treatment proved effective amongst 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 two 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 one 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 this 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 two different kinds of bespoke footwear. One group which customised its shoes based on shape and the other using 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. 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 team who can both assess risk and provide referral to orthotic teams to provide a high quality preventative treatment where appropriate.

4.6.6 Recommendations

19. 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 orthotics.
- 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 events.

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

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

4.6.7 Research recommendations

What is the clinical effectiveness of different dressing types (for example honey-based dressings) 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 role of education 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 a randomised control trial 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, 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 new educational measures to these patients.

What is the effectiveness of different footwear 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 from diabetes, rates and extent of amputation, rates of emergency and hospital admission for

1 foot problems resulting from diabetes, , and resource use and cost as a result of applying the
2 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, 90 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*1 *Table 26: Description of identified classification tools*

2 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.		

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4.7.2.21 Included studies on classification tools

4.7.2.2.12 Table 27: Classification tools

3 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

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4.7.2.3.3 *Table 30: Probe to bone tests for osteomyelitis*

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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

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4.7.2.3.42 ***Table 31: Imaging tests for osteomyelitis***

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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

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

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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

4.7.31 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

4.7.45 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 deep 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 done by making sure that those who have developed ulceration receive the correct treatment 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. Little evidence was available for the outcomes rate of reulceration, soft tissue infection, and gangrene.
Trade-off between benefits and harms	Regarding accuaracy the GDG considered that in instances of a true positive, referral to appropriate services and appropriate care results in decreased risk of ulceration, reulceration, infection, both minor and major amputation and death (see Section 4.3 Protocols and DFS and MDS) In instances of true negatives then 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 possibility 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 were mindful to consider 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 health care practitioners 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 factors 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 gradiation 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 felt that the bone culture performed well against superficial swab and tissue culture when bone culture was reference standard and therefore should be recommended as a method of infection sampling. 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

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

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

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

24. **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 superficial swab because it may provide useful information on the choice of antibiotic therapy.**

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

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

27. **Be aware that osteomyelitis may be present despite normal inflammatory markers, X-rays or probe-to-bone testing.**

28. **If osteomyelitis is suspected but is not confirmed by initial X-ray, consider 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 aimed to assess 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 major 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 footcare problems can help avoid un-necessary hospitalisation and longer term management of complication 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 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 footcare problems can help avoid un-necessary hospitalisation and longer term management of complication such as infection, gangrene and amputations. This will help avoid unnecessary resource use also. 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 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 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 is determined by health professionals with specialist knowledge. The GDG noted there is a triage of care which differs regionally and as such, they felt the timeframes for review should be kept broad. This flexibility was achieved by stating that the frequency of review should take into account the overall health of the person, how healing has progressed, and any deterioration. At the same time that a patient's agreed 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. For these reasons the GDG defined what they would consider to be severe/complex problems in need of immediate attention to be treated under secondary care (see section 4.14).

4.8.6 Recommendations

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

30. Ensure that the frequency of monitoring set out in the person's individualised treatment plan is maintained whether the person 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

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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.

4.9.51 Evidence to Recommendations

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3 **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 indeed 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 all of the patients will have already developed diabetic foot problems and it will be a case of primarily trying 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 mortality rate. Reducing the incidence of these complications will also result in reduced rates of hospital admission with implications for better 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 have to produce a clear improvement in clinical outcomes as listed above. The main complication that healthcare professionals are eager to be avoided 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 into practice in the real world. Potential harm as a result of offering the above management strategies could be as simple as having a direct adverse effect as a result of using the therapy or that 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 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 also agreed it was important to raise awareness that the presence of diabetic foot infections can increase the risk of cardiovascular disease. The committee felt it was appropriate to capture these considerations within the recommendations. 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 acknowledged the importance of providing written, verbal and pictorial information. For this reason, the GDG agreed it was appropriate to provide a list of useful information resources to assist patients in identifing foot problems. The GDG agreed there was limited evidence presented for all conditions covered within the review question, but felt there was a need to acknowledge 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 due to be covered in more detail under sections 3.3 and 3.14. There was no convincing evidence to show that a foot exercise intervention offered any benefit in terms of wound healing rate. The GDG felt it was important 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

31. Provide consistent, relevant information and clear explanations as part of the individualised treatment plan for people with a diabetic foot problem. Information should 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.

32. **If people present 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.**

4.9.7 Research recommendations

No research recommendations were drafted for this review question

4.10 Debridement, wound dressings and off-loading

4.10.1 Review Question

What is the clinical effectiveness of surgical or non-surgical debridement, wound dressings and off-loading 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, off-loading 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 off-loading.

The original and rerun searches identified 1289 abstracts 107 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). 13 newly identified papers were included in the final review. This included 7 papers for debridement and wound dressings and 6 papers for off-loading. Tallis,A.(2013). Piaggesi,A. (1998). Jensen,J.L. (1997). Gottrup,F. (2013), Donaghue,V.M, (1998), Armstrong DG, (2005), Caravaggi,C. (2000), 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 Off-loading 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)

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)
	Re-ulceration
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)

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1 **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
Off-loading					
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 (2010)	**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				
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:** 23 patients (11 received Total contact cast; 12 received Cast walker boot) **Age:** Mean age 54 years	Total contact cast versus Removable cast walker boot	• Wound healing • Healing time	Not reported	USA
Armstrong (2001)	**Patient characteristics:** Patients with non-infected diabetic plantar ulcers **Evaluable total:** 39 patients (19 received total contact cast; 20	Total contact cast versus Removable cast walker	• Wound healing • Healing time	12 weeks or until complete epithelisation	USA

Author (year)	Population	Comparisons	Outcomes of interest	Follow up	Study Location
	received removable cast walker) **Age:** Not reported				
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
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					

Author (year)	Population	Comparisons	Outcomes of interest	Follow up	Study Location
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; 17 received padding to the shoe) **Age:** Mean age 58 years	Felt deflective padding to skin versus Felt deflective padding in shoe	• Wound reduction	4 weeks or until healed	Australia

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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 four randomised control trials with 157 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 paramount as the critical outcome for this question and indeed 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 the case of this question all of the patients will have already developed diabetic foot problems and it will be a case of primarily trying 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 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	It was felt that the benefits of a good treatment strategy for people who have developed diabetic foot problems would have to produce a clear improvement in clinical outcomes as listed above. As we have mentioned, the main complication that we are eager to be treated is ulceration. If patients can have their foot ulceration healed quickly and reulceration prevented this

	can protect the development of further 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 into practice in the real world. Potential harm as a result of offering the above treatment strategies could be as simple as having a direct adverse effect as a result of using the therapy or that 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.
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 it was important to note the quality of evidence needed to reflect the application of certain types of dressings not commonly used in the UK population of interest. 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 association. The GDG felt that the comparison reported by Ganguly et al (2008) was inappropriate 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 provide separate recommendations to reflect this. 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 did not necessarily reflect the most appropriate dressings for patient needs and therefore felt it was important to note this in the recommendations. Off-loading: The GDG acknowledged that the effectiveness of off-loading 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 may be appropriate to acknowledge the development of pressure ulcers within people who have neuropathic foot ulcers. They therefore felt it appropriate to provide a cross-reference to recommendations made within the Pressure Ulcers guideline (NICE Clinical guideline 179)

4.10.6 Recommendations

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

- Off-loading.
- Control of foot infection.
- Control of ischaemia.
- Wound debridement.
- Moist wound dressings where appropriate.

34. Offer non-removable casting to off-load plantar neuropathic, non-ischaemic, uninfected forefoot and midfoot ulcers.

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

36. Debridement in hospital should only be done by healthcare professionals from the multidisciplinary foot care team, using the technique that best matches their specialist expertise and clinical experience, the site of the diabetic foot ulcer and the person's preference.

37. 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.

38. When deciding about wound dressings and off-loading, 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

No research recommendations were drafted for this review question.

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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

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 & antibiotics2. **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

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

Author (year)	Study type	Participants	Class of antibiotic	Drug comparisons	Route	Outcomes	Follow up	Location
	single blind RCT	skin & soft tissue infection[3]. **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

[3] 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

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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.

4.11.51 Evidence to recommendations

2 **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 paramount as the critical outcome for this question and indeed 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 all of the patients will have already developed diabetic foot infection and it will be a case of primarily trying to cure active foot ulceration/infection. This would 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 would have to produce a clear improvement in the clinical outcomes listed above. At this stage the main complication that we are eager to be treat is infection with a view to helping to heal the underlying foot ulceration. If patients can have their foot infection healed quickly, underlying ulceration treated 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 include the important consideration of whether the antibiotic could cause any serious adverse effect or be 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 burden on 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, was not sufficiently reflected by the quality assessment and GRADE methodology. Based on this discrepancy 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 (ie. It is irrelevant whether

	following antibiotics the investigator continues to isolate an organism or not as this 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. For this reason 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. 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 thought it was appropriate to consider 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.

4.11.6 Recommendations

39. 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.

40. Do not offer antibiotics to prevent foot infections.

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

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

43. **Use the clinical response to antibiotics and the results of the microbiological examination to decide the targeted antibiotic regimen.**

44. **Do not offer tigecycline unless other antibiotics are not suitable.**

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

46. **Do not use prolonged antibiotic therapy for mild soft tissue infections.**

47. **For moderate and severe foot infections, 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[d].

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

4.11.7 Research recommendations

No research recommendations were drafted for this review question.

[d] Please see table 2 in the Infectious Diseases Society of America (IDSA) guidelines, which shows the PEDIS grades and ISDA infection severity classifications for diabetic foot infections.

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, 309 papers were subsequently excluded because they did not fit the inclusion criteria (see Appendix B for a full list of excluded studies). Sixty one new papers from 57 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).)

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.

4.12.2.16 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 seven 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) 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) 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.

1 **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 cm^2. 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

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

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

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

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					

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

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					

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

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

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

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

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					

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

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 cm^2 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 cm^2 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

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

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 cm^2 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

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/cm^2 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

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 cm^2 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

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 cm^2 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

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 cm^2 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					

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 cm^2 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 mm^2	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

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 cm^2 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

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 cm^2, 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 cm^3 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 cm^3 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

Author (year)	Population	Comparisons	Outcomes of interest	Follow up	Study Location
		Saline placebo applied topically in a volume of 0.1 cm^3 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

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. Off-loading 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

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

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 mm^2, maximum 2700 mm^2 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

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 off-loading 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 off-loading (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

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

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
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	Vacuum compression therapy (1 hour a day, 4 times a week, for 10 sessions) Versus Wound care was standardised for all	• Adverse events:	Length of follow up was 3 weeks	Iran

Author (year)	Population	Comparisons	Outcomes of interest	Follow up	Study Location
	system	participants. Conventional therapy of debridement, blood glucose control agents, systemic antibiotics, wound cleaning with normal saline, offloading and daily wound dressings.			

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4.12.31 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.

4.12.41 Evidence Statements

2 Cure Rate

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

5 • Amniotic memory wound graft (low quality evidence from one study including 25
6 participants)
7 • Dermagraft (moderate quality evidence from 3 studies including 341 participants)
8 • Cultured allogeneic keratinocyte sheet (low quality evidence from 1 study including 59
9 participants)
10 • Apligraft (low quality evidence from 1 study including 71 participants)
11 • Hyperbaric oxygen therapy (low quality evidence from 3 studies including 126
12 participants)
13 • Processed lipoaspirate cell therapy (low quality evidence from 1 study including 52
14 participants)
15 • RGD peptide matrix (low quality evidence from 1 study including 65 participants)
16 • Negative pressure wound therapy (low quality evidence from 1 study including 335
17 participants)
18 • Grafix therapy (high quality evidence from 1 study including 97 participants)

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

21 • Topical platelet derived growth factors (very low quality evidence from four studies
22 including 997 participants)
23 • Topical transforming growth factor (very low quality evidence from 1 study including 177
24 participants)
25 • Topical basic fibroblast growth factor (very low quality evidence from 2 studies including
26 111 participants)
27 • Topical growth factor CT-102 activated platelet supernatant (very low quality evidence
28 from 1 study including 13 participants)
29 • Topical growth factor GAM501 (very low quality evidence form 1 study including 82
30 participants)
31 • Topical recombinant human vascular endothelial growth factor (moderate quality evidence
32 from 1 study including 55 participants)
33 • Topical autologous platelet-rich plasma gel (very low quality evidence from 1 study
34 including 72 participants)
35 • Oral incretine (low quality evidence from 1 study including 106 participants)
36 • Hyalograft-3D followed by Laserskin autograft (very low quality evidence from 2 studies
37 including 221 participants)
38 • Graftskin (very low quality evidence from 1 study including 208 participants)
39 • Graftjacket (very low quality evidence from 2 studies including 113 participants)
40 • Talactoferrin (very low quality evidence from 1 study including 46 participants)
41 • External shock wave therapy (very low quality evidence from 1 study including 30
42 participants)
43 • Topical thrombin peptide chrysalin (very low quality evidence from 1 study including 59
44 participants)
45 • 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 (low quality evidence from 1 study including 342 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)

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 Iamin 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)

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 paramount as the critical outcome for this question and indeed 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 review question all of the patients will have already developed diabetic foot problems and it will be a case of primarily trying to heal active foot ulceration and reduce the rate of reulceration. All of the patients will have received a good standard of care for the healing of diabetic foot ulcers and the aim will be to see if any adjunctive therapies have an additional benefit for ulcer healing when added to the treatment regime. 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 better health-related quality of life.
Trade-off between benefits and harms	It was felt that the benefits of an adjunctive therapy for people who have developed diabetic foot ulcers would have to have demonstrated clear improvement in the clinical outcomes listed above. As we have mentioned, 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 the development of further more severe complications such as infection, gangrene and amputation. Secondly this therapy should be safe and do no harm. Thirdly that it should be available and implementable into practice in the UK population. Potential harm as a result of offering the above treatment strategies could be as simple as having a direct adverse effect as a result of using the therapy or that 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 interevention 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 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 without 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 team. For negative pressure wound therapy one study was found to be appropriate to our inclusion criteria and showed that negative pressure wound therapy could be significantly effective in treating diabetic foot ulcer when compared to standard care.. The GDG noted that this treatment is usually applied after

	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.

4.12.61 Recommendations

49. Consider negative pressure wound therapy after debridement, on the advice of the multidisciplinary foot care service.

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

51. Do not offer the following treatments, 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.

4.12.74 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.

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

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:					

Study	Population	Intervention	Control	Follow-up	Conclusions
[1]BMI– body mass index [2]NCA- Neuropathic Charcot arthropathy					

1

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4.13.31 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

4.13.45 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.

4.13.59 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 riskfactors for Charcot foot was highly important 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 here was to make sure that anyone in whom Charcot was even 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 someone with identified Charcot foot, then referral to appropriate services and appropriate care 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 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. (see Section 4.3 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. (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 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 seen in the literature and in clinical experience. The group also discussed the various risk factors presented and agreed peripheral neuropathy and renal failure were the most appropriate risk factors of Charcot arthropathy. This was as they were more common risk factors for this complication. 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 preceed Charcot foot deformity the GDG wished to make a recommendation making 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 to be considered as well as people presenting with acute signs of Charcot.

4.13.6 Recommendations

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

53. 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.

54. Refer the person urgently (within 24 hours) to the multidisciplinary foot care service to confirm the diagnosis, and offer non-weight-bearing treatment until definitive treatment can be started.

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 paramount as the critical outcome for this question and indeed 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 primarily trying 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 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 team for the appropriate patients at the appropriate stage of disease would have the following desired outcomes: A patient with active disease would recieve the best available care at the earliest stage possible and this could 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 would be a better defined referral pathway. This would result in better patient satisfaction with the service. On the other hand an inappropriate referral to specialist services within the multidisciplinary foot care team could result in waste in 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 they 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	Though 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 outcomes of interest in any of the papers sifted. Unsatisfied with the idea of making recommendations without any evidence on this subject we broadened our protocol to include studies that show the effect of a multidisciplinary or integrated care pathway in the context of a hospital based multidisciplinary foot care team. Such studies would give an idea of the benefit of the 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 most likely and cost effective for patients to receive the hospital specialist 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 team 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 study showing benefit from implementation of multidisciplinary care. For example we could not prove that a particular referral pathway within a protocol (e.g. vascular) was effective since the study only showed the benefit of the implementation of a multidisciplinary 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.

Further 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 wanted to make recommendations that multidisciplinary 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, as within the evidence identified, should be based upon the recognised 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.

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.

Based on the evidence presented and the types of treatments received by the patients for which a detailed protocol was given the GDG was able to extrapolate the types of services that they would want providing treatments and protective management for patients at different risk levels. Based on this evidence the GDG decided that those who had developed active diabetic foot problems should be referred to the foot protection service or hospital multidisciplinary foot team depending on disease severity. The diabetic foot protection team could provide triage for the hospital multidisciplinary team and treat simple active problems. However more detailed guidelines would depend upon local protocols, resources and practice.

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 and multidisciplinary team service (within 24 hours). This would help to direct timely assessment of patients who had developed complications.

For those with more severe symptoms outlined in recommendation 50 the GDG felt that it had to be made clear

	that these patients should be referred immediately to secondary care as well as being referred to the hospital multidisciplinary service on the same day. 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) Also important was the need for the admitting team to provide immediate assessment and treatment for patients referred urgently to secondary care. The aim of this recommendation was to ensure that the patient received immediate care when required in hospital settings. This care should continue up until the multidisciplinary foot care team may choose to take over management. This recommendation aims to protect patients from receiving delayed care while a healthcare professional waits for the multidisciplinary foot care team to take over. (see section 4.3)

4.14.6 Recommendations & Research Recommendations

55. Refer people with an active diabetic foot problem to the foot protection service or multidisciplinary foot care service within 24 hours for appropriate triage according to local protocols.

56. If any of the following active diabetic foot problems are present, refer the person to the multidisciplinary foot care service within 24 hours so they can be assessed and an individualised treatment plan put in place according to local protocols:

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

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 team 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					

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.

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

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.

Study	Population	Intervention	Control	Follow-up	Conclusions
Abbreviations:					

1

4.15.31 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

4.15.45 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.

4.15.55 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 the 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 here was to make sure that anyone in whom Charcot was even 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, then referral to appropriate services and appropriate care 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 appropriate or 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 possibility of ulceration, deformity and both minor and major 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 services provided, 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 for the 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. 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 & research recommendations

57. If acute Charcot arthropathy is suspected, X-ray the affected foot. Consider an MRI if the X-ray is normal but clinical suspicion still remains.

58. 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, off-loading 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, off-loading 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 off-loading 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

1

2

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.

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.

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

Study	Population	Intervention	Control	Follow-up	Conclusions
	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.	cancellous tibio-talar bony surfaces	compression of cancellous tibio-talar bony surfaces		treatment group.

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.

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

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-weightbearing at initial presentation vs not treated with cast and total non-weightbearing at initial presentation for Charcot foot					
Retrospective cohort Pakarinen 2002 Finland	Total= 36 feet, 32 participants Treated with cast and total non-weightbearing at initial presentation= 18 Not treated with cast and total non-weightbearing 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-weightbearing at initial presentation Standard care may have varied	No cast and total non-weightbearing 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-weightbearing 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-weightbearing at initial presentation.

Study	Population	Intervention	Control	Follow-up	Conclusions
	disease.				
Non-weightbearing 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-weightbearing 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-weightbearing within 2 months of symptoms of fracture.

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.				

1

4.16.31 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

4.16.45 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-weightbearing at initial presentation vs no cast and total non-weightbearing 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-weightbearing 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-weightbearing at initial presentation.

Treatment with total non-weightbearing device within 2 months of symptoms vs weightbearing 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-weightbearing 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-weightbearing 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 paramount as the critical outcome for this question and indeed 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 all of the 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 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 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 an increased future risk of ulceration. Preventing ulceration could also reduce the likelihood of subsequent infection, gangrene, amputation and death.

	The potential harm of giving treatment could be as a result of direct adverse events, 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. 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, hindfoot charcot arthropathy to a surgical specialist was important, however this should be done under the decision making within the multidisciplinary foot care team (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 & research recommendations

59. If the multidisciplinary foot care service suspects acute Charcot arthropathy, offer treatment with a non-removable off-loading device. Only consider treatment with a removable off-loading device if a non-removable device is not advisable because of the clinical or the person's circumstances.

60. Do not offer bisphosphonates to treat acute Charcot arthropathy, unless as part of a clinical trial.

61. 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 measures 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 measures for the prevention of Charcot arthropathy or its sequelae.

5 References

5.1 Review question 1 included studies

Crane M, Werber B, Lavery LA (1999) Critical pathway approach to diabetic pedal infections in a multidisciplinary setting. Journal of Foot and Ankle Surgery 38: 82-3.

Dargis V, Pantelejeva O, Jonushaite A et al. (1998) Benefits of a multidisciplinary approach in the management of recurrent diabetic foot ulceration: a prospective study. 7th Malvern Diabetic Foot Conference; 1998, 13-15 May; Malvern, UK : 23.

Larsson J, Apelqvist J, Agardh CD et al. (1995) Decreasing incidence of major amputation in diabetic patients: a consequence of a multidisciplinary foot care team approach? Diabetic Medicine 12: 770-6.

Canavan RJ, Unwin NC, Kelly WF et al. (2008) Diabetes- and nondiabetes-related lower extremity amputation incidence before and after the introduction of better organized diabetes foot care: continuous longitudinal monitoring using a standard method. Diabetes Care 31: 459-63.

Driver VR, Madsen J, Goodman RA (2005) Reducing amputation rates in patients with diabetes at a military medical center: the limb preservation service model. Diabetes Care 28: 248-53.

5.2 Review question 2 included studies

Williams,D.T., Majeed,M.U., Shingler,G., Akbar,M.J., Adamson,D.G.. A diabetic foot service established by a department of vascular surgery: an observational study. Annals of Vascular Surgery 2012;26(5):700-06.

Sampson,M.J., Brennan,C., Dhatariya,K., Jones,C.. A national survey of in-patient diabetes services in the United Kingdom. Diabetic Medicine 2007;24(6):643-49.

El,Sakka K., Fassiadis,N., Gambhir,R.P., Halawa,M., Zayed,H., Doxford,M., et al. An integrated care pathway to save the critically ischaemic diabetic foot. International Journal of Clinical Practice 2006;60(6):667-69.

Winocour,P.H., Morgan,J., Ainsworth,A., Williams,D.R.. Association of British Clinical Diabetologists (ABCD): survey of specialist diabetes care services in the UK, 2000. 3. Podiatry services and related foot care issues. Diabetic Medicine 2002;19():Suppl-8.

Jude,E.B., Oyibo,S.O., Millichip,M.M.. A survey of physicians' involvement in the management of diabetic foot ulcers in secondary health care. Practical Diabetes International.20 (3) (pp 89-92), 2003.Date of Publication: April 2003. 2003;(3):89-92.

Housley,A. & Betts,C.. Diabetes foot health in Chorley and South Ribble: A step in the right direction. Practical Diabetes International.23 (4) (pp 161-165), 2006.Date of Publication: May 2006. 2006;(4):161-65.

National Diabetes Inpatient Audit, Diabetes UK (2013)

Gooday, C., Murchison, R., & Dhatariya, K. (2013). An analysis of clinical activity, admission rates, length of hospital stay, and economic impact after a temporary loss of 50% of the non-operative podiatrists from a tertiary specialist foot clinic in the United Kingdom. Diabetic foot & ankle, 4.

5.3 Review question 3 included studies

Gooday, C., Murchison, R., & Dhatariya, K. (2013). An analysis of clinical activity, admission rates, length of hospital stay, and economic impact after a temporary loss of 50% of the non-operative podiatrists from a tertiary specialist foot clinic in the United Kingdom. Diabetic foot & ankle, 4.

Patout, C. A., Birke, J. A., Horswell, R., Williams, D., & Cerise, F. P. (2000). Effectiveness of a comprehensive diabetes lower-extremity amputation prevention program in a predominantly low-income African-American population. Diabetes Care, 23(9), 1339-1342.

Rith-Najarian, S., Branchaud, C., Beaulieu, O., Gohdes, D., Simonson, G., & Mazze, R. (1998). Reducing lower-extremity amputations due to diabetes. Application of the staged diabetes management approach in a primary care setting. The Journal of family practice, 47(2), 127-132.

Birke, J. A., Horswell, R., Patout Jr, C. A., & Chen, S. L. (2002). The impact of a staged management approach to diabetes foot care in the Louisiana public hospital system. The Journal of the Louisiana State Medical Society: official organ of the Louisiana State Medical Society, 155(1), 37-42.

Armstrong, D. G., & Harkless, L. B. (1998). Outcomes of preventative care in a diabetic foot specialty clinic. The Journal of foot and ankle surgery, 37(6), 460-466.

Schraer, C. D., Weaver, D., Naylor, J. L., Provost, E., & Mayer, A. M. (2004). Reduction of amputation rates among Alaska Natives with diabetes following the development of a high-risk foot program. International journal of circumpolar health, 63.

Lavery, L. A., Wunderlich, R. P., & Tredwell, J. L. (2005). Disease management for the diabetic foot: effectiveness of a diabetic foot prevention program to reduce amputations and hospitalizations. Diabetes research and clinical practice, 70(1), 31-37.

Dargis, V., Pantelejeva, O. L. G. A., Jonushaite, A. L. A. N. T. A., Vileikyte, L. O. R. E. T. T. A., & Boulton, A. J. (1999). Benefits of a multidisciplinary approach in the management of recurrent diabetic foot ulceration in Lithuania: a prospective study. Diabetes care, 22(9), 1428-1431.

Driver, V. R., Goodman, R. A., Fabbi, M., French, M. A., & Andersen, C. A. (2010). The impact of a podiatric lead limb preservation team on disease outcomes and risk prediction in the diabetic lower extremity: a retrospective cohort study. Journal of the American Podiatric Medical Association, 100(4), 235-241.

Carrington, A. L., Abbott, C. A., Griffiths, J., Jackson, N., Johnson, S. R., Kulkarni, J., ... & Boulton, A. J. (2001). A foot care program for diabetic unilateral lower-limb amputees. Diabetes care, 24(2), 216-221.

Nason, G. J., Strapp, H., Kiernan, C., Moore, K., Gibney, J., Feeley, T. M., ... & Tierney, S. (2013). The cost utility of a multi-disciplinary foot protection clinic (MDFPC) in an Irish hospital setting. Irish journal of medical science, 182(1), 41-45.

5.4 Review question 4 included studies

5.4.1 Examination tools

Nather, A., Bee, C. S., Huak, C. Y., Chew, J. L., Lin, C. B., Neo, S., & Sim, E. Y. (2008). Epidemiology of diabetic foot problems and predictive factors for limb loss. Journal of Diabetes and its Complications, 22(2), 77-82.

Boyko, E. J., Ahroni, J. H., Cohen, V., Nelson, K. M., & Heagerty, P. J. (2006). Prediction of Diabetic Foot Ulcer Occurrence Using Commonly Available Clinical Information The Seattle Diabetic Foot Study. Diabetes care, 29(6), 1202-1207.

Abbott, C. A., Carrington, A. L., Ashe, H., Bath, S., Every, L. C., Griffiths, J., ... & Boulton, A. J. M. (2002). The North-West Diabetes Foot Care Study: incidence of, and risk factors for, new diabetic foot ulceration in a community-based patient cohort. Diabetic Medicine, 19(5), 377-384.

Carrington, A. L., Shaw, J. E., Van Schie, C. H., Abbott, C. A., Vileikyte, L., & Boulton, A. J. (2002). Can motor nerve conduction velocity predict foot problems in diabetic subjects over a 6-year outcome period?. Diabetes Care, 25(11), 2010-2015.

Kastenbauer, T., Sauseng, S., Sokol, G., Auinger, M., & Irsigler, K. (2001). A prospective study of predictors for foot ulceration in type 2 diabetes. Journal of the American Podiatric Medical Association, 91(7), 343-350.

Pham, H., Armstrong, D. G., Harvey, C., Harkless, L. B., Giurini, J. M., & Veves, A. (2000). Screening techniques to identify people at high risk for diabetic foot ulceration: a prospective multicenter trial. Diabetes care, 23(5), 606-611.

Adler, A. I., Boyko, E. J., Ahroni, J. H., & Smith, D. G. (1999). Lower-extremity amputation in diabetes. The independent effects of peripheral vascular disease, sensory neuropathy, and foot ulcers. Diabetes care, 22(7), 1029-1035.

Boyko, E. J., Ahroni, J. H., Stensel, V. I. C. T. O. R. I. A., Forsberg, R. C., Davignon, D. R., & Smith, D. G. (1999). A prospective study of risk factors for diabetic foot ulcer. The Seattle Diabetic Foot Study. Diabetes Care, 22(7), 1036-1042.

Litzelman, D. K., Marriott, D. J., & Vinicor, F. (1997). Independent physiological predictors of foot lesions in patients with NIDDM. Diabetes Care, 20(8), 1273-1278.

Young, M. J., Breddy, J. L., Veves, A., & Boulton, A. J. (1994). The prediction of diabetic neuropathic foot ulceration using vibration perception thresholds: a prospective study. Diabetes care, 17(6), 557-560.

Rith-Najarian, S. J., Stolusky, T., & Gohdes, D. M. (1992). Identifying diabetic patients at high risk for lower-extremity amputation in a primary health care setting: a prospective evaluation of simple screening criteria. Diabetes care, 15(10), 1386-1389.

Sriyani, K. A., Wasalathanthri, S., Hettiarachchi, P., & Prathapan, S. (2013). Predictors of Diabetic Foot and Leg Ulcers in a Developing Country with a Rapid Increase in the Prevalence of Diabetes Mellitus. PloS one, 8(11), e80856.

Leese, G. P., Feng, Z., Leese, R. M., Dibben, C., & Emslie-Smith, A. (2013). Impact of health-care accessibility and social deprivation on diabetes related foot disease. Diabetic Medicine, 30(4), 484-490.

5.4.27 Stratification systems

Leese,G.P., Reid,F., Green,V., McAlpine,R., Cunningham,S., Emslie-Smith,A.M., et al. Stratification of foot ulcer risk in patients with diabetes: a population-based study. International Journal of Clinical Practice 2006;60(5):541-45.

Monteiro-Soares,M., Vaz-Carneiro,A., Sampaio,S.. Validation and comparison of currently available stratification systems for patients with diabetes by risk of foot ulcer development. European Journal of Endocrinology 2012;167(3):401-07.

Monteiro-Soares,M., Boyko,E.J., Ribeiro,J., Ribeiro,I.. Risk stratification systems for diabetic foot ulcers: A systematic review. Diabetologia.54 (5) (pp 1190-1199), 2011.Date of Publication: May 2011. 2011;(5):1190-99.

Monteiro-Soares,M.. External validation and optimisation of a model for predicting foot ulcers in patients with diabetes. Diabetologia 2010;53(7):1525-33.

Peters,E.J. & Lavery,L.A.. Effectiveness of the diabetic foot risk classification system of the International Working Group on the Diabetic Foot. Diabetes Care 2001;24(8):1442-47.

5.5 Review question 5 included studies

No evidence was identified for this review

5.6 Review question 6 included studies

Lavery, Lawrence A., et al. "Preventing Diabetic Foot Ulcer Recurrence in High-Risk Patients Use of temperature monitoring as a self-assessment tool." Diabetes care 30.1 (2007): 14-20.

Armstrong, D. G., Holtz-Neiderer, K., Wendel, C., Mohler, M. J., Kimbriel, H. R., & Lavery, L. A. (2007). Skin temperature monitoring reduces the risk for diabetic foot ulceration in high-risk patients. The American journal of medicine, 120(12), 1042-1046.

Lavery, L. A., Higgins, K. R., Lanctot, D. R., Constantinides, G. P., Zamorano, R. G., Armstrong, D. G., ... & Agrawal, C. M. (2004). Home monitoring of foot skin temperatures to prevent ulceration. Diabetes care, 27(11), 2642-2647.

Annersten Gershater, M., Pilhammar, E., Apelqvist, J., & Alm-Roijer, C. (2011). Patient education for the prevention of diabetic foot ulcers. Interim analysis of a randomised controlled trial due to morbidity and mortality of participants.

McMurray, S. D., Johnson, G., Davis, S., & McDougall, K. (2002). Diabetes education and care management significantly improve patient outcomes in the dialysis unit. American journal of kidney diseases, 40(3), 566-575.

Bloomgarden, Z. T., Karmally, W., Metzger, M. J., Brothers, M., Nechemias, C., Bookman, J., ... & Brown, W. V. (1987). Randomized, controlled trial of diabetic patient education: improved knowledge without improved metabolic status. Diabetes care, 10(3), 263-272.

Lincoln, N. B., Radford, K. A., Game, F. L., & Jeffcoate, W. J. (2008). Education for secondary prevention of foot ulcers in people with diabetes: a randomised controlled trial. Diabetologia, 51(11), 1954-1961.

Malone, James M., et al. "Prevention of amputation by diabetic education." The American journal of surgery 158.6 (1989): 520-524.

Litzelman, D. K., Slemenda, C. W., Langefeld, C. D., Hays, L. M., Welch, M. A., Bild, D. E., ... & Vinicor, F. (1993). Reduction of lower extremity clinical abnormalities in patients with non-insulin-dependent diabetes mellitusA randomized, controlled trial. Annals of Internal Medicine, 119(1), 36-41.

Armstrong, D. G., Holtz, K., & Wu, S. (2005). Can the use of a topical antifungal nail lacquer reduce risk for diabetic foot ulceration? results from a randomised controlled pilot study. International wound journal, 2(2), 166-170.

LeMaster, J. W., Mueller, M. J., Reiber, G. E., Mehr, D. R., Madsen, R. W., & Conn, V. S. (2008). Effect of weight-bearing activity on foot ulcer incidence in people with diabetic peripheral neuropathy: feet first randomized controlled trial. Physical Therapy, 88(11), 1385-1398.

Cisneros, L. L. (2010). Evaluation of a neuropathic ulcers prevention program for patients with diabetes. Brazilian Journal of Physical Therapy, 14(1), 31-37.

Reiber, G. E., Smith, D. G., Wallace, C., Sullivan, K., Hayes, S., Vath, C., ... & LeMaster, J. (2002). Effect of therapeutic footwear on foot reulceration in patients with diabetes: a randomized controlled trial. Jama, 287(19), 2552-2558.

Lavery, L. A., LaFontaine, J., Higgins, K. R., Lanctot, D. R., & Constantinides, G. (2012). Shear-reducing insoles to prevent foot ulceration in high-risk diabetic patients. Advances in skin & wound care, 25(11), 519-524.

Uccioli, L., Faglia, E., Monticone, G., Favales, F., Durola, L., Aldeghi, A., ... & Menzinger, G. (1995). Manufactured shoes in the prevention of diabetic foot ulcers. Diabetes care, 18(10), 1376-1378.

Rizzo, L., Tedeschi, A., Fallani, E., Coppelli, A., Vallini, V., Iacopi, E., & Piaggesi, A. (2012). Custom-made orthesis and shoes in a structured follow-up program reduces the incidence of neuropathic ulcers in high-risk diabetic foot patients. The international journal of lower extremity wounds, 11(1), 59-64.

Scire, V., Leporati, E., Teobaldi, I., Nobili, L. A., Rizzo, L., & Piaggesi, A. (2009). Effectiveness and safety of using Podikon digital silicone padding in the primary prevention of neuropathic lesions in the forefoot of diabetic patients. Journal of the American Podiatric Medical Association, 99(1), 28-34.

Rönnemaa, T., Hämäläinen, H., Toikka, T., & Liukkonen, I. (1997). Evaluation of the impact of podiatrist care in the primary prevention of foot problems in diabetic subjects. Diabetes Care, 20(12), 1833-1837.

Hämäläinen, H., Rönnemaa, T., Toikka, T., & Liukkonen, I. (1998). Long-term effects of one year of intensified podiatric activities on foot-care knowledge and self-care habits in patients with diabetes. The Diabetes Educator, 24(6), 734-740.

McCabe, C. J., Stevenson, R. C., & Dolan, A. M. (1998). Evaluation of a diabetic foot screening and protection programme. Diabetic Medicine, 15(1), 80-84.

Plank, J., Haas, W., Rakovac, I., Gorzer, E et al (2003)Evaluation of the impact of chiropodist care in the secondary prevention of foot ulcerations in diabetic subjects, Diabetes Care 26 (6) 1691-1695

Ulbrecht, J. S., Hurley, T., Mauger, D. T., & Cavanagh, P. R. (2014). Prevention of Recurrent Foot Ulcers With Plantar Pressure–Based In-Shoe Orthoses: The CareFUL Prevention Multicenter Randomized Controlled Trial. Diabetes care, DC_132956.

Bus, S. A., Waaijman, R., Arts, M., de Haart, M., Busch-Westbroek, T., van Baal, J., & Nollet, F. (2013). Effect of Custom-made Footwear on Foot Ulcer Recurrence in Diabetes A multicenter randomized controlled trial. Diabetes care, 36(12), 4109-4116.

5.7 Review question 7 included studies

5.7.1 Included studies list (2013 review)

Abbas,Z.G., Lutale,J.K., Game,F.L. (2008) Comparison of four systems of classification of diabetic foot ulcers in Tanzania. Diabetic Medicine 25: 134-37.

Alvaro-Afonso,F.J., Lazaro-Martinez,J.L., et al (2013) Interobserver and intraobserver reproducibility of plain X-rays in the diagnosis of diabetic foot osteomyelitis. International Journal of Lower Extremity Wounds 12: 12-15.

Armstrong, DG, Lavery, LA, Harkless, LB Validation of a diabetic wound classification system. The contribution of depth, infection, and ischemia to risk of amputation. Diabetes Care 1998; 21: 855-59.

Asli,I.N., Javadi,H., et al (2011) The diagnostic value of (99m)Tc-IgG scintigraphy in the diabetic foot and comparison with (99m)Tc-MDP scintigraphy. Journal of Nuclear Medicine Technology 39: 226-30.

Beckert,S., Pietsch,A.M., et al (2009) M.A.I.D.: a prognostic score estimating probability of healing in chronic lower extremity wounds. Annals of Surgery 249, 677-81.

Beckert,S., Witte,M., et al (2006) A new wound-based severity score for diabetic foot ulcers: A prospective analysis of 1,000 patients. Diabetes Care 29: 988-92.

Bernard,L., Assal,M., Garzoni,C. (2011) Predicting the pathogen of diabetic toe osteomyelitis by two consecutive ulcer cultures with bone contact. European Journal of Clinical Microbiology & Infectious Diseases 30: 279-81.

Elamurugan,T.P., Jagdish,S., Kate,V. (2011) Role of bone biopsy specimen culture in the management of diabetic foot osteomyelitis. International Journal Of Surgery 9: 214-16.

Erdman,W.A., Buethe,J., et al (2012) Indexing severity of diabetic foot infection with 99mTc-WBC SPECT/CT hybrid imaging . Diabetes Care 35: 1826-31.

Garcia,Morales E., Lazaro-Martinez,J.L., et al (2011) Inter-observer reproducibility of probing to bone in the diagnosis of diabetic foot osteomyelitis. Diabetic Medicine 28: 1238-40.

Gul,A., Basit,A., et al (2006) Role of wound classification in predicting the outcome of diabetic foot ulcer. JPMA - Journal of the Pakistan Medical Association 56: 444-47.

Heiba,S.I., Kolker,D., et al (2010) The optimized evaluation of diabetic foot infection by dual isotope SPECT/CT imaging protocol. Journal of Foot & Ankle Surgery 49: 529-36.

Ince, P., Abbas, Z., et al (2008) Use of SINBAD classification system and score in comparing outcome of foot ulcer management on three continents. Diabetes Care 31: 964-967

Kagna,O., Srour,S., et al (2012) FDG PET/CT imaging in the diagnosis of osteomyelitis in the diabetic foot. European Journal of Nuclear Medicine & Molecular Imaging. 39: 1545-50.

Lavery,L.A., Armstrong,D.G., Peters,E.J. (2007) Probe-to-bone test for diagnosing diabetic foot osteomyelitis: reliable or relic? Diabetes Care 30: 270-74.

Lavery,L.A., Armstrong,D.G., et al (2007) Validation of the Infectious Diseases Society of America's diabetic foot infection classification system Clinical Infectious Diseases 44: 562-65.

Meyr,A.J., Singh,S., et al (2011) Statistical reliability of bone biopsy for the diagnosis of diabetic foot osteomyelitis. Journal of Foot & Ankle Surgery 50: 663-67.

Morales,Lozano R., Gonzalez Fernandez,M.L., et al (2010) Validating the probe-to-bone test and other tests for diagnosing chronic osteomyelitis in the diabetic foot. Diabetes Care 33: 2140-45.

Mutluoglu,M., Uzun,G., et al (2012) How reliable are cultures of specimens from superficial swabs compared with those of deep tissue in patients with diabetic foot ulcers? Journal of Diabetes & its Complications 26: 225-29.

Mutluoglu,M., Uzun,G., et al (2012) Performance of the probe-to-bone test in a population suspected of having osteomyelitis of the foot in diabetes. Journal of the American Podiatric Medical Association. 102: 369-73.

Nawaz,A., Torigian,D.A., et al (2010) Diagnostic performance of FDG-PET, MRI, and plain film radiography (PFR) for the diagnosis of osteomyelitis in the diabetic foot. Molecular Imaging & Biology 12: 335-42.

Oyibo,S.O., Jude,E.B., et al (2001) A comparison of two diabetic foot ulcer classification systems: the Wagner and the University of Texas wound classification systems. Diabetes Care 24: 84-88.

Parisi,M.C., Zantut-Wittmann,D.E., et al (2008) Comparison of three systems of classification in predicting the outcome of diabetic foot ulcers in a Brazilian population. European Journal of Endocrinology 159: 417-22.

Saeed,S., Zafar,J., et al (2013) Utility of 99mTc-labelled antimicrobial peptide ubiquicidin (29-41) in the diagnosis of diabetic foot infection. European Journal of Nuclear Medicine & Molecular Imaging 40: 737-43.

Treece,K.A., Macfarlane,R.M., et al (2004) Validation of a system of foot ulcer classification in diabetes mellitus. Diabetic Medicine 21:987-91.

Michail, M., Jude, E., Liaskos, C., Karamagiolis, S., Makrilakis, K., Dimitroulis, D., ... & Tentolouris, N. (2013). The performance of serum inflammatory markers for the diagnosis and follow-up of patients with osteomyelitis. The international journal of lower extremity wounds, 12(2), 94-99.

Wang, A., Sun, X., Wang, W., & Jiang, K. (2014). A study of prognostic factors in Chinese patients with diabetic foot ulcers. Diabetic foot & ankle, 5.

Won, S. H., Chung, C. Y., Park, M. S., Lee, T., Sung, K. H., Lee, S. Y., ... & Lee, K. M. (2014). Risk Factors Associated with Amputation-Free Survival in Patient with Diabetic Foot Ulcers. Yonsei medical journal, 55(5), 1373-1378.

Tsai, C. Y., Chu, S. Y., Wen, Y. W., Hsu, L. A., Chen, C. C., Peng, S. H., ... & Huang, Y. Y. (2013). The value of Doppler waveform analysis in predicting major lower extremity amputation among dialysis patients treated for diabetic foot ulcers. Diabetes research and clinical practice, 100(2), 181-188.

Wukich, D. K., Hobizal, K. B., & Brooks, M. M. (2013). Severity of diabetic foot infection and rate of limb salvage. Foot & Ankle International, 34(3), 351-358.

5.7.20 Included studies list (CG119)

Al-Khawari HA, Al-Saeed OM, Jumaa TH et al. (2005) Evaluating diabetic foot infection with magnetic resonance imaging: Kuwait experience. Medical Principles & Practice 14: 165-72.

Beltran J, Campanini DS, Knight C et al. (1990) The diabetic foot: magnetic resonance imaging evaluation. Skeletal Radiology 19: 37-41.

Croll SD, Nicholas GG, Osborne MA et al. (1996) Role of magnetic resonance imaging in the diagnosis of osteomyelitis in diabetic foot infections. Journal of Vascular Surgery 24: 266-70.

Devillers A, Moisan A, Hennion F et al. (1998) Contribution of technetium-99m hexamethylpropylene amine oxime labelled leucocyte scintigraphy to the diagnosis of diabetic foot infection. European Journal of Nuclear Medicine 25: 132-8.

Ertugrul BM, Savk O, Ozturk B et al. (2009) The diagnosis of diabetic foot osteomyelitis: examination findings and laboratory values. Medical Science Monitor 15: CR307-CR312.

Ertugrul MB, Baktiroglu S, Salman S et al. (2006) The diagnosis of osteomyelitis of the foot in diabetes: microbiological examination vs. magnetic resonance imaging and labelled leucocyte scanning. Diabetic Medicine 23: 649-53.

Grayson ML, Gibbons GW, Balogh K et al. (1995) Probing to bone in infected pedal ulcers. A clinical sign of underlying osteomyelitis in diabetic patients. JAMA 273: 721-3.

Harwood SJ, Valdivia S, Hung GL et al. (1999) Use of Sulesomab, a radiolabeled antibody fragment, to detect osteomyelitis in diabetic patients with foot ulcers by leukoscintigraphy. Clinical Infectious Diseases 28: 1200-5.

Harvey, J and Cohen, MM (1997) Technetium-99-labelled leukocytes in diagnosing diabetic osteomyelitis in the foot. Journal of Foot and Ankle Surgery 36: 209-14.

Kaleta JL, Fleischli JW, Reilly CH (2001) The diagnosis of osteomyelitis in diabetes using erythrocyte sedimentation rate: a pilot study. Journal of the American Podiatric Medical Association 91: 445-50.

Keenan AM, Tindel NL, Alavi A (1989) Diagnosis of pedal osteomyelitis in diabetic patients using current scintigraphic techniques. Archives of Internal Medicine 149: 2262-6.

Larcos G, Brown ML, Sutton RT (1991) Diagnosis of osteomyelitis of the foot in diabetic patients: Value of 111-In-leukocyte scintigraphy. American Journal of Roentgenology 157: 527-31.

Levine SE, Neagle CE, Esterhai JL et al. (1994) Magnetic resonance imaging for the diagnosis of osteomyelitis in the diabetic patient with a foot ulcer. Foot & Ankle International 15: 151-6.

Malabu UH, Al-Rubeaan KA, Al-Derewish M (2007) Diabetic foot osteomyelitis: usefulness of erythrocyte sedimentation rate in its diagnosis. West African Journal of Medicine 26: 113-6.

Morrison WB, Schweitzer ME, Wapner KL et al. (1995) Osteomyelitis in feet of diabetics: clinical accuracy, surgical utility, and cost-effectiveness of MR imaging. Radiology 196: 557-64.

Newman LG, Waller J, Palestro CJ et al. (1991) Unsuspected osteomyelitis in diabetic foot ulcers. Diagnosis and monitoring by leukocyte scanning with indium in 111 oxyquinoline. JAMA 266: 1246-51.

Newman LG, Waller J, Palestro CJ et al. (1992) Leukocyte scanning with 111In is superior to magnetic resonance imaging in diagnosis of clinically unsuspected osteomyelitis in diabetic foot ulcers. Diabetes Care 15: 1527-30.

Palestro CJ, Caprioli R, Love C et al. (2003) Rapid diagnosis of pedal osteomyelitis in diabetics with a technetium-99m-labeled monoclonal antigranulocyte antibody. Journal of Foot & Ankle Surgery 42: 2-8.

Poirier JY, Garin E, Derrien C et al. (2002) Diagnosis of osteomyelitis in the diabetic foot with a 99mTc/-HMPAO leucocyte scintigraphy combined with a 99mTc/-MDP bone scintigraphy. Diabetes and Metabolism 28: 485-90.

Remedios D, Valabhji J, Oelbaum R et al. (1998) 99mTc-nanocolloid scintigraphy for assessing osteomyelitis in diabetic neuropathic feet. [Review] [34 refs]. Clinical Radiology 53: 120-5.

Rozzanigo U, Tagliani A, Vittorini E et al. (2009) Role of magnetic resonance imaging in the evaluation of diabetic foot with suspected osteomyelitis. Radiologia Medica 114: 121-32.

Rubello D, Casara D, Maran A et al. (2004) Role of anti-granulocyte Fab' fragment antibody scintigraphy (LeukoScan) in evaluating bone infection: acquisition protocol, interpretation criteria and clinical results. Nuclear Medicine Communications 25: 39-47.

Shone A, Burnside J, Chipchase S et al. (2006) Probing the validity of the probe-to-bone test in the diagnosis of osteomyelitis of the foot in diabetes. Diabetes Care 29: 945-6.

1 Slater RA, Lazarovitch T, Boldur I et al. (2004) Swab cultures accurately identify bacterial
2 pathogens in diabetic foot wounds not involving bone. Diabetic Medicine 21: 705-9.

3 Wang A, Weinstein D, Greenfield L et al. (1990) MRI and diabetic foot infections. Magnetic
4 Resonance Imaging 8: 805-9.

5 Weinstein D, Wang A, Chambers R et al. (1993) Evaluation of magnetic resonance imaging
6 in the diagnosis of osteomyelitis in diabetic foot infections. Foot & Ankle 14: 18-22.

7 Yuh WTC, Corson JD, Baraniewsky HM et al (1989) Osteomyelitis of the Foot in Diabetic
8 People: Evaluation with Plain Film, 99mTc-MDP Bone Scintigraphy, and MR Imaging. AJR,
9 vol. 152, pp. 795-800.

5.80 Review question 8 included studies

11 Warriner,R.A.,III; Wilcox,J.R.; Carter,M.J.; Stewart,D.G. (2012) More frequent visits to wound
12 care clinics result in faster times to close diabetic foot and venous leg ulcers, Advances in
13 Skin & Wound Care, 25 (11) 494-501

5.94 Review question 9 included studies

15 Malone,J.M.; Snyder,M.; Anderson,G.; Bernhard,V.M.; Holloway,G.A.; Bunt,T.J.1989)
16 Prevention of amputation by diabetic education, American Journal of Surgery, 158 (6) 520-
17 23.

18 Al-Wahbi,A.M. (2010) Impact of a diabetic foot care education program on lower limb
19 amputation rate, Vascular Health & Risk Management 6, 923-34.

20 Rerkasem,K.; Kosachunhanun,N.; Tongprasert,S.; Khwanngern,K.; Matanasarawoot,A.;
21 Thongchai,C.; Chimplee,K.; Buranapin,S.; Chaisrisawadisuk,S.; Manklabruks,A. (2007) The
22 development and application of diabetic foot protocol in Chiang Mai University Hospital with
23 an aim to reduce lower extremity amputation in Thai population: a preliminary
24 communication, International Journal of Lower Extremity Wounds 6 (1) 18-21.

25 Weck,M.; Slesaczeck,T.; Paetzold,H.; Muench,D.; Nanning,T.; von,Gagern G.; Brechow,A.;
26 Dietrich,U.; Holfert,M.; Bornstein,S.; Barthel,A.; Thomas,A.; Koehler,C.; Hanefeld,M. (2013)
27 Structured health care for subjects with diabetic foot ulcers results in a reduction of major
28 amputation rates, Cardiovascular Diabetology, 12 45.

29 Aragon-Sanchez,J.; Lazaro-Martinez,J.L. (2011) Impact of perioperative glycaemia and
30 glycated haemoglobin on the outcomes of the surgical treatment of diabetic foot
31 osteomyelitis, Diabetes Research & Clinical Practice, 94 (3) 83-85.

32 Markuson,M.; Hanson,D.; Anderson,J.; Langemo,D.; Hunter,S.; Thompson,P.; Paulson,R.;
33 Rustvang,D. (2009) The relationship between hemoglobin A(1c) values and healing time for
34 lower extremity ulcers in individuals with diabetes, Advances in Skin & Wound Care 22 (8)
35 365-72.

36 Young,M.J.; McCardle,J.E.; Randall,L.E.; Barclay,J.I. (2008) Improved survival of diabetic
37 foot ulcer patients 1995-2008: possible impact of aggressive cardiovascular risk
38 management, Diabetes Care, 31 (11) 2143-47.

39 Flahr, D (2010) The effect of nonweight-bearing exercise and protocol adherence on diabetic
40 foot ulcer healing: a pilot study, Ostomy Wound Management, 56 (10) 40-50.

41 Alzahrani, H., Bedir, Y., & Al-Hayani, A. (2013). Efficacy of shellac, a natural product, for the
42 prevention of wet gangrene. Journal of International Medical Research, 0300060513483391.

5.10 Review question 10 included studies

Tallis,A. Motley,T.A. Wunderlich,R.P. Dickerson,J.E.,Jr. Waycaster,C. Slade,H.B.(2013) Clinical and economic assessment of diabetic foot ulcer debridement with collagenase: results of a randomized controlled study, Clinical Therapeutics, 35 (11) 1805-20.

Piaggesi,A. Schipani,E. Campi,F. Romanelli,M. Baccetti,F. Arvia,C. Navalesi,R. (1998) Conservative surgical approach versus non-surgical management for diabetic neuropathic foot ulcers: a randomized trial, Diabetic Medicine 15 (5) 412-17

Jensen,J.L. Seeley,J. Gillin,B. (1997) Diabetic foot ulcerations. A controlled, randomized comparison of two moist wound healing protocols: Carrasyn Hydrogel Wound dressing and wet-to-moist saline gauze, Advances in Wound Care 11(7:Suppl):Suppl-4.

Gottrup,F. Cullen,B.M. Karlsmark,T. Bischoff-Mikkelsen,M. Nisbet,L. Gibson,M.C. (2013) Randomized controlled trial on collagen/oxidized regenerated cellulose/silver treatment, Wound Repair & Regeneration 21 (2) 216-25.

Donaghue,V.M, Chrzan,J.S. Rosenblum,B.I. Giurini,J.M. Habershaw,G.M.; Veves,A. (1998) Evaluation of a collagen-alginate wound dressing in the management of diabetic foot ulcers, Advances in Wound Care 11(3) 114-19.

Armstrong DG, Lavery LA, Wu S, Boulton AJ. (2005) Evaluation of removable and irremovable cast walkers in the healing of diabetic foot wounds: a randomized controlled trial. Diabetes Care 28 (3) 551-4

Caravaggi,C. Faglia,E. De,Giglio R. Mantero,M. Quarantiello,A. Sommariva,E. Gino,M. Pritelli,C. et al (2000) Effectiveness and safety of a nonremovable fiberglass off-bearing cast versus a therapeutic shoe in the treatment of neuropathic foot ulcers: a randomized study, Diabetes Care 23 (12) 1746-51

Faglia,E. Caravaggi,C. Clerici,G. Sganzaroli,A. Curci,V. Vailati,W. Simonetti,D. Sommalvico,F. (2010) Effectiveness of removable walker cast versus nonremovable fiberglass off-bearing cast in the healing of diabetic plantar foot ulcer: a randomized controlled trial, Diabetes Care 33 (7) 1419-23.

Gutekunst,D.J. Hastings,M.K. Bohnert,K.L. Strube,M.J. Sinacore,D.R. (2011) Removable cast walker boots yield greater forefoot off-loading than total contact casts, Clinical Biomechanics 26 (6)649-54.

Zimny,S. Schatz,H. Pfohl,U. (2003) The effects of applied felted foam on wound healing and healing times in the therapy of neuropathic diabetic foot ulcers, Diabetic Medicine 20 (8) 622-25.

Zhang, Y., & Xing, S. Z. (2014). Treatment of Diabetic Foot Ulcers using Mepilex Lite Dressings: A Pilot Study. Experimental and Clinical Endocrinology & Diabetes, 122(04), 227-230.

Lavery, L. A., Higgins, K. R., La Fontaine, J., Zamorano, R. G., Constantinides, G. P., & Kim, P. J. (2014). Randomised clinical trial to compare total contact casts, healing sandals and a shear-reducing removable boot to heal diabetic foot ulcers. International wound journal.

Foster AVM, Greenhill MT, Edmonds ME (1994) Comparing two dressings in the treatment of diabetic foot ulcers. Journal of Wound Care 3: 224-8.

Piaggesi A, Baccetti F, Rizzo L et al. (2001) Sodium carboxyl-methyl-cellulose dressings in the management of deep ulcerations of diabetic foot. Diabetic Medicine 18: 320-4.

Jude EB, Apelqvist J, Spraul M et al. (2007) Prospective randomized controlled study of Hydrofiber dressing containing ionic silver or calcium alginate dressings in non-ischaemic diabetic foot ulcers. Diabetic Medicine 24: 280-8.

Clever, H. U., & Dreyer, M. (1996). Comparing two wound dressings for the treatment of neuropathic diabetic foot ulcers. In Proceedings of the 5th European Conference on Advances in Wound Management (pp. 201-203).

Veves, A, Sheehan, P, Pham, HT A randomized, controlled trial of Promogran (a collagen/oxidized regenerated cellulose dressing) vs standard treatment in the management of diabetic foot ulcers. Archives of Surgery 2002; 137: 822-27.

Jeffcoate, WJ, Price, PE, Phillips, CJ, Game, FL, Mudge, E, Davies, S, Amery, CM, Edmonds, ME, Gibby, OM, Johnson, AB, Jones, GR, Masson, E, Patmore, JE, Price, D, Rayman, G, Harding, KG Randomised controlled trial of the use of the three dressing preparations in the management of chronic ulceration of the foot in diabetes. Health Technology Assessment 2009; 13(54): 1-110.

Van De Weg, FB, Van Der Windt, DA, Vahl, AC Wound healing: total contact cast vs. custom-made temporary footwear for patients with diabetic foot ulceration. Prosthetics & Orthotics International 2008; 32: 3-11.

Armstrong, DG, Nguyen, HC, Lavery, LA, van Schie, CH, Boulton, AJ, Harkless, LB Off-loading the diabetic foot wound: a randomized clinical trial.[Erratum appears in Diabetes Care 2001 Aug;24(8):1509]. Diabetes Care 2001; 24: 1019-22.

Piaggesi, A, Macchiarini, S, Rizzo, L, Palumbo, F, Tedeschi, A, Nobili, LA, Leporati, E, Scire, V, Teobaldi, I, Del, PS An off-the-shelf instant contact casting device for the management of diabetic foot ulcers: a randomized prospective trial versus traditional fiberglass cast. Diabetes Care 2007; 30: 586-90.

Katz, IA, Harlan, A, Miranda-Palma, B, Prieto-Sanchez, L, Armstrong, DG, Bowker, JH, Mizel, MS, Boulton, AJ A randomized trial of two irremovable off-loading devices in the management of plantar neuropathic diabetic foot ulcers. Diabetes Care 2005; 28: 555-59.

Mueller, MJ, Diamond, JE, Sinacore, DR, Delitto, A, Blair, VP, III, Drury, DA, Rose, SJ Total contact casting in treatment of diabetic plantar ulcers. Controlled clinical trial. Diabetes Care 1989; 12: 384-88.

Nube¸, VL, Molyneaux, L, Bolton, T, Clingan, T, Palmer, E, Yue, DK The use of felt deflective padding in the management of plantar hallux and forefoot ulcers in patients with diabetes. Foot 2006; 16: 38-44.

5.11 Review question 11 included studies

Clay,P.G. Graham,M.R. Lindsey,C.C. Lamp,K.C. Freeman,C. Glaros,A. (2004) Clinical efficacy, tolerability, and cost savings associated with the use of open-label metronidazole plus ceftriaxone once daily compared with ticarcillin/clavulanate every 6 hours as empiric treatment for diabetic lower-extremity infections in older males, American Journal of Geriatric Pharmacotherapy 2 (3)181-89

Schaper,N.C. Dryden,M. Kujath,P. Nathwani,D. Arvis,P. Reimnitz,P. Alder,J.; Gyssens,I.C. (2012) Efficacy and safety of IV/PO moxifloxacin and IV piperacillin/tazobactam followed by PO amoxicillin/clavulanic acid in the treatment of diabetic foot infections: results of the RELIEF study, Infection 41 (1) 175-86.

Saltoglu,N. Dalkiran,A. Tetiker,T. Bayram,H. Tasova,Y. Dalay,C. Sert,M. (2010) Piperacillin/tazobactam versus imipenem/cilastatin for severe diabetic foot infections: a prospective, randomized clinical trial in a university hospital, Clinical Microbiology & Infection 16 (8) 1252-57.

Siami,G. Christou,N. Eiseman,I. Tack,K.J. (2001) Clinafloxacin versus piperacillin-tazobactam in treatment of patients with severe skin and soft tissue infections, Antimicrobial Agents & Chemotherapy 45 (2) 525-31.

Vick-Fragoso,R. Hernandez-Oliva,G. Cruz-Alcazar,J. Amabile-Cuevas,C.F. Arvis,P. Reimnitz,P. Bogner,J.R.(2009) Efficacy and safety of sequential intravenous/oral moxifloxacin vs intravenous/oral amoxicillin/clavulanate for complicated skin and skin structure infections, Infection 37 (5) 407-17.

Lipsky,B.A. Kuss,M. Edmonds,M. Reyzelman,A. Sigal,F. (2012) Topical application of a gentamicin-collagen sponge combined with systemic antibiotic therapy for the treatment of diabetic foot infections of moderate severity: a randomized, controlled, multicenter clinical trial.Journal of the American Podiatric Medical Association 102 (4) 323-32.

File, Jr and Tan,J.S. (1983) Amdinocillin plus cefoxitin versus cefoxitin alone in therapy of mixed soft tissue infections (including diabetic foot infections) American Journal of Medicine 75 (2 A) 100-105.

Bradsher, T and Snow, J.M. (1984) Ceftriaxone treatment of skin and soft tissue infections in a once daily regimen, American Journal of Medicine 77 (4) 63-67.

Lipsky, BA, Baker, PD, Landon, GC, Fernau, R Antibiotic therapy for diabetic foot infections: comparison of two parenteral-to-oral regimens. Clinical Infectious Diseases 1997; 24: 643-48.

Grayson, ML, Gibbons, GW, Habershaw, GM, Freeman, DV, Pomposelli, FB, Rosenblum, BI, Levin, E, Karchmer, AW Use of ampicillin/sulbactam versus imipenem/cilastatin in the treatment of limb-threatening foot infections in diabetic patients.[Erratum appears in Clin Infect Dis 1994 Oct;19(4):820]. Clinical Infectious Diseases 1994; 18: 683-93.

Erstad, BL, McIntyre, J Prospective, randomized comparison of ampicillin/sulbactam and cefoxitin for diabetic foot infections. Vascular Surgery 1997; 31: 419-26.

Harkless, L, Boghossian, J, Pollak, R, Caputo, W, Dana, A, Gray, S, Wu, D An open-label, randomized study comparing efficacy and safety of intravenous piperacillin/tazobactam and ampicillin/sulbactam for infected diabetic foot ulcers. Surgical Infections 2005; 6: 27-40.

Tan, JS, Wishnow, RM, Talan, DA, Duncanson, FP, Norden, CW Treatment of hospitalized patients with complicated skin and skin structure infections: double-blind, randomized, multicenter study of piperacillin-tazobactam versus ticarcillin-clavulanate. The Piperacillin/Tazobactam Skin and Skin Structure Study Group. Antimicrobial Agents & Chemotherapy 1993; 37: 1580-1586.

Bouter, KP, Visseren, FLJ, Van Loenhout, RMM, Bartelink, AKM, Erkelens, DW, Diepersloot, RJA Treatment of diabetic foot infection: An open randomised comparison of imipenem/cilastatin and piperacillin/clindamycin combination therapy. International Journal of Antimicrobial Agents 1996; 7: 143-47.

Lipsky, BA, Giordano, P, Choudhri, S, Song, J Treating diabetic foot infections with sequential intravenous to oral moxifloxacin compared with piperacillin-tazobactam/amoxicillin-clavulanate. Journal of Antimicrobial Chemotherapy 2007; 60: 370-376.

1 Lipsky, BA, Itani, K, Norden, C, Linezolid Diabetic Foot Infections Study Group Treating foot
2 infections in diabetic patients: a randomized, multicenter, open-label trial of linezolid versus
3 ampicillin-sulbactam/amoxicillin-clavulanate. Clinical Infectious Diseases 2004; 38: 17-24.

4 Lipsky, BA, Stoutenburgh, U Daptomycin for treating infected diabetic foot ulcers: evidence
5 from a randomized, controlled trial comparing daptomycin with vancomycin or semi-synthetic
6 penicillins for complicated skin and skin-structure infections. Journal of Antimicrobial
7 Chemotherapy 2005; 55: 240-245.

8 Lipsky, BA, Armstrong, DG, Citron, DM, Tice, AD, Morgenstern, DE, Abramson, MA
9 Ertapenem versus piperacillin/tazobactam for diabetic foot infections (SIDESTEP):
10 prospective, randomised, controlled, double-blinded, multicentre trial. Lancet 2005; 366:
11 1695-703

12 Hughes, CE, Johnson, CC, Bamberger, DM, Reinhardt, JF, Peterson, LR, Mulligan, ME,
13 Gerding, DN, George, WL, Finegold, SM Treatment and long-term follow-up of foot infections
14 in patients with diabetes or ischemia: a randomized, prospective, double-blind comparison of
15 cefoxitin and ceftizoxime. Clinical Therapeutics 1987; 10: Suppl-49.

16 Lipsky BA, Pecoraro RE, Larson SA et al. (1990) Outpatient management of uncomplicated
17 lower-extremity infections in diabetic patients. Archives of Internal Medicine 150: 790-7.

18 Lauf, L., Ozsvár, Z., Mitha, I., Regöly-Mérei, J., Embil, J. M., Cooper, A., ... & Maroko, R.
19 (2014). Phase 3 study comparing tigecycline and ertapenem in patients with diabetic foot
20 infections with and without osteomyelitis. Diagnostic microbiology and infectious disease,
21 78(4), 469-480.

5.12.2 Review question 12 included studies

23 Edmonds, M. (2009). Apligraf in the treatment of neuropathic diabetic foot ulcers. The
24 international journal of lower extremity wounds, 8(1), 11-18.

25 Abidia, A., Laden, G., Kuhan, G., Johnson, B. F., Wilkinson, A. R., Renwick, P. M., ... &
26 McCollum, P. T. (2003). The role of hyperbaric oxygen therapy in ischaemic diabetic lower
27 extremity ulcers: a double-blind randomised-controlled trial. European Journal of Vascular
28 and Endovascular Surgery, 25(6), 513-518.

29 Ma, L., Li, P., Shi, Z., Hou, T., Chen, X., & Du, J. (2013). A prospective, randomized,
30 controlled study of hyperbaric oxygen therapy: effects on healing and oxidative stress of
31 ulcer tissue in patients with a diabetic foot ulcer.Ostomy/wound management, 59(3), 18-24.

32 Löndahl, M., Katzman, P., Nilsson, A., & Hammarlund, C. (2010). Hyperbaric oxygen therapy
33 facilitates healing of chronic foot ulcers in patients with diabetes. Diabetes care, 33(5), 998-
34 1003.

35 Löndahl, M., Landin-Olsson, M., & Katzman, P. (2011). Hyperbaric oxygen therapy improves
36 health-related quality of life in patients with diabetes and chronic foot ulcer. Diabetic
37 Medicine, 28(2), 186-190.

38 Katarina, H., Magnus, L., Per, K., & Jan, A. (2009). Diabetic persons with foot ulcers and
39 their perceptions of hyperbaric oxygen chamber therapy. Journal of clinical nursing, 18(14),
40 1975-1985.

41 Faglia, E., Favales, F., Aldeghi, A., Calia, P., Quarantiello, A., Oriani, G., ... & Morabito, A.
42 (1996). Adjunctive systemic hyperbaric oxygen therapy in treatment of severe prevalently
43 ischemic diabetic foot ulcer: a randomized study. Diabetes care, 19(12), 1338-1343.

Gentzkow, G. D., Iwasaki, S. D., Hershon, K. S., Mengel, M., Prendergast, J. J., Ricotta, J. J., ... & Lipkin, S. (1996). Use of dermagraft, a cultured human dermis, to treat diabetic foot ulcers. Diabetes care, 19(4), 350-354.

Veves, A., Falanga, V., Armstrong, D. G., & Sabolinski, M. L. (2001). Graftskin, a Human Skin Equivalent, Is Effective in the Management of Noninfected Neuropathic Diabetic Foot Ulcers A prospective randomized multicenter clinical trial. Diabetes Care, 24(2), 290-295.

Veves,A., Pham,H.T., Rosenblum,B.I., Lyons,T.E., Giurini,J.M.. Evaluation of graftskin (Apligraf), a human skin equivalent, for the treatment of diabetic foot ulcers. American Diabetes Association, 59th Scientific Sessions; 1999, June; San Diego, CA 1999;():n. pag..

Sams,H.H. & Chen,J.. Graftskin treatment of difficult to heal diabetic foot ulcers: one center's experience. Dermatologic Surgery 2002;28(8):698-703.

Marston, W. A., Hanft, J., Norwood, P., & Pollak, R. (2003). The Efficacy and Safety of Dermagraft in Improving the Healing of Chronic Diabetic Foot Ulcers Results of a prospective randomized trial. Diabetes Care, 26(6), 1701-1705.

Hanft, J. R., & Surprenant, M. S. (2002). Healing of chronic foot ulcers in diabetic patients treated with a human fibroblast-derived dermis. The Journal of foot and ankle surgery, 41(5), 291-299.

Zelen, C. M., Serena, T. E., Denoziere, G., & Fetterolf, D. E. (2013). A prospective randomised comparative parallel study of amniotic membrane wound graft in the management of diabetic foot ulcers. International wound journal, 10(5), 502-507.

Caravaggi, C., De Giglio, R., Pritelli, C., Sommaria, M., Dalla Noce, S., Faglia, E., ... & Morabito, A. (2003). HYAFF 11-Based Autologous Dermal and Epidermal Grafts in the Treatment of Noninfected Diabetic Plantar and Dorsal Foot Ulcers A prospective, multicenter, controlled, randomized clinical trial.Diabetes Care, 26(10), 2853-2859.

Uccioli, L., Giurato, L., Ruotolo, V., Ciavarella, A., Grimaldi, M. S., Piaggesi, A., ... & Ghirlanda, G. (2011). Two-step autologous grafting using HYAFF scaffolds in treating difficult diabetic foot ulcers: results of a multicenter, randomized controlled clinical trial with long-term follow-up. The international journal of lower extremity wounds, 10(2), 80-85.

Rajendra Prasad Agrawal, Ashok Jhajharia, Niranjana Mohta, Rutba Dogra, Vineeta Chaudhari, Kailash Chandra Nayak “Use of a platelet derived growth factor gel in chronic diabetic foot ulcers” The Diabetic Foot Journal 2009, 12(2), 80-88.

Robson, M. C., Payne, W. G., Garner, W. L., Biundo, J., Giacalone, V. F., Cooper, D. M., & Ouyang, P. (2005). Integrating the Results of Phase IV (Postmarketing) Clinical Trial With Four Previous Trials Reinforces the Position that Regranex (Becaplermin) Gel 0.01% Is an Effective Adjunct to the Treatment of Diabetic Foot Ulcers. Journal of Applied Research, 5(1).

Smiell, J. M., Wieman, T. J., Steed, D. L., Perry, B. H., Sampson, A. R., & Schwab, B. H. (1999). Efficacy and safety of becaplermin (recombinant human platelet-derived growth factor-BB) in patients with nonhealing, lower extremity diabetic ulcers: a combined analysis of four randomized studies. Wound Repair and Regeneration, 7(5), 335-346.

Wieman, T. J., Smiell, J. M., & Su, Y. (1998). Efficacy and Safely of a Topical Gel Formulation of Recombinant Human Platelet-Derived Growth Factor-BB (Becaplermin) in Patients With Chronic Neuropathic Diabetic Ulcers: A phase III randomized placebo-controlled double-blind study. Diabetes care, 21(5), 822-827.

Robson,M.C. & Steed,D.L.. Effects of transforming growth factor beta2 on wound healing in diabetic foot ulcers: a randomized controlled safety and dose-ranging trial. Journal of Applied Research 2002;2(2):133-45.

Steed, D. L. (2006). Clinical evaluation of recombinant human platelet-derived growth factor for the treatment of lower extremity ulcers. Plastic and reconstructive surgery, 117(7S), 143S-149S.

Hardikar, J. V., Reddy, Y. C., Bung, D. D., Varma, N., Shilotri, P. P., Prasad, E. D., ... & Suresh, K. R. (2005). Efficacy of recombinant human platelet-derived growth factor (rhPDGF) based gel in diabetic foot ulcers: a randomized, multicenter, double-blind, placebo-controlled study in India. WOUNDS-A COMPENDIUM OF CLINICAL RESEARCH AND PRACTICE, 17(6), 141-152.

Jaiswal, S. S., Gambhir, R. P. S., Agrawal, A., & Harish, S. (2010). Efficacy of topical recombinant human platelet derived growth factor on wound healing in patients with chronic diabetic lower limb ulcers. Indian Journal of Surgery,72(1), 27-31.

Bhansali, A., Venkatesh, S., Dutta, P., Dhillon, M. S., Das, S., & Agrawal, A. (2009). Which is the better option: recombinant human PDGF-BB 0.01% gel or standard wound care, in diabetic neuropathic large plantar ulcers off-loaded by a customized contact cast?. Diabetes research and clinical practice, 83(1), e13-e16.

Robson, M. C., Steed, D. L., McPherson, J. M., & Pratt, B. M. (1999, August). Use of transforming growth factor-β2 (TGF-β2) in the treatment of chronic foot ulcers in diabetic patients. In 3rd Joint Meeting of the European Tissue Repair Society and Wound Healing Society. Bordeaux, France.

Richard, J. L., Parer-Richard, C., Daures, J. P., Clouet, S., Vannereau, D., Bringer, J., ... & Comte-Bardonnet, M. (1995). Effect of topical basic fibroblast growth factor on the healing of chronic diabetic neuropathic ulcer of the foot: a pilot, randomized, double-blind, placebo-controlled study. Diabetes Care, 18(1), 64-69.

Steed, D. L., Goslen, J. B., Holloway, G. A., Malone, J. M., Bunt, T. J., & Webster, M. W. (1992). Randomized prospective double-blind trial in healing chronic diabetic foot ulcers: CT-102 activated platelet supernatant, topical versus placebo. Diabetes Care, 15(11), 1598-1604.

Uchi, H., Igarashi, A., Urabe, K., Koga, T., Nakayama, J., Kawamori, R., ... & Furue, M. (2009). Clinical efficacy of basic fibroblast growth factor (bFGF) for diabetic ulcer. European Journal of Dermatology, 19(5), 461-468.

Hanft, J. R., Pollak, R. A., Barbul, A., Van Gils, C., Kwon, P. S., Gray, S. M., ... & Breen, T. J. (2008). Phase I trial on the safety of topical rhVEGF on chronic neuropathic diabetic foot ulcers. J Wound Care, 17(1), 30-2.

Steed, D. L., Ricotta, J. J., Prendergast, J. J., Kaplan, R. J., Webster, M. W., McGill, J. B., & Schwartz, S. L. (1995). Promotion and acceleration of diabetic ulcer healing by arginine-glycine-aspartic acid (RGD) peptide matrix. Diabetes Care, 18(1), 39-46.

Brigido, S. A., Boc, S. F., & Lopez, R. C. (2004). Effective management of major lower extremity wounds using an acellular regenerative tissue matrix: a pilot study. Orthopedics, 27(1 Suppl), s145-9.

Brigido, S. A. (2006). The use of an acellular dermal regenerative tissue matrix in the treatment of lower extremity wounds: a prospective 16-week pilot study. International wound journal, 3(3), 181-187.

Reyzelman, A., Crews, R. T., Moore, J. C., Moore, L., Mukker, J. S., Offutt, S., ... & Armstrong, D. G. (2009). Clinical effectiveness of an acellular dermal regenerative tissue matrix compared to standard wound management in healing diabetic foot ulcers: a prospective, randomised, multicentre study. International wound journal, 6(3), 196-208.

Akbari, A., Moodi, H., Ghiasi, F., Sagheb, H. M., & Rashidi, H. (2007). Effects of vacuum-compression therapy on healing of diabetic foot ulcers: randomized controlled trial. Journal of Rehabilitation Research & Development, 44(5).

Blume, P., Driver, V. R., Tallis, A. J., Kirsner, R. S., Kroeker, R., Payne, W. G., ... & Sosnowski, B. K. (2011). Formulated collagen gel accelerates healing rate immediately after application in patients with diabetic neuropathic foot ulcers. Wound Repair and Regeneration, 19(3), 302-308.

Kaviani, A., Djavid, G. E., Ataie-Fashtami, L., Fateh, M., Ghodsi, M., Salami, M., ... & Larijani, B. (2011). A randomized clinical trial on the effect of low-level laser therapy on chronic diabetic foot wound healing: a preliminary report.Photomedicine and laser surgery, 29(2), 109-114.

Yingsakmongkol, N., Maraprygsavan, P., & Sukosit, P. (2011). Effect of WF10 (Immunokine) on Diabetic Foot Ulcer Therapy: A Double-blind, Randomized, Placebo-controlled Trial. The Journal of Foot and Ankle Surgery, 50(6), 635-640.

Yingsakmongkol, N., Clinical outcomes of WF10 adjunct to standard treatment of diabetic foot ulcers. Journal of Wound Care 134/;22(3):130-32.

Han, S. K., Kim, H. R., & Kim, W. K. (2010). The treatment of diabetic foot ulcers with uncultured, processed lipoaspirate cells: a pilot study. Wound Repair and Regeneration, 18(4), 342-348.

Tallis, A., Motley, T. A., Wunderlich, R. P., Dickerson Jr, J. E., Waycaster, C., & Slade, H. B. (2013). Clinical and Economic Assessment of Diabetic Foot Ulcer Debridement with Collagenase: Results of a Randomized Controlled Study. Clinical therapeutics, 35(11), 1805-1820.

Moretti, B., Notarnicola, A., Maggio, G., Moretti, L., Pascone, M., Tafuri, S., & Patella, V. (2009). The management of neuropathic ulcers of the foot in diabetes by shock wave therapy. BMC musculoskeletal disorders, 10(1), 54.

Lyons, T. E., Miller, M. S., Serena, T., Sheehan, P., Lavery, L., Kirsner, R. S., ... & Veves, A. (2007). Talactoferrin alfa, a recombinant human lactoferrin promotes healing of diabetic neuropathic ulcers: a phase 1/2 clinical study. The American journal of surgery, 193(1), 49-54.

Veves, A., Sheehan, P., & Pham, H. T. (2002). A randomized, controlled trial of Promogran (a collagen/oxidized regenerated cellulose dressing) vs standard treatment in the management of diabetic foot ulcers. Archives of Surgery,137(7), 822-827.

You, H. J., Han, S. K., Lee, J. W., & Chang, H. (2012). Treatment of diabetic foot ulcers using cultured allogeneic keratinocytes—A pilot study. Wound Repair and Regeneration, 20(4), 491-499.

Jeffcoate, W.J., Price, P. E., Phillips, C. J., Game, F. L., Mudge, E., Davies, S., Amery, C. M., ... & Harding, K. G. (2009). Randomised controlled trial of the use of three dressing preparations in the management of chronic ulceration of the foot in diabetes. Prepress Projects Limited.

Driver, V. R., Hanft, J., Fylling, C. P., & Beriou, J. M. (2006). A prospective, randomized, controlled trial of autologous platelet-rich plasma gel for the treatment of diabetic foot ulcers. Ostomy Wound Management, 52(6), 68.

Tom, W. L., Peng, D. H., Allaei, A., Hsu, D., & Hata, T. R. (2005). The effect of short-contact topical tretinoin therapy for foot ulcers in patients with diabetes.Archives of dermatology, 141(11), 1373-1377.

Fife, C., Mader, J. T., Stone, J., Brill, L., Satterfield, K., Norfleet, A., ... & Carney, D. H. (2007). Thrombin peptide Chrysalin® stimulates healing of diabetic foot ulcers in a placebo-controlled phase I/II study. Wound repair and regeneration, 15(1), 23-34.

Peters, E. J., Lavery, L. A., Armstrong, D. G., & Fleischli, J. G. (2001). Electric stimulation as an adjunct to heal diabetic foot ulcers: a randomized clinical trial.Archives of physical medicine and rehabilitation, 82(6), 721-725.

Marfella, R., Sasso, F. C., Rizzo, M. R., Paolisso, P., Barbieri, M., Padovano, V., ... & Canonico, S. (2012). Dipeptidyl peptidase 4 inhibition may facilitate healing of chronic foot ulcers in patients with type 2 diabetes. Experimental diabetes research, 2012.

Gottrup, F., Cullen, B. M., Karlsmark, T., Bischoff-Mikkelsen, M., Nisbet, L., & Gibson, M. C. (2013). Randomized controlled trial on collagen/oxidized regenerated cellulose/silver treatment. Wound Repair and Regeneration, 21(2), 216-225.

Alvarez, O. M., Rogers, R. S., Booker, J. G., & Patel, M. (2003). Effect of noncontact normothermic wound therapy on the healing of neuropathic (diabetic) foot ulcers: an interim analysis of 20 patients. The Journal of foot and ankle surgery, 42(1), 30-35.

Larijani, B., Heshmat, R. A. M. I. N., Bahrami, A., Delshad, H., Mohammad, K., Heidarpour, R., ... & Madani, S. H. (2008). Effects of intravenous Semelil (ANGIPARSTM) on diabetic foot ulcers healing: A multicenter clinical trial.DARU Journal of Pharmaceutical Sciences, 16(Suppl. 1).

Bahrami, A., Kamali, K., Ali-Asgharzadeh, A., Hosseini, P., Heshmat, R. A. M. I. N., Gharibdoust, F., ... & Larijani, B. (2008). Clinical application of oral form of ANGIPARSTM and in combination with topical form as a new treatment for diabetic foot ulcers: A randomized clinical trial. DARU Journal of Pharmaceutical Sciences, 16(Suppl. 1).

Mulder, G. D., Patt, L. M., Sanders, L., Rosenstock, J., Altman, M. I., Hanley, M. E., & Duncan, G. W. (1994). Enhanced healing of ulcers in patients with diabetes by topical treatment with glycyl-l-histidyl-l-lysine copper. Wound Repair and Regeneration, 2(4), 259-269.

Bashmakov, Y. K., Assaad-Khalil, S. H., Abou Seif, M., Udumyan, R., Megallaa, M., Rohoma, K. H., ... & Petyaev, I. M. (2014). Resveratrol Promotes Foot Ulcer Size Reduction in Type 2 Diabetes Patients. International Scholarly Research Notices, 2014.

Siavash, M., Shokri, S., Haghighi, S., Shahtalebi, M. A., & Farajzadehgan, Z. (2013). The efficacy of topical royal jelly on healing of diabetic foot ulcers: a double-blind placebo-controlled clinical trial. International wound journal.

Lavery, L. A., Fulmer, J., Shebetka, K. A., Regulski, M., Vayser, D., Fried, D., ... & Nadarajah, J. (2014). The efficacy and safety of Grafix® for the treatment of chronic diabetic foot ulcers: results of a multi-centre, controlled, randomised, blinded, clinical trial. International wound journal, 11(5), 554-560.

Gomez-Villa, R., Aguilar-Rebolledo, F., Lozano-Platonoff, A., Teran-Soto, J. M., Fabian-Victoriano, M. R., Kresch-Tronik, N. S., ... & Contreras-Ruiz, J. (2014). Efficacy of intralesional recombinant human epidermal growth factor in diabetic foot ulcers in Mexican patients: A randomized double-blinded controlled trial. Wound Repair and Regeneration, 22(4), 497-503.

Mueller, M. J., Sinacore, D. R., Hastings, M. K., Strube, M. J., & Johnson, J. E. (2003). Effect of Achilles Tendon Lengthening on Neuropathic Plantar Ulcers* A Randomized Clinical Trial. The Journal of Bone & Joint Surgery, 85(8), 1436-1445.

Blume, P. A., Walters, J., Payne, W., Ayala, J., & Lantis, J. (2008). Comparison of negative pressure wound therapy using vacuum-assisted closure with advanced moist wound therapy

in the treatment of Diabetic Foot Ulcers A multicenter randomized controlled trial. Diabetes care, 31(4), 631-636.

5.13 Review question 13 included studies

Ross, A. J., Mendicino, R. W., & Catanzariti, A. R. (2013). Role of Body Mass Index in Acute Charcot Neuroarthropathy. The Journal of Foot and Ankle Surgery, 52(1), 6-8.

Foltz, K. D., Fallat, L. M., & Schwartz, S. (2004). Usefulness of a brief assessment battery for early detection of Charcot foot deformity in patients with diabetes. The Journal of foot and ankle surgery, 43(2), 87-92.

Stuck, R. M., Sohn, M. W., Budiman-Mak, E., Lee, T. A., & Weiss, K. B. (2008). Charcot arthropathy risk elevation in the obese diabetic population. The American journal of medicine, 121(11), 1008-1014.

5.14 Review question 14 included studies

MILLS, J. L., BECKETT, W. C., & TAYLOR, S. M. (1991). The diabetic foot: consequences of delayed treatment and referral. Southern Medical Journal, 84(8), 970-974.

Alexandrescu, V., Hubermont, G., Coessens, V., Philips, Y., Guillaumie, B., Ngongang, C., ... & Macoir, C. (2008). Why a multidisciplinary team may represent a key factor for lowering the inferior limb loss rate in diabetic neuro-ischaemic wounds: application in a departmental institution. Acta chirurgica Belgica, 109(6), 694-700.

Edmonds, M. E., Blundell, M. P., Morris, M. E., Thomas, E. M., Cotton, L. T., & Watkins, P. J. (1986). Improved survival of the diabetic foot: the role of a specialised foot clinic. QJM, 60(2), 763-771.

Weck, M., Slesaczeck, T., Paetzold, H., Muench, D., Nanning, T., Von Gagern, G., ... & Hanefeld, M. (2013). Structured health care for subjects with diabetic foot ulcers results in a reduction of major amputation rates. Cardiovascular diabetology, 12(1), 45**.**

Rerkasem, K. (2008). Reducing lower extremity amputations due to diabetes: the application of diabetic-foot protocol in Chiang Mai University Hospital. The international journal of lower extremity wounds.

Larsson, J., Stenström, A., Apelqvist, J., & Agardh, C. D. (1995). Decreasing incidence of major amputation in diabetic patients: a consequence of a multidisciplinary foot care team approach?. Diabetic Medicine, 12(9), 770-776.

Armstrong, D. G., Bharara, M., White, M., Lepow, B., Bhatnagar, S., Fisher, T., ... & Mills, J. L. (2012). The impact and outcomes of establishing an integrated interdisciplinary surgical team to care for the diabetic foot. Diabetes/metabolism research and reviews, 28(6), 514-518.

Yesil, S., Akinci, B., Bayraktar, F., Havitcioglu, H., Karabay, O., Yapar, N., ... & Eraslan, S. (2009). Reduction of major amputations after starting a multidisciplinary diabetic foot care team: single centre experience from Turkey. Experimental and clinical endocrinology & diabetes, 117(7), 345.

Faglia, E., Favales, F., Aldeghi, A., Calia, P., Quarantiello, A., Barbano, P., ... & Morabito, A. (1998). Change in major amputation rate in a center dedicated to diabetic foot care during the 1980s: prognostic determinants for major amputation. Journal of Diabetes and its Complications, 12(2), 96-102.

Trautner, C., Haastert, B., Mauckner, P., Gätcke, L. M., & Giani, G. (2007). Reduced Incidence of Lower-Limb Amputations in the Diabetic Population of a German City, 1990–2005 Results of the Leverkusen Amputation Reduction Study (LARS). Diabetes Care, 30(10), 2633-2637.

Nather, A., Bee, C. S., Lin, W. K., Valerie, C. X. B., Liang, S., Tambyah, P. A., ... & Nambiar, A. (2010). Value of team approach combined with clinical pathway for diabetic foot problems: a clinical evaluation. Diabetic foot & ankle, 1.

Hedetoft, C., Rasmussen, A., Fabrin, J., & Kølendorf, K. (2009). Four-fold increase in foot ulcers in type 2 diabetic subjects without an increase in major amputations by a multidisciplinary setting. Diabetes research and clinical practice, 83(3), 353-357.

Chiu, C. C., Huang, C. L., Weng, S. F., Sun, L. M., Chang, Y. L., & Tsai, F. C. (2011). A multidisciplinary diabetic foot ulcer treatment programme significantly improved the outcome in patients with infected diabetic foot ulcers. Journal of Plastic, Reconstructive & Aesthetic Surgery, 64(7), 867-872.

Cahn, A., Elishuv, O., & Olshtain-Pops, K. (2014). Establishing a multidisciplinary diabetic foot team in a large tertiary hospital: a Workshop. Diabetes/metabolism research and reviews.

Williams, D. T., Majeed, M. U., Shingler, G., Akbar, M. J., Adamson, D. G., & Whitaker, C. J. (2012). A diabetic foot service established by a department of vascular surgery: an observational study. Annals of vascular surgery, 26(5), 700-706.

Setacci, C., Sirignano, P., Mazzitelli, G., Setacci, F., Messina, G., Galzerano, G., & de Donato, G. (2013). Diabetic foot: surgical approach in emergency. International journal of vascular medicine, 2013.

Elgzyri, T., Larsson, J., Nyberg, P., Thörne, J., Eriksson, K. F., & Apelqvist, J. (2014). Early Revascularization after Admittance to a Diabetic Foot Center Affects the Healing Probability of Ischemic Foot Ulcer in Patients with Diabetes. European Journal of Vascular and Endovascular Surgery, 48(4), 440-446.

Rubio, J. A., Aragón-Sánchez, J., Jiménez, S., Guadalix, G., Albarracín, A., Salido, C., ... & Álvarez, J. (2014). Reducing Major Lower Extremity Amputations After the Introduction of a Multidisciplinary Team for the Diabetic Foot. The international journal of lower extremity wounds, 13(1), 22-26.

5.15.2 Review question 15 included studies

Chantelau, E. A., & Richter, A. (2013). The acute diabetic Charcot foot managed on the basis of magnetic resonance imaging–a review of 71 cases.Swiss Med Wkly, 143, w13831.

Chantelau, E., & Poll, L. W. (2006). Evaluation of the diabetic Charcot foot by MR imaging or plain radiography-an observational study. Experimental and clinical endocrinology & diabetes, 114(08), 428-431.

Chantelau, E. (2005). The perils of procrastination: effects of early vs. delayed detection and treatment of incipient Charcot fracture. Diabetic medicine, 22(12), 1707-1712.

Basu, S., Chryssikos, T., Houseni, M., Malay, D. S., Shah, J., Zhuang, H., & Alavi, A. (2007). Potential role of FDG PET in the setting of diabetic neuro-osteoarthropathy: can it differentiate uncomplicated Charcot's neuroarthropathy from osteomyelitis and soft-tissue infection?. Nuclear medicine communications, 28(6), 465-472.

Moura-Neto, A., Fernandes, T. D., Zantut-Wittmann, D. E., Trevisan, R. O., Sakaki, M. H., Santos, A. L. G., ... & Parisi, M. C. R. (2012). Charcot foot: skin temperature as a good

clinical parameter for predicting disease outcome.Diabetes research and clinical practice, 96(2), e11-e14.

Höpfner, S., Krolak, C., Kessler, S., Tiling, R., Brinkbäumer, K., Hahn, K., & Dresel, S. (2004). Preoperative imaging of Charcot neuroarthropathy in diabetic patients: comparison of ring PET, hybrid PET, and magnetic resonance imaging. Foot & ankle international, 25(12), 890-895.

Beltran, J., Campanini, D. S., Knight, C., & McCalla, M. (1990). The diabetic foot: magnetic resonance imaging evaluation. Skeletal radiology, 19(1), 37-41.

5.16 Review question 16 included studies

Pakarinen, T. K., Laine, H. J., Mäenpää, H., Mattila, P., & Lahtela, J. (2011). The Effect of Zoledronic Acid on the Clinical Resolution of Charcot Neuroarthropathy A pilot randomized controlled trial. Diabetes care, 34(7), 1514-1516.

Chantelau, E., & Schnabel, T. (1997). Palliative radiotherapy for acute osteoarthropathy of diabetic feet: a preliminary study. Practical Diabetes International, 14(6), 154-156.

Hanft, J. R., Goggin, J. P., Landsman, A., & Surprenant, M. (1998). The role of combined magnetic field bone growth stimulation as an adjunct in the treatment of neuroarthropathy/Charcot joint: an expanded pilot study. The Journal of foot and ankle surgery, 37(6), 510-515.

Shah, N. S., & De, S. D. (2011). Comparative analysis of uniplanar external fixator and retrograde intramedullary nailing for ankle arthrodesis in diabetic Charcot's neuroarthropathy. Indian journal of orthopaedics, 45(4), 359.

Bharath, R., Bal, A., Sundaram, S., Unnikrishnan, A. G., Praveen, V. P., Bhavani, N., ... & Kumar, H. (2013). A comparative study of zoledronic acid and once weekly Alendronate in the management of acute Charcot arthropathy of foot in patients with diabetes mellitus. Indian journal of endocrinology and metabolism, 17(1), 110.

Game, F. L., Catlow, R., Jones, G. R., Edmonds, M. E., Jude, E. B., Rayman, G., & Jeffcoate, W. J. (2012). Audit of acute Charcot’s disease in the UK: the CDUK study. Diabetologia, 55(1), 32-35.

Pakarinen, T. K., Laine, H. J., Honkonen, S. E., Peltonen, J., Oksala, H., & Lahtela, J. (2002). Charcot arthropathy of the diabetic foot. Current concepts and review of 36 cases. Scandinavian journal of surgery, 91(2), 195-201.

Clohisy, D. R., & Thompson, R. C. (1988). Fractures associated with neuropathic arthropathy in adults who have juvenile-onset diabetes. The Journal of Bone & Joint Surgery, 70(8), 1192-1200.

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