Appendix I: GRADE profiles

I.1 Review question 1 full GRADE profiles

GRADE profile 1: Key components of care

Quality assessment							Summary of findings			
							No of patients		Effect	Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control	Summary of results	
Outcome: Amputation										
1 [Cr]	Cohort	Serious[1]	no serious	no serious	Serious[2]	none	60	25	Percentage of major amputation: Intervention = 7%, control = 29%, p = 0.02	Very low
1 [D]	Cohort	no serious	no serious	no serious	Serious[2]	none	56	89	Percentage of amputation (major and minor): Intervention = 7%, control = 13.7%	Very low
1 [L]	Cohort	Serious[1]	no serious	no serious	Serious[3]	none	294	NK[4]	The incidence of major amputations decreased by 78% from 16.1 to 3.6/100 000 (p<0.001).	Very low
1 [Ca]	Cohort	Serious[5]	no serious	no serious	Serious[6]	none	223	NK[7]	Lower extremity amputation rates: From 564.3/100,000 persons in the 1st year to 176.0/100,000 persons in the 5th year.	Very low
1 [Dr]	Cohort	Serious[5]	no serious	no serious	Serious[6]	none	223	NK[7]	Lower extremity amputation rates: From 9.9/1000 persons in the 1st year to 1.8/1000 persons in the 5th year.	Very low
Hospital length of stay										
1 [Cr]	Cohort	Serious[1]	no serious	no serious	Serious[2]	none	60	25	Mean hospital length of stay (days): [year 1995]: Intervention = 5.4, control = 7.8, p < 0.05	Very low

									[year 1996]: Intervention = 3.6, control = 8.7, p < 0.05	
Hospital readmission										
1 [Cr]	Cohort	Serious[1]	no serious	no serious	Serious[2]	none	60	25	Percentage of hospital readmission: [year 1995]: Intervention = 7%, control = 18% [year 1996]: Intervention = 15%, control = 15%	Very low
Ulcer recurrence										
1 [D]	Cohort	no serious	no serious	no serious	Serious[2]	none	56	89	Percentage of ulcer recurrence: Intervention = 30.4%, control = 58.4%	Very low

[Ca] = Canavan et al. (2008): key components = Organized Diabetes Foot Care compared to standard care (composition of the organised care not described).

[Cr] = Crane et al. (1999): key components = Critical pathway approach to diabetic foot infections compared to standard care (the pathway was initiated in the emergency department utilizing committee-approved standing physician's orders and clinical progress records to facilitate transitions between departments).

[D] = Dargis et al. (1999): key components = Multidisciplinary approach compared to standard care (the multidisciplinary team staffed by a diabetologist, a rehabilitation physician, a podiatrist, orthopaedic, surgeons, and shoemakers).

[Dr] = Driver et al. (2005): key components = Multidisciplinary Foot Care (Limb Preservation Service Model) compared to 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).

[L] = Larsson et al. (1995): key components = Multidisciplinary Foot Care Team Approach compared to standard care (the team consisting of a diabetologist 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. A programme for patient and staff education was also started).

NK = not known

[1] Pre- and post- design with historical control.

[2] Small sample.

[3] Unable to assess as sample of historical control group unknown.

[4] Actual number unknown, only reported participants treated prior to 1983.

[5] Simple uncontrolled trend analysis over 5 years period.

[6] Unable to assess.

[7] Actual number unknown, not reported.

I.2 Review question 2 full GRADE profiles

A narrative review was performed of descriptive evidence for compositional models. Evidence was not subject to critical appraisal.

I.3 Review question 3 full GRADE profiles

1.1.1.1 Rates (and recurrent rates) of foot ulceration, infection and gangrene resulting from diabetes

Quality assessment							No of patients	Effect Rates of foot ulceration, infection and gangrene (results)	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	consideration	Intervention			
Ulceration										
Armstrong 1998	Observational prospective	No serious imprecision	no serious inconsistency	no serious inconsistency	very serious[2, 5, 8, 10]	none	341 people with diabetes all assessed by University of Texas Foot Classification system. Compliant group= 311 Non-compliant group= 30 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.	Rates (and recurrent rates) of foot ulceration, infection and gangrene resulting from diabetes When comparing the higher risk patients in each cohort (category 3), those in the non-compliant group were approximately 54 times more likely to ulcerate than patients who returned regularly for their scheduled care. (81.8% ulcer prevalence vs 5.4% p<0.0001) Odds ratio 54.0 Confidence interval 7.5-1,425.0)	VERY LOW	IMPORTANT

Group	Compliant group, n	Incidence of ulceration/1000/year	Non compliant group, n	Incidence of ulceration /1000/year
Foot category 0	108	0	10	0
Foot category 1	94	0	4	83.3
Foot category 2	72	3.5	5	66.6
Foot category 3	37	18.0	11	272.7
total	311	3.1	30	122.2

Patout 2000	Observational retrospective	No serious imprecision	no serious inconsistency	no serious inconsistency	very serious [2, 4, 7, 8, 10, 11]	none	All patients with a diagnosis of diabetes or related disorders with neuropathic foot complications referred from local and regional physicians within the Louisiana State Hospital system. Rates were given per patient year Comparison with standard care outcomes 1 year prior to enrolment in the LEAP program. Enrolment in a comprehensive diabetes lower-extremity amputation prevention programme. Assessment of risk and management.	Rates (and recurrent rates) of foot ulceration, infection and gangrene resulting from diabetes Comparison of 1 year of standard foot care and 1 year of comprehensive lower extremity prevention programme in 197 patients for the outcome of number of ulcer days rate per patient year (mean ± SD): Standard care period: 73.944 ± 17.245 CD-LEAP period: 37.513 ± 10.179 % change (paired t test comparison): 49%	VERY LOW	IMPORTANT
Dargis 1999	Observational prospective	No serious imprecision	no serious inconsistency	no serious inconsistency	very serious [2, 4, 5, 6]	none	A total of 145 patients with a past history of neuropathic foot ulcers but no evidence of peripheral vascular disease were followed for 2 years. Intervention group (n=56)= 30.4% Standard care group (n=89)= 58.4% A multidisciplinary foot clinic. Staff consisted of a diabetologist, rehabilitation physician, orthopaedic surgeon, podiatrist, and shoe makers.	Rates (and recurrent rates) of foot ulceration, infection and gangrene resulting from diabetes New recurrent ulceration presentations New ulcers and ulcers appearing at a previous ulcer site are included in the term recurrent ulcers, only the first recurrence was counted. Intervention group (n=56)= 30.4% Standard care group (n=89)= 58.4% Odds ratio (95% CI)= 0.31 (0.14-0.67), P<0.001 i.e. significant difference	VERY LOW	IMPORTANT
Driver 2010	Observational	No serious imprecision	no serious inconsistency	no serious inconsistency	very serious [2, 3, 4, 5, 6, 7, 8, 11]	none	Total n= 485 diabetic patients Number of people seen under podiatric specialist service=311 Number seen by non-limb preservation team service= 174 Referral to the limb protection team: employing: Podiatric and vascular surgery, a orthotist, a wound care nurse and a research unit.	Rates (and recurrent rates) of foot ulceration, infection and gangrene resulting from diabetes Ulceration Limb preservation team group= mean 1.8 per year Non-limb preservation team group= mean 2.7 ulcers per year Not statistically significant	VERY LOW	IMPORTANT

[1]Unclear if the reason for allocation was or was not related to any other confounding factors. It is unclear if groups were comparable at baseline including all major confounding factors as such data was not provided per group. Unclear if the comparison groups received the same care. Participants were not blinded to intervention allocation. Individuals administering care were not blinded to intervention allocation. Unclear if groups were comparable for compliance or intervention completion. Unclear if groups were comparable for availability of outcome data. A valid and reliable method may not have been used

[2] Non Randomised

[3]Unclear if groups were comparable at baseline for all prognostic factors, no attempt to balance groups for confounding factors. Or groups not comparable for all confounding factors.

[4]Unclear if comparison group received the same care apart from intervention studied

[5]Non Blinded

[6]Only crude incidence rates recorded, no analysis to adjust for confounding factors

[7]Unclear if groups were comparable for adherence, clinic attendance or treatment completion
[8]Unclear if groups were comparable for outcome data available or loss to follow up
[9]Groups were not comparable for length of observation or unclear if patients were followed up for a similar amount of time (or adjustments not made)
[10]No precise definition of outcome
[11]Method of determination of outcome not valid or reliable or unclear (for example; retrospective or administrative data set)
[12]Length of follow up/observation inappropriate/unclear

1.1.1.2 Resource use and costs (including referral rates)

Quality assessment							No of patients	Effect Resource use and costs (results)	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	consideration	Intervention			
Resource use and costs										
Gooday 2013	Observational prospective	No serious imprecision	no serious inconsistency	no serious inconsistency	very serious[2,3,4, 5, 6,7,8, 9]	none	Foot clinic activity increased from 4197 to 5270 people seen between the years 2005 and 2012. 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.Replacement of podiatry footcare team members with non-specialist community non-operative podiatrists for some of this time.Specialist staffing levels and activity levels were eventually restored more than 7 months after the original loss. This study shows the effect of the loss of these staff in a diabetic foot clinic.	Resource use and costs (including referral rates) At this institution a hospital bed day costs £275 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	VERY LOW	IMPORTANT
Patout 2000	Observational retrospective	No serious imprecision	no serious inconsistency	no serious inconsistency	very serious [2, 4, 7, 8,10, 11]	none	All patients with a diagnosis of diabetes or related disorders with neuropathic foot complications referred from local and regional physicians within the Louisiana State Hospital system. Rates were given per patient year Comparison with standard care outcomes 1 year prior to enrolment in the LEAP program. Enrolment in a comprehensive diabetes lower-extremity amputation prevention programme. Assessment of risk and management.	Resource use and costs (including referral rates) Comparison of 1 year of standard foot care and 1 year of comprehensive lower extremity prevention programme in 197 patients for the outcome of number of missed workdays rate per patient year (mean ± SD): Standard care period: 17.538 ± 9.356 CD-LEAP period: 5.273 ± 5.094 % change (paired t test comparison): 70%	VERY LOW	IMPORTANT

[1]Unclear if the reason for allocation was or was not related to any other confounding factors. It is unclear if groups were comparable at baseline including all major confounding factors as such data was not provided per group. Unclear if the comparison groups received the same care. Participants were not blinded to intervention allocation. Individuals administering care were not blinded to intervention allocation. Unclear if groups were comparable for compliance or intervention completion. Unclear if groups were comparable for availability of outcome data. A valid and reliable method may not have been used

[2] Non Randomised

[3]Unclear if groups were comparable at baseline for all prognostic factors, no attempt to balance groups for confounding factors. Or groups not comparable for all confounding factors.

[4]Unclear if comparison group received the same care apart from intervention studied

[5]Non Blinded

[6]Only crude incidence rates recorded, no analysis to adjust for confounding factors

[7]Unclear if groups were comparable for adherence, clinic attendance or treatment completion

[8]Unclear if groups were comparable for outcome data available or loss to follow up

[9]Groups were not comparable for length of observation or unclear if patients were followed up for a similar amount of time (or adjustments not made)

[10]No precise definition of outcome

[11]Method of determination of outcome not valid or reliable or unclear (for example; retrospective or administrative data set)

[12]Length of follow up/observation inappropriate/unclear

1.1.1.3 Rates of hospital admission for foot problems resulting from diabetes

Quality assessment							No of patients	Effect Rates of hospital admission (results)	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	consideration	Intervention			
Rates of hospital admission										

<table>
<tr>
<td>Gooday 2013</td>
<td>Observational prospective</td>
<td>No serious imprecision</td>
<td>no serious inconsistency</td>
<td>no serious inconsistency</td>
<td>very serious[2,3,4, 5, 6,7,8, 9]</td>
<td>none</td>
<td>Foot clinic activity increased from 4197 to 5270 people seen between the years 2005 and 2012. 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.Replacement of podiatry foot care team members with non-specialist community non-operative podiatrists for some of this time. Specialist staffing levels and activity levels were eventually restored more than 7 months after the original loss. This study shows the effect of the loss of these staff in a diabetic foot clinic.</td>
<td>Rates of hospital admission for foot problems resulting from diabetes
<table>
<tr><th>Year</th><th>Clinical activity (number of people seen)</th><th>Number of admissions</th><th>Admissions as a % of total activity</th><th>Total bed days</th><th>Mean length of hospital stay (±SD)</th></tr>
<tr><td>2005</td><td>2835</td><td>30</td><td>1</td><td>515</td><td>17.2 (9.2)</td></tr>
<tr><td>2006</td><td>2921</td><td>43</td><td>1.5</td><td>775</td><td>17.2 (19.2)</td></tr>
<tr><td>2007</td><td>3325</td><td>39</td><td>1.1</td><td>570</td><td>14.6 (11.3)</td></tr>
<tr><td>2008</td><td>4197</td><td>50</td><td>1.2</td><td>919</td><td>18.4 (16.8)</td></tr>
<tr><td>2009</td><td>4799</td><td>58</td><td>1.2</td><td>867</td><td>14.7 (11.3)</td></tr>
<tr><td>2010</td><td>4058</td><td>72</td><td>1.8</td><td>1194</td><td>16.5 (12.3)</td></tr>
<tr><td>2011</td><td>4294</td><td>41</td><td>0.95</td><td>838</td><td>20.4 (16.6)</td></tr>
<tr><td>2012</td><td>5270</td><td>45</td><td>0.89</td><td>733</td><td>16.2 (15.1)</td></tr>
</table>
</td>
<td>VERY LOW</td>
<td>IMPORTANT</td>
</tr>
<tr>
<td>Lavery 2005</td>
<td>Observational retrospective</td>
<td>No serious imprecision</td>
<td>no serious inconsistency</td>
<td>no serious inconsistency</td>
<td>very serious[2,3,4, 5, 7,8, 9, 10, 11]</td>
<td>none</td>
<td>2738 persons with diabetes

Incidence rates of amputation reported per 1000 diabetics per year

Implementation of a lower extremity disease management program consisting of screening and treatment protocols diabetic members in a managed care organization. Patients were stratified into high and low risk groups and implemented preventive or acute care protocols. Utilization 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.</td>
<td>Rates of hospital admission for foot problems resulting from diabetes

The number of foot-related hospital admissions decreased 37.8% from 22.86 per 1000 members per year to 14.23 (37.8%)
The number of skilled nursing facility admissions per 1000 members per year decreased 69.8%</td>
<td>VERY LOW</td>
<td>IMPORTANT</td>
</tr>
</table>

<table>
<tr>
<td>Birke 2003</td>
<td>Observational retrospective</td>
<td>No serious imprecision</td>
<td>no serious inconsistency</td>
<td>no serious inconsistency</td>
<td>very serious [2, 4, 5, 7, 10, 11]</td>
<td>none</td>
<td>All diabetic patients within the Louisiana State University Health Care Services Division Hospitals, data given per 100 person years.

Disease management initiative and
the 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.</td>
<td>Rates of hospital admission for foot problems resulting from diabetes

Foot related hospitalisation rates among Louisiana State University Health Care services Hospitals before 1998 and after 1999, the implementation of a disease management initiative with and without access to a diabetes foot program.
<table>
<tr><td>Facility</td><td>1998 Hospitalisation Rate (per 100 person-years)</td><td>1999 Hospitalisation rate (per 100 person-years)</td><td>Percent change</td></tr>
<tr><td>1</td><td>2.52</td><td>1.93</td><td>-23%</td></tr>
<tr><td>2</td><td>2.50</td><td>1.03</td><td>-59%</td></tr>
<tr><td>3</td><td>1.22</td><td>0.19</td><td>-84%</td></tr>
<tr><td>4</td><td>2.46</td><td>2.31</td><td>-6%</td></tr>
<tr><td>5</td><td>4.09</td><td>2.36</td><td>-42%</td></tr>
<tr><td>6</td><td>2.71</td><td>2.34</td><td>-14%</td></tr>
<tr><td>7</td><td>3.95</td><td>3.05</td><td>-23%</td></tr>
<tr><td>8</td><td>1.07</td><td>1.57</td><td>+47%</td></tr>
<tr><td colspan="4">Facility group:</td></tr>
<tr><td>DMI and DFP</td><td>2.44</td><td>1.37</td><td>-44%</td></tr>
<tr><td>DMI alone</td><td>2.71</td><td>2.29</td><td>-15%</td></tr>
</table>
</td>
<td>VERY LOW</td>
<td>IMPORTANT</td>
</tr>
</table>

Patout 2000	Observational retrospective	No serious imprecision	no serious inconsistency	no serious inconsistency	very serious [2, 4, 7, 8, 10, 11]	none	All patients with a diagnosis of diabetes or related disorders with neuropathic foot complications referred from local and regional physicians within the Louisiana State Hospital system. Rates were given per patient year Comparison with standard care outcomes 1 year prior to enrolment in the LEAP program. Enrolment in a comprehensive diabetes lower-extremity amputation prevention programme. Assessment of risk and management.	Rates of hospital admission for foot problems resulting from diabetes Comparison of 1 year of standard foot care and 1 year of comprehensive lower extremity prevention programme in 197 patients for the outcome of number of number of hospitalisations rate per patient year (mean ± SD): Standard care period: 0.3517 ± 0.106 CD-LEAP period: 0.0401 ± 0.031 % change (paired t test comparison): 89% Comparison of 1 year of standard foot care and 1 year of comprehensive lower extremity prevention programme in 197 patients for the outcome of number of emergency room visits rate per patient year (mean ± SD): Standard care period: 0.487 ± 0.236 CD-LEAP period: 0.091 ± 0.057 % change (paired t test comparison): 81%	VERY LOW	IMPORTANT
Dargis 1999	Observational prospective	No serious imprecision	no serious inconsistency	no serious inconsistency	very serious [2, 4, 5, 6]	none	A total of 145 patients with a past history of neuropathic foot ulcers but no evidence of peripheral vascular disease were followed for 2 years. Intervention group (n=56)= 30.4% Standard care group (n=89)= 58.4% A multidisciplinary foot clinic. Staff consisted of a diabetologist, rehabilitation physician, orthopaedic surgeon, podiatrist, and shoe makers.	Rates of hospital admission for foot problems resulting from diabetes Hospitalisation Intervention group (n=56)= 2 patients Standard care group (n=89)= 8 patients	VERY LOW	IMPORTANT

[1]Unclear if the reason for allocation was or was not related to any other confounding factors. It is unclear if groups were comparable at baseline including all major confounding factors as such data was not provided per group. Unclear if the comparison groups received the same care. Participants were not blinded to intervention allocation. Individuals administering care were not blinded to intervention allocation. Unclear if groups were comparable for compliance or intervention completion. Unclear if groups were comparable for availability of outcome data. A valid and reliable method may not have been used

[2] Non Randomised

[3]Unclear if groups were comparable at baseline for all prognostic factors, no attempt to balance groups for confounding factors. Or groups not comparable for all confounding factors.

[4]Unclear if comparison group received the same care apart from intervention studied

[5]Non Blinded

[6]Only crude incidence rates recorded, no analysis to adjust for confounding factors

[7]Unclear if groups were comparable for adherence, clinic attendance or treatment completion

[8]Unclear if groups were comparable for outcome data available or loss to follow up

[9]Groups were not comparable for length of observation or unclear if patients were followed up for a similar amount of time (or adjustments not made)

[10]No precise definition of outcome
[11]Method of determination of outcome not valid or reliable or unclear (for example; retrospective or administrative data set)
[12]Length of follow up/observation inappropriate/unclear

1.1.1.4 Length of hospital stay

Quality assessment							No of patients	Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	consideration	Intervention	Length of hospital stay (results)		
Length of hospital stay										
Gooday 2013	Observational prospective	No serious imprecision	no serious inconsistency	no serious inconsistency	very serious[2,3,4, 5, 6,7,8, 9]	none	Foot clinic activity increased from 4197 to 5270 people seen between the years 2005 and 2012. 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.Replacement of podiatry foot care team members with non-specialist community non-operative podiatrists for some of this time. Specialist staffing levels and activity levels were eventually restored more than 7 months after the original loss. This study shows the effect of the loss of these staff in a diabetic foot clinic.	Length of hospital stay See table above, which shows the drop in number of people seen when the number of staff dropped, but a corresponding increase in the proportion of people admitted, and an increase in their hospital length of stay. (see year 2010) Following staffing and activity levels returning to normal it took more than a year to reduce the number of hospital admissions directly from the diabetic foot clinic back to 45 in 2012 which reflected the average of the 5 years preceding the staff loss.	VERY LOW	IMPORTANT
Lavery 2005	Observational retrospective	No serious imprecision	no serious inconsistency	no serious inconsistency	very serious[2,3,4, 5, 7,8, 9, 10, 11]	none	2738 persons with diabetes Incidence rates of amputation reported per 1000 diabetics per year Implementation of a lower extremity disease management program consisting of screening and treatment protocols diabetic members in a managed care organization. Patients were stratified into high and low risk groups and implemented preventive or acute care protocols. Utilization 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.	Length of hospital stay The average inpatient length of stay was reduced 21.7% from 4.75 to 3.72 (p=<0.05) The length of skilled nursing facility bed days decreased 38.2% from 8.72 to 6.52 (p<0.05)	VERY LOW	IMPORTANT

Patout 2000	Observational retrospective	No serious imprecision	no serious inconsistency	no serious inconsistency	very serious [2, 4, 7, 8, 10, 11]	none	All patients with a diagnosis of diabetes or related disorders with neuropathic foot complications referred from local and regional physicians within the Louisiana State Hospital system. Rates were given per patient year Comparison with standard care outcomes 1 year prior to enrolment in the LEAP program. Enrolment in a comprehensive diabetes lower-extremity amputation prevention programme. Assessment of risk and management.	Length of hospital stay Comparison of 1 year of standard foot care and 1 year of comprehensive lower extremity prevention programme in 197 patients for the outcome of number of hospital days rate per patient year (mean ± SD): Standard care period: 3.756 ± 1.530 CD-LEAP period: 0.371 ± 0.366 % change (paired t test comparison): 90%	VERY LOW	IMPORTANT
Nason 2013	Observational prospective	No serious imprecision	no serious inconsistency	no serious inconsistency	very serious [2, 3, 4, 5, 6, 7, 9, 11]	none	Total n= 251 patients at high risk of foot ulceration (neuropathy or absent pulses with deformity), with active ulceration or previous minor amputations. A dedicated bi-weekly consultant led multidisciplinary foot protection clinic employing vascular surgery, endocrinology, orthopaedic surgery, podiatry, orthotics, tissue viability established in an Irish university hospital as part of an integrated foot protection service. 131 in the control period 120 in the study period	Hospital length of stay for foot problems resulting from diabetes The establishment of the foot protection clinic coincided with a reduction in the median length of stay for each admission with diabetic foot complication as the presenting complaint under diabetic foot clinic= 12 days (range 1-258) Control period= 15 days (range 4-194)	VERY LOW	IMPORTANT

[1]Unclear if the reason for allocation was or was not related to any other confounding factors. It is unclear if groups were comparable at baseline including all major confounding factors as such data was not provided per group. Unclear if the comparison groups received the same care. Participants were not blinded to intervention allocation. Individuals administering care were not blinded to intervention allocation. Unclear if groups were comparable for compliance or intervention completion. Unclear if groups were comparable for availability of outcome data. A valid and reliable method may not have been used

[2] Non Randomised

[3]Unclear if groups were comparable at baseline for all prognostic factors, no attempt to balance groups for confounding factors. Or groups not comparable for all confounding factors.

[4]Unclear if comparison group received the same care apart from intervention studied

[5]Non Blinded

[6]Only crude incidence rates recorded, no analysis to adjust for confounding factors

[7]Unclear if groups were comparable for adherence, clinic attendance or treatment completion

[8]Unclear if groups were comparable for outcome data available or loss to follow up

[9]Groups were not comparable for length of observation or unclear if patients were followed up for a similar amount of time (or adjustments not made)

[10]No precise definition of outcome

[11]Method of determination of outcome not valid or reliable or unclear (for example; retrospective or administrative data set)

[12]Length of follow up/observation inappropriate/unclear

1.1.1.5 Rates and extent of amputation

Quality assessment							No of patients	Effect Rates and extent of amputation (results)	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	consideration	Intervention			
Amputation										
Lavery 2005	Observational retrospective	No serious imprecision	no serious inconsistency	no serious inconsistency	very serious[2,3,4,5,7,8,9,10,11]	none	2738 persons with diabetes Incidence rates of amputation reported per 1000 diabetics per year Implementation of a lower extremity disease management program consisting of screening and treatment protocols diabetic members in a managed care organization. Patients were stratified into high and low risk groups and implemented preventive or acute care protocols. Utilization 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.	Rates and extent of amputation After the implementation of the health disease management program the incidence of amputations decreased 47.4% from 12.89 per 1000 diabetics per year to 6.18 (P=<0.05)	VERY LOW	IMPORTANT

<table>
<tr>
<td>Schraer 2004</td>
<td>Observational retrospective</td>
<td>No serious imprecision</td>
<td>no serious inconsistency</td>
<td>no serious inconsistency</td>
<td>very serious[2,3,4,5,6,7,8,10,11]</td>
<td>none</td>
<td>Alaska’s Indian, Eskimo and Aleut populations with diabetes. (1996-2001).

Pre-program= 4226 diabetic person-years
Post program= 5908 diabetic person-years

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 in anchorage. 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.</td>
<td>Rates and extent of amputation

All diabetes related amputations amongst all Alaska Natives with Diabetes 1996-2001
<table>
<tr><th>Ethnic group</th><th colspan="3">Pre-program (1996-1998)</th><th colspan="3">Post-program (1999-2001)</th><th>Reduction %</th><th>P value</th></tr>
<tr><th></th><th>Diabetic person years</th><th>Amputations</th><th>Incidence per 1000</th><th>Diabetic person-years</th><th>Amputations</th><th>Incidence per 1000</th><th></th><th></th></tr>
<tr><td>Eskimo</td><td>1355</td><td>9</td><td>6.6</td><td>1979.5</td><td>4</td><td>2.0</td><td>70%</td><td>0.047</td></tr>
<tr><td>Indian</td><td>1950</td><td>7</td><td>3.6</td><td>2655.5</td><td>8</td><td>3.0</td><td>16%</td><td>0.94</td></tr>
<tr><td>Aleut</td><td>921.5</td><td>16</td><td>17.4</td><td>1273</td><td>4</td><td>3.1</td><td>82%</td><td><0.001</td></tr>
<tr><td>All Native</td><td>4226.5</td><td>32</td><td>7.6</td><td>5908</td><td>16</td><td>2.7</td><td>64%</td><td><0.001</td></tr>
</table>
All diabetes related amputations amongst all Alaska Natives with Diabetes ≥10 years duration 1996-2001
<table>
<tr><th>Ethnic group</th><th colspan="3">Pre-program (1996-1998)</th><th colspan="3">Post-program (1999-2001)</th><th>Reduction %</th><th>P value</th></tr>
<tr><th></th><th>Diabetic person years</th><th>Amputations</th><th>Incidence per 1000</th><th>Diabetic person-years</th><th>Amputations</th><th>Incidence per 1000</th><th></th><th></th></tr>
<tr><td>Eskimo</td><td>405.5</td><td>7</td><td>17.3</td><td>501.5</td><td>4</td><td>8.0</td><td>54%</td><td>0.235</td></tr>
<tr><td>Indian</td><td>610.5</td><td>7</td><td>11.5</td><td>742</td><td>6</td><td>8.1</td><td>29%</td><td>0.722</td></tr>
<tr><td>Aleut</td><td>326</td><td>8</td><td>24.5</td><td>384.5</td><td>1</td><td>2.6</td><td>89%</td><td>0.01</td></tr>
<tr><td>All Native</td><td>1342</td><td>22</td><td>16.4</td><td>1628</td><td>11</td><td>6.8</td><td>59%</td><td>0.021</td></tr>
</table>
</td>
<td>VERY LOW</td>
<td>IMPORTANT</td>
</tr>
</table>

<table>
<tr>
<td>Armstrong 1998</td>
<td>Observational prospective</td>
<td>No serious imprecision</td>
<td>no serious inconsistency</td>
<td>no serious inconsistency</td>
<td>very serious[2, 5, 8, 10,</td>
<td>none</td>
<td>341 people with diabetes all assessed by University of Texas Foot Classification system.

Compliant group= 311
Non-compliant group= 30

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, ophthalmology, diabetes nurse education and nutritional and social services with an active vascular consultancy.</td>
<td>Rates and extent of amputation

When comparing the higher risk patients in each cohort (category 3), those in the non-compliant group were over 20 times more likely to receive amputation than category 3 compliant patients. (45.5% amputation prevalence vs 2.7% p<0.002) Odds ratio 2.5-819.0)
<table>
<tr><th>Group</th><th>Compliant group, n</th><th>Incidence of amputation/1000/year</th><th>Non compliant group, n</th><th>Incidence of amputation /1000/year</th></tr>
<tr><td>Foot category 0</td><td>108</td><td>0</td><td>10</td><td>0</td></tr>
<tr><td>Foot category 1</td><td>94</td><td>0</td><td>4</td><td>0</td></tr>
<tr><td>Foot category 2</td><td>72</td><td>0</td><td>5</td><td>0</td></tr>
<tr><td>Foot category 3</td><td>37</td><td>9.0</td><td>11</td><td>151.5</td></tr>
<tr><td>total</td><td>311</td><td>1.1</td><td>30</td><td>5.5</td></tr>
</table>
</td>
<td>VERY LOW</td>
<td>IMPORTANT</td>
</tr>
</table>

<table>
<tr>
<td>Birke 2003</td>
<td>Observational retrospective</td>
<td>No serious imprecision</td>
<td>no serious inconsistency</td>
<td>no serious inconsistency</td>
<td>very serious [2, 4, 5, 7, 10, 11]</td>
<td>none</td>
<td>all diabetic patients within the Louisiana State University Health Care Services Division Hospitals, data given per 100 person years.

Disease management initiative and
the 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.</td>
<td>Rates and extent of amputation

Foot-related

Foot related amputation rates among Louisiana State University Health Care services Hospitals before 1998 and after 1999, the implementation of a disease management initiative with and without access to a diabetes foot program.
<table>
<tr><th>Facility</th><th>1998 Amputation Rate (per 100 person-years)</th><th>1999 Amputation rate (per 100 person-years)</th><th>Percent change</th></tr>
<tr><td>1</td><td>0.92</td><td>0.90</td><td>-2</td></tr>
<tr><td>2</td><td>0.71</td><td>0.33</td><td>-54</td></tr>
<tr><td>3</td><td>1.22</td><td>0.00</td><td>-100</td></tr>
<tr><td>4</td><td>0.78</td><td>0.23</td><td>-71</td></tr>
<tr><td>5</td><td>2.32</td><td>0.99</td><td>-67</td></tr>
<tr><td>6</td><td>0.84</td><td>0.70</td><td>-17</td></tr>
<tr><td>7</td><td>1.94</td><td>1.56</td><td>-20</td></tr>
<tr><td>8</td><td>0.48</td><td>0.76</td><td>+58</td></tr>
<tr><td colspan="4">Facility group:</td></tr>
<tr><td>DMI and DFP</td><td>0.84</td><td>0.56</td><td>-33</td></tr>
<tr><td>DMI alone</td><td>1.13</td><td>0.80</td><td>-29</td></tr>
</table>
</td>
<td>VERY LOW</td>
<td>IMPORTANT</td>
</tr>
<tr>
<td>Patout 2000</td>
<td>Observational retrospective</td>
<td>No serious imprecision</td>
<td>no serious inconsistency</td>
<td>no serious inconsistency</td>
<td>very serious [2, 4, 7, 8, 10, 11]</td>
<td>none</td>
<td>All patients with a diagnosis of diabetes or related disorders with neuropathic foot complications referred from local and regional physicians within the Louisiana State Hospital system.

Rates were given per patient year

Comparison with standard care outcomes 1 year prior to enrolment in the LEAP program. Enrolment in a comprehensive diabetes lower-extremity amputation prevention programme. Assessment of risk and management.</td>
<td>Rates and extent of amputation

Comparison of 1 year of standard foot care and 1 year of comprehensive lower extremity prevention programme in 197 patients for the outcome of number of lower extremity amputations rate per patient year (mean ± SD):
Standard care period: 0.096 ± 0.048
CD-LEAP period: 0.020 ± 0.020
% change (paired t test comparison): 79%</td>
<td>VERY LOW</td>
<td>IMPORTANT</td>
</tr>
</table>

<table>
<tr>
<td>Rith-Najarian 1998</td>
<td>Observational prospective</td>
<td>No serious imprecision</td>
<td>no serious inconsistency</td>
<td>no serious inconsistency</td>
<td>very serious [2, 4, 5, 7, 8]</td>
<td>none</td>
<td>639 American Indians with diabetes in a rural primary care clinic

Results were given per patient year

Standard care period=428 patients
Public health period= 449 patients
Staged diabetes management= 475 patients

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.</td>
<td>Rates and extent of amputation
Amongst 639 American Indians contributing 4322 diabetic person years during 11 years of observation

Average annual incidence of lower-extremity amputation among patients by intervention period
<table>
<tr><th>Period</th><th>Person-years at risk</th><th>No. of cases of lower extremity amputation</th><th>Lower extremity amputations/1000 diabetic person-years</th><th>% change</th><th>P value</th></tr>
<tr><td colspan="6">Standard care</td></tr>
<tr><td>Any LEA</td><td>1464</td><td>42</td><td>29</td><td>-</td><td></td></tr>
<tr><td>First LEA</td><td>1414</td><td>30</td><td>21</td><td>-</td><td></td></tr>
<tr><td>Major LEA</td><td>1464</td><td>16</td><td>11</td><td>-</td><td></td></tr>
<tr><td colspan="6">Public Health</td></tr>
<tr><td>Any LEA</td><td>1543</td><td>33</td><td>21</td><td>-28</td><td>0.20</td></tr>
<tr><td>First LEA</td><td>1467</td><td>18</td><td>12</td><td>-43</td><td>0.06</td></tr>
<tr><td>Major LEA</td><td>1543</td><td>12</td><td>8</td><td>-27</td><td>0.37</td></tr>
<tr><td colspan="6">Staged Diabetes Management</td></tr>
<tr><td>Any LEA</td><td>1313</td><td>20</td><td>15</td><td>-48</td><td>0.016</td></tr>
<tr><td>First LEA</td><td>1246</td><td>7</td><td>6</td><td>-71</td><td>0.0006</td></tr>
<tr><td>Major LEA</td><td>1313</td><td>11</td><td>8</td><td>-27</td><td>0.49</td></tr>
</table>
Incidence rates of Lower-extremity amputation, by intervention period and selected risk groups
Rates per 1000 person-years
<table>
<tr><th>Risk group</th><th>Standard care</th><th>Public Health</th><th>Staged diabetes Management</th></tr>
<tr><td>Male</td><td>34</td><td>36</td><td>20</td></tr>
<tr><td>Female</td><td>25</td><td>11</td><td>12</td></tr>
<tr><td>Age <55 years</td><td>17</td><td>11</td><td>13</td></tr>
<tr><td>Age ≥55 years</td><td>41</td><td>33</td><td>18</td></tr>
<tr><td>Diabetes duration <10 years</td><td>9</td><td>3</td><td>1</td></tr>
<tr><td>Diabetes duration ≥10 years</td><td>59</td><td>47</td><td>32</td></tr>
</table>
For patients aged ≥ 55 years, Diabetes duration <10 years, Diabetes duration ≥10 years were found to be significantly different when the staged diabetes management period was compared to the baseline rate.</td>
<td>VERY LOW</td>
<td>IMPORTANT</td>
</tr>
</table>

<table>
<tr>
<td>Nason 2013</td>
<td>Observational prospective</td>
<td>No serious imprecision</td>
<td>no serious inconsistency</td>
<td>no serious inconsistency</td>
<td>very serious[2,3,4,5,6,7,9,11]</td>
<td>none</td>
<td>Total n= 251 patients at high risk of foot ulceration (neuropathy or absent pulses with deformity), with active ulceration or previous minor amputations.

A dedicated bi-weekly consultant led multidisciplinary foot protection clinic employing vascular surgery, endocrinology, orthopaedic surgery, podiatry, orthotics, tissue viability established in an Irish university hospital as part of an integrated foot protection service.

131 in the control period
120 in the study period</td>
<td>Rates and extent of amputation

Number of above knee amputations
Under diabetic foot clinic period= 3 amputations
Control period= 8 amputations

Number of below knee amputations
Under diabetic foot clinic period= 4 amputations
Control period= 4 amputations</td>
<td>VERY LOW</td>
<td>IMPORTANT</td>
</tr>
<tr>
<td>Carrington 2001</td>
<td>Observational retrospective</td>
<td>No serious imprecision</td>
<td>no serious inconsistency</td>
<td>no serious inconsistency</td>
<td>very serious[2,3,5,6,7,9,11,]</td>
<td>none</td>
<td>143 diabetic lower-limb unilateral amputees referred to a subregional rehabilitation clinic for prosthetic care. Patients were observed for a 2 year period after initial assessment.

Focused foot care program. Peripheral vascular and nerve assessment, education and podiatry were provided for each patient.</td>
<td>Rates and extent of amputation

Major amputation rate (above or below knee)
<table>
<tr><th></th><th>Patients referred before the clinic established (n=148)</th><th>Patients seen in the clinic (n=143)</th><th>P value</th></tr>
<tr><td>Bilateral amputations</td><td>21 (14.2%)</td><td>22 (15.4%)</td><td>NS</td></tr>
<tr><td>Number of deaths</td><td>39</td><td>27</td><td>NS</td></tr>
<tr><td>Bilateral amputation and death</td><td>3</td><td>1</td><td>NS</td></tr>
</table>
</td>
<td>VERY LOW</td>
<td>IMPORTANT</td>
</tr>
</table>

Dargis 1999	Observational prospective	No serious imprecision	no serious inconsistency	no serious inconsistency	very serious [2, 4, 5, 6]	none	A total of 145 patients with a past history of neuropathic foot ulcers but no evidence of peripheral vascular disease were followed for 2 years. Intervention group (n=56)= 30.4% Standard care group (n=89)= 58.4% A multidisciplinary foot clinic. Staff consisted of a diabetologist, rehabilitation physician, orthopaedic surgeon, podiatrist, and shoe makers.	Rates and extent of amputation Amputations Intervention group (n=56)= 7% (3 minor and 1 major) Standard care group (n=89)= 13.7% (8 minor and 4 major)	VERY LOW	IMPORTANT
Driver 2010	Observational retrospective	No serious imprecision	no serious inconsistency	no serious inconsistency	very serious [2,3,4, 5, 6,7,8, 11]	none	Total n= 485 diabetic patients Number of people seen under podiatric specialist service=311 Number seen by non-limb preservation team service= 174 Referral to the limb protection team: employing: Podiatric and vascular surgery, an orthotist, a wound care nurse and a research unit.	Rates and extent of amputation Minor amputation Limb preservation team group= 52 of 311 patients (17%) Non-limb preservation team group= 27 of 174 patients (15%) P=0.0006 i.e. significant difference	VERY LOW	IMPORTANT

[1]Unclear if the reason for allocation was or was not related to any other confounding factors. It is unclear if groups were comparable at baseline including all major confounding factors as such data was not provided per group. Unclear if the comparison groups received the same care. Participants were not blinded to intervention allocation. Individuals administering care were not blinded to intervention allocation. Unclear if groups were comparable for compliance or intervention completion. Unclear if groups were comparable for availability of outcome data. A valid and reliable method may not have been used

[2] Non Randomised

[3]Unclear if groups were comparable at baseline for all prognostic factors, no attempt to balance groups for confounding factors. Or groups not comparable for all confounding factors.

[4]Unclear if comparison group received the same care apart from intervention studied

[5]Non Blinded

[6]Only crude incidence rates recorded, no analysis to adjust for confounding factors

[7]Unclear if groups were comparable for adherence, clinic attendance or treatment completion

[8]Unclear if groups were comparable for outcome data available or loss to follow up

[9]Groups were not comparable for length of observation or unclear if patients were followed up for a similar amount of time (or adjustments not made)

[10]No precise definition of outcome
[11]Method of determination of outcome not valid or reliable or unclear (for example; retrospective or administrative data set)
[12]Length of follow up/observation inappropriate/unclear

1.1.1.6 Health related quality of life

Quality assessment							No of patients	Effect Health related quality of life (results)	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	consideration	Intervention			
Health related quality of life										
Driver 2010	Observational	No serious imprecision	no serious inconsistency	no serious inconsistency	very serious[2,3,4,5,6,7,8,11]	none	Total n= 485 diabetic patients Number of people seen under podiatric specialist service=311 Number seen by non-limb preservation team service= 174 Referral to the limb protection team: employing: Podiatric and vascular surgery, an orthotist, a wound care nurse and a research unit.	Health related quality of life Survival Limb preservation team group= 7.7% died Non-limb preservation team group= 19.5% died P=0.0001 i.e. significant difference	VERY LOW	IMPORTANT

[1]Unclear if the reason for allocation was or was not related to any other confounding factors. It is unclear if groups were comparable at baseline including all major confounding factors as such data was not provided per group. Unclear if the comparison groups received the same care. Participants were not blinded to intervention allocation. Individuals administering care were not blinded to intervention allocation. Unclear if groups were comparable for compliance or intervention completion. Unclear if groups were comparable for availability of outcome data. A valid and reliable method may not have been used
[2] Non Randomised
[3]Unclear if groups were comparable at baseline for all prognostic factors, no attempt to balance groups for confounding factors. Or groups not comparable for all confounding factors.
[4]Unclear if comparison group received the same care apart from intervention studied
[5]Non Blinded
[6]Only crude incidence rates recorded, no analysis to adjust for confounding factors
[7]Unclear if groups were comparable for adherence, clinic attendance or treatment completion
[8]Unclear if groups were comparable for outcome data available or loss to follow up
[9]Groups were not comparable for length of observation or unclear if patients were followed up for a similar amount of time (or adjustments not made)
[10]No precise definition of outcome

[11]Method of determination of outcome not valid or reliable or unclear (for example; retrospective or administrative data set)
[12]Length of follow up/observation inappropriate/unclear

I.4 Review question 4 full GRADE profiles

Table 1: Summary of risk stratification systems

Model	Summary	
IWGDF	Four categories: 0 No DN 1 DN 2 DN and (FD or PVD) 3 History of FU or LEA	Modified version: 0 No DN or PVD 1 DN, no PVD or FD 2a DN and FD, no PVD 2b PVD 3a History of FU 3b LEA
SIGN	Three categories: Low – No risks factors - No PVD, no previous FU or FD and no VI Moderate – One risk factor - DN or PVD or VI or PI or FD with or without callous High – Previous FU or LEA, or PVD and DN, or more than one risk factor and callous 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 DN 1 DN and/or FD 2 DN and/or PVD 3 History of FU and LEA	
UT	Four categories: 0 No DN 1 DN 2 DN and FD 3 DN, FD and history of LEA	

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

Table 2: Modified-GRADE summary for studies on risk stratification systems

Study	Design	Risk of bias	Indirectness	Imprecision	Other	Participants	Quality
Monteiro-Soares (2012)	Retrospective cohort study	Serious[1]	Serious[2]	No serious imprecision	None	364	Low
Monteiro-Soares (2010)	Retrospective cohort study	Serious[1]	Serious[2]	No serious imprecision	None	360	Low
Leese (2006)	Prospective cohort study	No serious risk of bias	No serious indirectness	No serious imprecision	None	3526	High
Peters (2001)	Prospective case control	No serious risk of bias	No serious indirectness	No serious imprecision	Serious[3]	236	Moderate

[1] Downgrade one level - retrospective study
[2] Downgrade one level - tertiary referral setting with higher prevalence of DFU
[3] Downgrade one level – unclear loss to follow up

Table 3: Predictive accuracy of risk stratification systems

System	Paper	Category	Se	Sp	LR+	LR-
IWGDF	Peters (2001)	3	74 (62-86)	86 (81-92)	5.35 (3.52-8.14)	0.30 (0.19-0.47)
		3+2	87 (78-96)	58 (51-66)	2.10 (1.70-2.59)	0.22 (0.11-0.45)
Modified IWGDF	Monteiro-Soares (2012)	3A+3B	88 (77-99)	71 (66-76)	3.00 (2.40-3.70)	0.20 (0.07-0.40)
		2A+2B+3A+3B	100 (NC)	45 (39-50)	1.80 (1.60-1.90)	NC
		1+2A+2B+3A+3B	100 (NC)	38 (33-44)	1.60 (1.50-1.80)	NC
SIGN	Monteiro-Soares (2012)	High	100 (NC)	52 (46-57)	2.10 (1.80-2.30)	NC
		High + moderate	100 (NC)	9 (6-12)	1.10 (1.00-1.10)	NC
	Leese (2006)	High	84 (79-90)	90 (89-91)	8.41 (7.45-9.49)	0.17 (0.12-0.25)
		High + moderate	95 (92-98)	67 (65-68)	2.97 (2.70-3.04)	0.07 (0.04-0.14)
Seattle	Monteiro-Soares (2012)	Highest	70 (54-85)	83 (79-87)	4.20 (3.00-5.80)	0.40 (0.20-0.60)
		Highest + next to highest	85 (73-97)	70 (65-75)	2.80 (2.20-3.50)	0.20 (0.10-0.50)
		Highest + next to highest + next to lowest	94 (86-100)	44 (39-49)	1.70 (1.50-1.90)	0.10 (0.04-0.50)
	Monteiro-Soares (2010)	Highest	61 (51-70)	87 (83-91)	4.7 (3.33-6.76)	0.45 (0.35-0.58)
		Highest + next to highest	84 (75-90)	70 (65-75)	2.83 (2.34-3.47)	0.23 (0.14-0.36)
		Highest + next to highest + next to lowest	95 (88-98)	50 (44-56)	1.88 (1.65-2.13)	0.10 (0.05-0.25)
ADA	Monteiro-Soares (2012)	3	91 (81-100)	70 (66-75)	3.10 (2.50-3.70)	0.10 (0.04-0.40)
		2+3	100 (NC)	56 (51-61)	2.30 (2.00-2.60)	NC
		1+2+3	100 (NC)	13 (9-17)	1.10 (1.10-1.20)	NC
UT	Monteiro-Soares (2012)	3	58 (41-74)	85 (81-89)	3.70 (2.50-5.50)	0.50 (0.30-0.70)
		2+3	64 (47-80)	73 (68-78)	2.30 (1.70-3.20)	0.50 (0.30-0.80)
		1+2+3	73 (58-88)	66 (61-71)	2.10 (1.60-2.80)	0.40 (0.20-0.70)

Table 4: Modified-GRADE summary for studies on assessment tests

Study	Design	Risk of bias	Indirectness	Imprecision	Other	Participants	Quality
Nather (2008)	Prospective cohort	Serious[1]	Serious[2]	Very serious[3]	No serious	202	Very low
Boyko (2006)	Prospective cohort	Serious[1]	No serious	Serious[4]	No serious	1285	Low
Abbott (2002)	Prospective cohort	Serious[5]	No serious	Very serious[3]	No serious	6613	Very low
Carrington (2002)	Prospective cohort	Serious[1]	No serious	Very serious[3]	No serious	169	Very low
Kastenbauer (2001)	Prospective cohort	Serious[5]	Serious[6]	Very serious[3]	No serious	187	Very low
Pham (2000)	Prospective cohort	Serious[5]	Serious[7]	Very serious[3]	No serious	248	Very low
Adler (1999)	Prospective cohort	No serious	Serious[8]	Very serious[3]	No serious	776	Very low
Boyko (1999)	Prospective cohort	No serious	No serious	Very serious[3]	No serious	1483 (limbs)	Low
Litzelman (1997)	Prospective cohort	No serious	Serious[9]	Serious[4]	No serious	352	Low
Young (1994)	Prospective cohort	Serious[5]	No serious	Very serious[3]	No serious	469	Very low
Rith-Najarian (1992)	Prospective cohort	Serious[5]	No serious	Very serious[10]	No serious	358	Very low

[1] Downgrade one level - Unclear whether important potential confounders (other than the risk factors of interest) are appropriately accounted for.
[2] Downgrade one level - Setting – patients were already managed by the hospital multidisciplinary team (Singapore therefore high prevalence of DFU (rather than community).
[3] Downgrade two levels – No model diagnostics were reported; no further validation of identified risk factors
[4] Downgrade one level – No further validation of identified risk factors
[5] Downgrade one level – Potential confounders (other than the risk factors of interest) are not appropriately accounted for.
[6] Downgrade one level – Non-consecutive recruitment (i.e. on every second day of the screening period, the first two patients who met the criteria were recruited); hospital setting.
[7] Downgrade one level – Both patients who attended tertiary centre and primary care clinics were included.
[8] Downgrade one level – Study population - only US veterans with diabetes (98.2% male).
[9] Downgrade one level – Study population - only non-insulin dependent patients who were socioeconomically disadvantaged.
[10] Downgrade two levels – Only simple chi-squared analysis; no further validation of identified risk factors

Table 5: Independent predictors of foot ulceration from multi-variate analysis

	Boyko (2006)	Abbott (2002)	Carrington (2002)	Kastenbauer (2001)	Pham (2000)	Boyko (1999)	Litzelman (1997)	Young (1994)
Monofilament	HR 2.03 (1.50-2.76) [P=<0.001]	RR 1.80 (1.36-2.39) P=<0.0001	NS	NS	Adjusted OR 2.4 (1.1-5.3) P=0.036	RR 2.17 (1.52-3.08) P=<0.001	Adjusted OR 5.23 (2.26-12.13) P=<0.001	
Plantar pressure, Novel platform	-			RR 6.3 (1.2-32.7)				
Plantar pressure, f scan mat					OR 2.0 (1.2-3.3) P=0.007			
Neuropathy symptom score		NS						
Neuropathy disability score		RR 2.32 (1.61-3.35) P=<0.0001			OR 3.1 (1.3-7.6) P=0.013			
Foot deformity score		RR 1.57 (1.22-2.02) P=0.0004						
Warm and cool rods		NS						
Pain sensation Neurotip		NS						
Achilles tendon reflex		NS				NS		
Sensortek							NS	
Goniometer								
Neurothesiometer			NS					
Biothesiometer				RR 25.4 (3.1-205)	Adjusted OR 3.4 (1.7-6.8) P=0.001			VPT>25 vs VPT <15 adjusted OR = 6.82 (2.75-16.92) P=<0.01
MNCV			RR 0.90 (0.84-0.96) P=0.001					

(a) Blank cells indicate the test was not examined by the study. NS = Included in univariate analysis but not significant in multivariate analysis
(b) Abbreviations OR, odds ratio; HR, hazard ratio; MNCV, motor nerve conduction velocity

Table 6: Independent predictors of lower limb amputation from multi-variate analysis

	Nather (2008)	Carrington (2002)	Adler (1999)
Monofilament	NS	RR 5.18 (1.96-13.68) P=0.001	AAI model 2.2 (0.8-6.2) TcPO2 model 2.9 (1.1-7.8) Pulse model 2.5 (0.9-6.8)
Plantar pressure, Novel platform			
Plantar pressure, f scan mat			
Neuropathy symptom score			
Neuropathy disability score			
Foot deformity score			
Warm and cool rods			
Pain sensation Neurotip			
Achilles tendon reflex			
Sensortek			
Goniometer			
Neurothesiometer			
Biothesiometer			
MNCV		NS	

(a) Blank cells indicate the test was not examined by the study. NS = Included in univariate analysis but not significant in multivariate analysis
(b) Abbreviations OR, odds ratio; HR, hazard ratio; NS, not significant; MNCV, motor nerve conduction velocity

Table 7: Independent predictors of death from multi-variate analysis

	Carrington (2002)
Monofilament	NS
Plantar pressure, Novel platform	
Plantar pressure, f scan mat	
Neuropathy symptom score	
Neuropathy disability score	
Foot deformity score	
Warm and cool rods	
Pain sensation Neurotip	
Achilles tendon reflex	
Sensortek	
Goniometer	
Neurothesiometer	NS
Biothesiometer	
MNCV	RR 0.84 (0.73-0.97) P=0.016

(a) Blank cells indicate the test was not examined by the study. NS = Included in univariate analysis but not significant in multivariate analysis
(b) Abbreviations HR, hazard ratio; MNCV, motor nerve conduction velocity

I.5 Review question 5 full GRADE profiles

No evidence was found for this review

I.6 Review question 6 full GRADE profiles

I.6.1 Table 1: GRADE profile of studies on temperature monitoring

Question: Should Temperature monitoring vs Standard care be used for preventing diabetic foot?

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Temperature monitoring	Standard care	Relative (95% CI)	Absolute		
Ulceration (Lavery 2007, Armstrong 2007, Lavery 2004)												
3	randomised trials	very serious[1,3, 4,5,6]	no serious inconsistency	no serious indirectness	serious[2]	none	11/206 (5.3%)	38/215 (17.7%)	RR 0.30 (0.16 to 0.56)	124 fewer per 1000 (from 78 fewer to 148 fewer)	VERY LOW	CRITICAL
Amputation (Lavery 2004)												
1	randomised trials	very serious[1,4,5,6]	no serious inconsistency	no serious indirectness	Very serious[2]	none	0/41 (0%)	2/44 (4.5%)	RR 0.21 (0.01 to 4.43)	36 fewer per 1000 (from 45 fewer to 156 more)	VERY LOW	CRITICAL
Number who developed Charcot fracture (Lavery 2004)												
1	randomised trials	very serious[1,4,5,6]	no serious inconsistency	no serious indirectness	Very serious[2]	none	0/41 (0%)	2/44 (4.5%)	RR 0.21 (0.01 to 4.33)	36 fewer per 1000 (from 45 fewer to 156 more)	VERY LOW	CRITICAL

[1] Inadequate blinding
[2] Number of events less than 300
[3] Unclear loss to follow up in one study
[4] Unclear definitions of outcome provided in one study
[5] Unclear method of randomisation in one study
[6] length of follow up may not have been adequate in one study

I.6.2 Table 2: GRADE profile of studies on education

Question: Should Education vs Standard care be used for Prevention of diabetic foot problems?

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Education	Standard care	Relative (95% CI)	Absolute		
Ulceration (Gershater 2011)												
1	randomised trials	very serious[1,2,3,4,5,6,7]	no serious inconsistency	no serious indirectness	serious[8]	none[9]	19/40 (47.5%)	22/58 (37.9%)	RR 1.25 (0.79 to 1.99)	95 more per 1000 (from 80 fewer to 376 more)	VERY LOW	CRITICAL
Amputation (McMurray 2002)												
1	randomised trials	very serious[1,2,5,7,10]	no serious inconsistency	no serious indirectness	serious[8]	none	0/45 (0%)	5/38 (13.2%)	RR 0.08 (0.00 to 1.35)	121 fewer per 1000 (from 132 fewer to 46 more)	VERY LOW	CRITICAL
Hospitalisation (McMurray 2002)												
1	randomised trials	very serious[1,2,5,7,10]	no serious inconsistency	no serious indirectness	no serious imprecision[8]	none	1/45 (2.2%)	10/38 (26.3%)	RR 0.08 (0.01 to 0.63)	263 fewer per 1000 (from 263 fewer to 263 fewer)	LOW	CRITICAL
Ulceration (Bloomgarden 1987)												
1	randomised trials	very serious[1,2,3,4,5,7]	no serious inconsistency	no serious indirectness	Very serious[8]	none	4/127 (3.1%)	5/139 (3.6%)	RR 0.88 (0.24 to 3.19)	4 fewer per 1000 (from 27 fewer to 79 more)	VERY LOW	CRITICAL
Ulceration (Lincoln 2008)												
1	randomised trials	serious[2,4,11]	no serious inconsistency	no serious indirectness	Very serious[8]	none	36/87 (41.4%)	35/85 (41.2%)	RR 1.00 (0.70 to 1.44)	0 fewer per 1000 (from 124 fewer to 181 more)	VERY LOW	CRITICAL
Amputation (Lincoln 2008)												
1	randomised trials	serious[2,4,11]	no serious inconsistency	no serious indirectness	very serious[8]	none	9/87 (10.3%)	9/85 (10.6%)	RR 0.98 (0.41 to 2.34)	2 fewer per 1000 (from 62 fewer to 142 more)	VERY LOW	CRITICAL
Ulceration (Malone 1989)												
1	randomised trials	very serious[1,2,4,7,10,11]	no serious inconsistency	no serious indirectness	no serious imprecision[8]	none	8/177 (4.5%)	26/177 (14.7%)	RR 0.31 (0.14 to 0.66)	101 fewer per 1000 (from 50 fewer to 126 fewer)	LOW	CRITICAL
Amputation (Malone 1989)												
1	randomised trials	very serious[1,2,4,7,10,11]	no serious inconsistency	no serious indirectness	serious[8]	none	7/177 (4%)	21/177 (11.9%)	RR 0.33 (0.15 to 0.76)	79 fewer per 1000 (from 28 fewer to 101 fewer)	VERY LOW	
Infection (Malone 1989)												
1	randomised trials	very serious[1,2,4,7,10,11]	no serious inconsistency	no serious indirectness	very serious[8]	none	2/177 (1.1%)	2/177 (1.1%)	RR 1.00 (0.14 to 7.02)	0 fewer per 1000 (from 10 fewer to 68 more)	VERY LOW	
Amputation (Litzelman 1993)												
1	randomised trials	very serious[1,2,3,7,11,12]	no serious inconsistency	no serious indirectness	serious[8]	none	1/191 (0.52%)	4/205 (2%)	RR 0.27 (0.03 to 2.38)	14 fewer per 1000 (from 19 fewer to 27 more)	VERY LOW	CRITICAL

[1] Unclear or dubious method of randomisation
[2] Lack of blinding or inadequate

[3] Groups not comparable at baseline for all important factors
[4] Unclear definitions employed
[5] Large loss to follow up, unclear if groups were equally affected
[6] Inadequate duration of follow up
[7] Unclear method of allocation concealment
[8] Number of events <300
[9] Some funding from suppliers of shoes
[10] Many important variables not reported at baseline
[11] Unclear if method of obtaining outcome reliable
[12] Unclear if groups were comparable for loss to follow up

I.6.3 Table 3: GRADE profile of studies on augmented foot examination

Question: Should augmented foot examination vs standard care be used for prevention of diabetic foot problems?

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Augmented foot examination	Standard care	Relative (95% CI)	Absolute		
Ulceration (Lavery 2007)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	17/58 (29.3%)	17/56 (30.4%)	RR 0.97 (0.55 to 1.70)	9 fewer per 1000 (from 137 fewer to 212 more)	VERY LOW	CRITICAL
Ulceration (Armstrong 2005)												
1	randomised trials	very serious[1,3,4,5,6]	no serious inconsistency	no serious indirectness	very serious[2]	none[7]	2/34 (5.9%)	2/36 (5.6%)	RR 1.06 (0.16 to 7.10)	3 more per 1000 (from 47 fewer to 339 more)	VERY LOW	CRITICAL

[1] Lack of blinding or inadequate
[2] Event number less than 300
[3] Unclear if allocation concealment
[4] Many important baseline variables were not reported
[5] Unclear if methods used were reliable
[6] Lack of a precise definition of outcomes
[7] Industry funded

I.6.4 Table 4: GRADE profile of studies on weight bearing activities

Question: Should Weight bearing activity vs Standard care be used for the prevention of diabetic foot problems?

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Weight bearing activity	Standard care	Relative (95% CI)	Absolute		
Ulceration (Lemaster 2008)												
1	randomised trials	serious[1,2]	no serious inconsistency	no serious indirectness	serious[3]	none	9/41 (22%)	9/38 (23.7%)	RR 0.93 (0.41 to 2.09)	17 fewer per 1000 (from 140 fewer to 258 more)	LOW	
Amputation (Lemaster 2008)												
1	randomised trials	serious[1,2]	no serious inconsistency	no serious indirectness	serious[3]	none	0/41 (0%)	0/38 (0%)	-	-	LOW	
Hospitalisation (Lemaster 2008)												
1	randomised trials	serious[1,2]	no serious inconsistency	no serious indirectness	serious[3]	none	0/41 (0%)	0/38 (0%)	-	-	LOW	

[1] Patients in the intervention group also received motivational phonecalls from a nurse
[2] Lack of blinding or inadequate
[3] event number less than 300

I.6.5 Table 5: GRADE profile of studies on education with therapeutic footwear (orthotics)

Question: Should Education with therapeutic footwear vs standard therapy be used for the prevention of diabetic foot problems?

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Education with therapeutic footwear	Standard therapy	Relative (95% CI)	Absolute		
Ulceration (Cisneros 2010)												
1	randomised trials	very serious[1,2,3,4,5,6]	no serious inconsistency	no serious indirectness	very serious[7]	none[8]	8/21 (38.1%)	8/14 (57.1%)	RR 0.67 (0.33 to 1.35)	189 fewer per 1000 (from 383 fewer to 200 more)	VERY LOW	CRITICAL

[1] Unclear method of randomisation
[2] Many important variables were not reported at baseline
[3] Lack of blinding or inadequate
[4] unclear effect of loss to follow up to composition of groups
[5] precise definition of outcomes not provided

[6] unclear if valid and reliable methods were used
[7] number of events less than 300
[8] unclear source of funding

I.6.6 Table 6: GRADE profile of studies on therapeutic footwear and cork or polyurethane inserts

Question: Should Footwear and cork insert vs Footwear and polyurethene insert be used for the prevention of diabetic foot problems?

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Footwear and cork insert	Footwear and polyurethene insert	Relative (95% CI)	Absolute		
Ulceration (Reiber 2002)												
1	randomised trials	serious[1,2,3]	no serious inconsistency	no serious indirectness	very serious[4]	none	18/121 (14.9%)	17/119 (14.3%)	RR 1.04 (0.56 to 1.92)	6 more per 1000 (from 63 fewer to 131 more)	VERY LOW	CRITICAL

[1] unclear allocation concealment
[2] Groups were not comparable for all major variables
[3] Lack of blinding or inadequate
[4] Event number less than 300

I.6.7 Table 7: GRADE profile of studies on pressure customised orthoses and standard foot wear

Question: Should pressure customised footwear vs standard of care footwear be used for the prevention of diabetic foot problems?

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pressure customised footwear	Shape Customised Footwear	Relative (95% CI)	Absolute		
Ulceration (Ulbrecht 2014, Bus 2013)												
2	Randomised trials	Serious[5, 2, 6, 8]	no serious inconsistency	no serious indirectness	Very serious[4,9]	none	39/151 (25.8%)	54/150 (36%)	RR 0.62 (0.26 to 1.47)	137 fewer per 1000 (from 266 fewer to 169 more)	VERY LOW	CRITICAL

[1] unclear allocation concealment
[2] Groups were not comparable for all major variables in one study
[3] Lack of blinding or inadequate
[4] Effect estimate crosses one line of minimum important effect in one study

[5] Investigator blinded only
[6] Some differences at baseline but would favour control group in one study
[7] Unclear method of randomisation
[8] Unclear if participants received the same care in all cases in one study
[9] Effect estimate crosses two lines of minimum important effect in one study

I.6.8 Table 8: GRADE profile of studies on off-the-shelf insoles

Question: Should Off-the-shelf insoles vs standard care be used for the prevention of diabetic foot problems?

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Insole group	Standard care	Relative (95% CI)	Absolute		
Ulceration (Reiber 2002)												
1	randomised trials	serious[1,2,3]	no serious inconsistency	no serious indirectness	Very serious[4]	none	17/119 (14.3%)	27/160 (16.9%)	RR 0.85 (0.48 to 1.48)	25 fewer per 1000 (from 88 fewer to 81 more)	VERY LOW	CRITICAL
Ulceration (Reiber 2002)												
1	randomised trials	serious[1,2,3]	no serious inconsistency	no serious indirectness	very serious[4]	none	18/121 (14.9%)	27/160 (16.9%)	RR 0.88 (0.51 to 1.52)	20 fewer per 1000 (from 83 fewer to 88 more)	VERY LOW	CRITICAL

[1] unclear allocation concealment
[2] groups not comparable for all major variables
[3] lack of blinding or inadequate
[4] event numbers less than 300
[5] unclear method of randomisation
[6] Many important variables not reported at baseline
[7] Unclear if groups were comparable for loss to follow up or outcome data available
[8] No precise definition of outcomes
[9] Unclear if a valid and reliable method used
[10] Study industry funded
[11] large loss to follow up
[12] Unclear if groups received same care other than intervention of study
[13] length of follow up may have been inadequate

I.6.9 Table 9: GRADE profile of studies on therapeutic shoe with shear reducing insole

Question: Should Therapeutic shoe vs Therapeutic shoe with shear reducing insole be used for the prevention of diabetic foot problems?

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Orthotics	Standard care	Relative (95% CI)	Absolute		
Ulceration (Lavery 2012)												
1	randomised trials	serious[1,3,5]	no serious inconsistency	no serious indirectness	serious[4]	none	3/149 (2%)	10/150 (6.7%)	RR 0.30 (0.08 to 1.08)	47 fewer per 1000 (from 61 fewer to 5 more)	LOW	CRITICAL

[1] unclear allocation concealment
[2] groups not comparable for all major variables
[3] lack of blinding or inadequate
[4] event numbers less than 300
[5] unclear method of randomisation
[6] Many important variables not reported at baseline
[7] Unclear if groups were comparable for loss to follow up or outcome data available
[8] No precise definition of outcomes
[9] Unclear if a valid and reliable method used
[10] Study industry funded
[11] large loss to follow up
[12] Unclear if groups received same care other than intervention of study
[13] length of follow up may have been inadequate

I.6.10 Table 10: GRADE profile of studies on bespoke orthoses

Question: Should bespoke orthoses vs standard care be used for the prevention of diabetic foot problems?

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Bespoke othotics	Standard care	Relative (95% CI)	Absolute		
Ulceration (Uccioli 1995, Rizzo 2012)												
2	randomised trials	very serious[1,3,5,6,7,8,9,11]	no serious inconsistency	no serious indirectness	serious[4]	none[10]	26/181 (14.4%)	79/186 (42.5%)	RR 0.36 (0.23 to 0.56)	272 fewer per 1000 (from 187 fewer to 327 fewer)	VERY LOW	CRITICAL

[1] unclear allocation concealment
[2] groups not comparable for all major variables
[3] lack of blinding or inadequate
[4] event numbers less than 300
[5] unclear method of randomisation in one study

[6] Many important variables not reported at baseline
[7] Unclear if groups were comparable for loss to follow up or outcome data available
[8] No precise definition of outcomes
[9] Unclear if a valid and reliable method used
[10] One study industry funded
[11] large loss to follow up
[12] Unclear if groups recieved same care other than intervention of study
[13] length of follow up may have been inadequate

I.6.11 Table 11: GRADE profile of studies on silicone orthotic protection

Question: Should Therapeutic shoe vs Therapeutic shoe with silicone orthotic protection be used for the prevention of diabetic foot problems?

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Orthotics	Standard care	Relative (95% CI)	Absolute		
Ulceration (Scire 2009)												
1	randomised trials	very serious[1,3,8,12,13]	no serious inconsistency	no serious indirectness	no serious imprecision[4]	none	1/89 (1.1%)	12/78 (15.4%)	RR 0.07 (0.01 to 0.55)	143 fewer per 1000 (from 69 fewer to 152 fewer)	LOW	CRITICAL

[1] unclear allocation concealment
[2] groups not comparable for all major variables
[3] lack of blinding or inadequate
[4] event numbers less than 300
[5] unclear method of randomisation
[6] Many important variables not reported at baseline
[7] Unclear if groups were comparable for loss to follow up or outcome data available
[8] No precise definition of outcomes
[9] Unclear if a valid and reliable method used
[10] Study industry funded
[11] large loss to follow up
[12] Unclear if groups received same care other than intervention of study
[13] length of follow up may have been inadequate

I.6.12 Table 12: GRADE profile of studies on free of charge podiatry care

Question: Should Podiatrist care vs standard care be used for the prevention of diabetic foot problems?

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Podiatrist care	Standard care	Relative (95% CI)	Absolute		
Amputation (Ronnemaa 1997)												
1	randomised trials	very serious[1,2,3,4,5,6,7]	no serious inconsistency	no serious indirectness	very serious[8]	none[9]	2/169 (1.2%)	0/163 (0%)	RR 4.82 (0.23 to 99.71)	-	VERY LOW	CRITICAL
Ulceration (Ronnemaa 1997)												
1	randomised trials	very serious[1,2,3,4,5,6,7]	no serious inconsistency	no serious indirectness	very serious[10]	none[9]	1/169 (0.59%)	1/163 (0.61%)	RR 0.96 (0.06 to 15.29)	0 fewer per 1000 (from 6 fewer to 88 more)	VERY LOW	
Ulceration (Plank 2003)												
1	randomised trials	serious[4,6]	no serious inconsistency	no serious indirectness	serious[8]	none	18/47 (38.3%)	25/44 (56.8%)	RR 0.67 (0.43 to 1.05)	187 fewer per 1000 (from 324 fewer to 28 more)	LOW	CRITICAL
Ampution (Plank 2003)												
1	randomised trials	serious[4,6]	no serious inconsistency	no serious indirectness		none	2/47 (4.3%)	1/44 (2.3%)	RR 1.87 (0.18 to 19.93)	20 more per 1000 (from 19 fewer to 430 more)		CRITICAL

[1] Unclear method of randomisation
[2] Unclear if adequate allocation concealment
[3] Unclear if groups comparable at baseline for all major confounding factors
[4] Lack of blinding or inadequate
[5] Loss to follow up was large
[6] Unclear definition of important outcomes
[7] Unclear if reliable methods were used for determining outcome
[8] event number less than 300
[9] Unclear source of funding
[10] Crosses two lines of minimum important difference

I.6.13 Table 13: GRADE profile of studies on risk stratification and foot protection programme

Question: Should Diabetic risk stratification and protection programme vs standard care be used for the prevention of diabetic foot problems?

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Diabetic risk stratification and protection programme	Standard care	Relative (95% CI)	Absolute		
Ulceration (McCabe 2009)												
1	randomised trials	very serious[1,2,3,4,5,6,7]	no serious inconsistency	no serious indirectness	serious imprecision[8]	none	24/1001 (2.4%)	35/1000 (3.5%)	RR 0.69 (0.41 to 1.14)	11 fewer per 1000 (from 21 fewer to 5 more)	VERY LOW	CRITICAL
Amputation (McCabe 2009)												
1	randomised trials	very serious[1,2,3,4,5,6,7]	no serious inconsistency	no serious indirectness	serious[8]	none	7/1001 (0.7%)	23/1000 (2.3%)	RR 0.30 (0.13 to 0.71)	16 fewer per 1000 (from 7 fewer to 20 fewer)	VERY LOW	CRITICAL

[1] Unclear method of randomisation
[2] Unclear if allocation concealment
[3] Unclear if groups were comparable at baseline
[4] Lack of blinding or inadequate
[5] Unclear if groups were comparable for outcome data not available
[6] No clear definition of outcomes was used
[7] Valid and reliable methods may not always have been used
[8] Event number less than 300

I.7 Review question 7 full GRADE profiles

I.7.1 Table 8: GRADE profile of studies on classification tools

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. There are four quality categories, namely 'High', 'Moderate', 'Low' and 'Very low'. As this part of the review question was not assessing the accuracy of tests themselves, studies were not downgraded for using clinical judgement in the diagnosis of infection, bone involvement or ischemia.

Study	Design	Participants	Risk of bias	Indirectness	Imprecision	Other	Results	Quality
University of Texas								
Armstrong (1998)	Retrospective cohort	360	S[1]	NS	S[2]	NS	Increased prevalence of amputation as wounds increased in depth (x^2 trend = 143.1, P<0.001) and stage (x^2 trend = 91, P<0.001). Patients 11 times more likely to receive midfoot or higher amputation if wound grade 3 (18.3 v 2.0%, P<0.001, x^2 trend 31.5, OR 11.1 [CI 4-31.3]) Patients 90 times more likely to receive midfoot or higher amputation if stage D compared to lower stages (76.5 v 3.5%, P<0.001, x2 trend 133.5, OR 89.6 [CI 25-316])	LOW
Oyibo (2001)	Prospective cohort	194	NS	S[3]	S[2]	NS	Positive trend for grade (x2 trend 23.7, P<0.0001) and stage (x2 trend = 15.1, P=0.0001) with increased number of amputations.	LOW
Gul (2006)	Retrospective cohort	383	S[1]	NS	S[2]	S[4]	Chances of amputation: Grade 2 v Grade 1: OR 2.9, 95%CI 0.37-23.93. Grade 3 v Grade 1: OR 9.5, 95%CI 1.15-77.27. Stage C and D v A and B: OR 2.7, 95%CI 1.31-5.41.	VERY LOW

Study	Design	Participants	Risk of bias	Indirectness	Imprecision	Other	Results	Quality
Parisi (2008)	Prospective cohort	105	NS	S[5]	NS	NS	Chance of healing: Stage A v Stage D adj OR=4.6, 95%CI 1.37-15.49, P=0.014. Stage B v Stage D adj OR=1.68, 95%CI 0.46-6.11, P=0.433. Stage C v Stage D adj OR=2.26, 95%CI 0.62-8.32, P=0.219. Grade 1 v Grade 2+3 adj OR=2.87, 95%CI 1.08-7.64, P=0.035.	MOD
Abbas (2008)	Retrospective cohort	326	S[1]	S[5]	S[2]	S[4]	x^2 trend observed between healing and depth of ulcer grade (70.558) and UT stage (32.929)	VERY LOW
Wagner								
Oyibo (2001)	Prospective cohort	194	NS	S[3]	S[2]	NS	Positive trend with increased number of amputations (x2 trend= 21.0, P <0.0001).	LOW
Gul (2006)	Retrospective cohort	383	S[1]	NS	S[2]	S[4]	More likely to have amputation if Grade 4 or 5 compared to 1 (OR 45.5, 95%CI 3.48-594.68)	VERY LOW
Parisi (2008)	Prospective cohort	105	NS	S[5]	NS	NS	Chance of healing: Grade 1 v Grade 2+3 adj OR=3.48, 95%CI 1.38-8.76, P=0.008	MOD
Abbas (2008)	Retrospective cohort	326	S[1]	S[5]	S[2]	S[4]	x^2 trend observed between healing and Wagner score (82.923)	VERY LOW

Study	Design	Participants	Risk of bias	Indirectness	Imprecision	Other	Results	Quality
Won (2014)	Retrospective cohort	173	S[1]	NS	NS	S[4]	Risk of all lower limb amputation was found to be significantly greater in those with higher Wagner grade: HR 7.99 (95% CI 3.12-20.47) P=<0.01 Risk of major limb amputation was found to be significantly greater in those with higher Wagner grade: HR 8.02 (95% CI 0.97-66.33) P=0.05 Risk of minor limb amputation was found to be significantly greater in those with higher Wagner grade: HR 9.36 (95% CI 3.25-26.92) <P=0.01	LOW
Tsai (2013)	Retrospective cohort	658	S[1]	NS	NS	S[4]	Risk of major lower limb amputation was found to be significantly greater in those with Wagner grade 4 or 5 when compared to those with Wagner grade 1,2 or 3 in the non-dialysis population: OR 3.80 (95% CI 1.25-11.56) P=0.019 Risk of major lower limb amputation was found not to be significantly greater in those with Wagner grade 4 or 5 when compared to those with Wagner grade 1,2 or 3 in the dialysis population: OR 3.70 (95% CI 0.85-16.09) P=0.081	LOW
Wang (2014)	Retrospective case control	194	S[1]	NS	NS	S[4]	Wagner grade was found to have an Odds ratio of 0.262 (95% CI 0.261-0.037) p=<0.01	LOW
S(AD) SAD								
Treece (2004)	Prospective cohort	302	NS	NS	S[2]	NS	Differences in outcome according to: Area x^2 = 25.9, P<0.001 Depth x^2 = 33.8, P<0.001 Sepsis x^2 = 13.5, P=0.004 Arteriopathy x^2 = 33.7, P<0.001 Denervation x^2 = 5.1, P=0.16	MOD

Study	Design	Participants	Risk of bias	Indirectness	Imprecision	Other	Results	Quality
Parisi (2008)	Prospective cohort	105	NS	S[5]	NS	NS	Chance of healing: Score <=9 v >10 adj OR=7.64, 95%CI 2.72-21.45, P<0.0001.	MOD
Abbas (2008)	Retrospective cohort	326	S[1]	S[5]	S[2]	S[4]	x^2 trend observed between healing and depth of ulcer (70.558) and infection (61.774)	VERY LOW
SINBAD								
Ince (2008)	Retrospective cohort	1340	S[1]	NS	S[2]	NS	Time to healing in days (range) for ulcers that healed showed significant difference between scores (x2 37.324, P=0). Multi-variate analysis showed significant independent association between variables and outcome (healing v non-healing, death and amputation).	LOW
DUSS								
Beckert (2006)	Prospective cohort	1000	NS	NS	NS	S[4]	93% probability of healing for uncomplicated ulcer (score 0), decreasing to 57% for score 4 (P<0.0001)	MOD
IDSA/IWGDF								
Lavery (2007)	Prospective cohort	247	S[6]	NS	S[2]	NS	Trend toward increased risk of amputation (x^2 trend 108.00, P<0.001), an increased atomic level of amputation (x^2 trend 113.3, P<0.001) and an increased need for lower extremity related hospitalisation (x^2 118.6, P<0.001).	LOW

Study	Design	Participants	Risk of bias	Indirectness	Imprecision	Other	Results	Quality
Wukich (2013)	Retrospective cohort	100	S1	NS	S[2]	S[4]	Amputations were more common among patients with a severe diabetic foot infection (55%) than those with moderate diabetic foot infection (42%) but this was non-significant (P=0.22) Hospital length of stay was longer in those with severe infection (median 8 days) than for those with moderate infection (median 5 days) (P=0.021) Limb salvage was greater in those with moderate infections (94%) when compared to those with severe infections (80%) but the difference was non-significant (P=0.081)	VERY LOW
PEDIS								
Abbas (2008)	Retrospective cohort	326	S[1]	S[5]	S[2]	S[4]	x^2 trend observed between healing and infection (70.558)	VERY LOW
MAID								
Beckert (2009)	Prospective cohort	2019	NS	NS	NS	S[4]	With increasing MAID score, the probability of healing at 365d decreased from 84% (grade 0) to 31% (grade 4) (P<0.0001; x^2=191.230).	MOD
CSI								
Erdman (2012)	Retrospective cohort	77	S[1]	VS[7,8]	S[2]	NS	CSI 0 = PPV 92% declining incrementally to 25% for CSI >=7 Odds ratio for people with CSI >2, 15.1 (4.4-51.5 CI 95%)	VERY LOW

Abbreviations: NS, None serious; S, Serious; VS, Very Serious.
[1] *Retrospective cohort study*
[2] *Baseline characteristics or potential confounder unadjusted.*
[3] *Small number of Wagner grade 4 or 5 ulcers included*

[4] *Incomplete data analysis or loss to follow up*
[5] *Population generally younger and has less peripheral arterial disease than UK population*
[6] *Unclear if treatment differed by grade of infection*
[7] *No details of the patient population were presented*
[8] *Patients only include if documented follow up of at least 3 months and technically satisfactory image*

I.7.2 Table 9: GRADE profile of studies on swab culture for soft tissue infection

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. There are four quality categories in modified-GRADE, namely 'High', 'Moderate', 'Low' and 'Very low'.

Study	Participants (samples)	Outcomes	Association between swab and deep tissue culture (%)	Risk of bias	Indirectness	Imprecision	Other	Quality
Superficial swab v deep tissue biopsy								
2 [S, Mu(b)]	54 and 56 (60 and 89)	Swab and deep tissue culture identical	Range: 62-73	VS[1,2,3]	NS	S[4]	S[5]	VERY LOW
2 [S, Mu(b)]	54 and 56 (60 and 89)	Swab contained all organisms found in deep tissue biopsy plus additional organisms	Range: 11-20	VS[1,2,3]	NS	S[4]	S[5]	VERY LOW
2 [S, Mu(b)]	54 and 56 (60 and 89)	Swab lacked organism(s) found in deep tissue biopsy	Range: 9-18	VS[1,2,3]	NS	S[4]	S[5]	VERY LOW
2 [S, Mu(b)]	54 and 56 (60 and 89)	Swab found identical or more isolates than deep tissue biopsy	Range: 82-84	VS[1,2,3]	NS	S[4]	S[5]	VERY LOW

[S] = Slater et al. (1997): reference standard deep tissue biopsy
[Mu(b)] = Mutluoglu (2012b): reference standard deep tissue biopsy
Abbreviations: NS, None serious; S, Serious; VS, Very Serious.
[1] *No blinding*
[2] *No details of time between tests*
[3] *Retrospective*
[4] *Very small sample size (<100)*
[5] *No direct accuracy analysis of swab culture, lack of data.*

I.7.3 Table 10: GRADE profile of studies on swab or tissue culture for osteomyelitis

Study	Participants (wounds)	Risk of bias	Indirectness	Imprecision	Other	Pre-test probability %	Sensitivity %	Specificity %	Concordance between index and reference test (cultures)	Quality
Superficial swab and deep tissue culture v histological examination of bone biopsy specimen										
Morales Lozano (2010) ID834	132 (132)	VS[1]	NS	NS	S[2]	80	86	19	NA	VERY LOW
2 consecutive bone contact swab cultures v bone biopsy (histological or microbiological)										
Bernard (2010) ID732	68 (68)	S[3]	NS	S[4]	NS	71	96	79	NA	LOW
Superficial ulcer swab from the base of ulcer v bone biopsy culture										
Elamurugan (2010) ID662	144 (144)	VS[1]	NS	NS	NS	-	-	-	I = 11.8% A1 = 26.4% Dif = 61.8%	LOW

Abbreviations: NA, Not available; NS, None serious; S, Serious; VS, Very Serious.
I = Identical culture findings; A1 = At least 1 organism similar; Dif = Different culture findings
[1] Unclear blinding, unclear selection (whether consecutive or not), no details on time between tests.
[2] Unclear the correlation between the superficial swab culture and the deep tissue culture, unclear which culture contributed to final accuracy analysis.
[3] Unclear blinding, unclear selection (whether consecutive or not).
[4] Small sample size (<100)

I.7.4 Table 11: GRADE profile of studies on probe to bone test for osteomyelitis

Study	Participants (wounds)	Risk of bias	Indirectness	Imprecision	Inconsistency	Pre-test probability %	Sensitivity %	Specificity %	Agreement	Quality
Probe to bone v Bone biopsy culture										
5 [G, Lav, Mo, Mu(a), S]	Range: 65 to 247	S[1]	NS	S[2]	S[3]	Range: 0.12 to 0.66	Range: 38 to 98	Range: 78 to 92	-	VERY LOW
Probe to bone inter-rater reliability [Ga, Me]	*39 and 75*	*NS*	*S[11]*	*NS*	*NS*	-	-	-	*0.31 and 0.593*	*MODERATE*

[G] = Grayson (1995): reference standard = histological and microbiology tests in detecting osteomyelitis
[Ga] = Garcia-Morales (2011)
[Me] = Meyr (2011)

[Lav] = Lavery (2007): reference standard = bone biopsy culture
[Mo] = Morales Lozano (2010): reference standard = histological analysis of bone biopsy
[Mu(a)] = Mutluoglu (2012a): reference standard = bone biopsy culture or MRI
[S] = Shone (2006): reference standard = Clinical signs of osteomyelitis, supported by MRI and microbiologic analysis of deep tissue samples.
Abbreviations: NA, Not available; NS, None serious; S, Serious; VS, Very Serious.
[1] All 5 studies – unclear blinding, 3 studies unclear selection (whether consecutive or not).
[2] Wide ranges of confidence intervals (see forest plot).
[3] Heterogeneity in reference standards being used.

I.7.5 Table 12: GRADE profile of studies on imaging tests for osteomyelitis

Study	Participants (wounds)	Risk of bias	Indirectness	Imprecision	Inconsistency	Pre-test probability %	Sensitivity % (95% CI)	Specificity % (95% CI)	Quality
SINGLE TEST - MULTIPLE STUDIES									
MRI									
11 [A, B, C, E, L, M, Na, R, W, We, Y]	Range: 14 to 94	S[1]	NS	S[2]	S[3]	Range: 0.25 to 0.86	Range: 77 to 100	Range: 60 to 100	VERY LOW
99mTc-MDP scintigraphy									
12 [As, C, D, E, Hd, Hy, K, L, N, Pa, Po, Y]	Range: 22 to 94	S[4]	NS	S[2]	S[3]	Range: 0.29 to 0.88	Range: 50 to 100	Range: 0 to 67	VERY LOW
99mTc-HMPAO-labelled scintigraphy									
3 [D, Hd, Hy]	Range: 52 to 122	S[5]	NS	NS	S[3]	Range: 0.40 to 0.66	Range: 86 to 91	Range: 56 to 97	LOW
In-WBC									
8 [C, Hd, K, La, L, N1, N2, Pa]	Range: 12 to 111	S[6]	NS	S[2]	S[3]	Range: 0.27 to 0.68	Range: 33 to 100	Range: 22 to 78	VERY LOW
Plain film radiography									
10 [C, D, La, L, Mo, N, Na, W, We, Y]	Range: 26 to 200	S[7]	NS	S[2]	S[3]	Range: 0.25 to 0.86	Range: 22 to 90	Range: 17 to 94	VERY LOW
Plain film radiography inter-rater reliability									
Alvaro-Alfonso (2013) ID5226	*123 (123)*	*S[4]*	*NS*	*NS*	*NS*	*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)*			*MOD*

Study	Participants (wounds)	Risk of bias	Indirectness	Imprecision	Inconsistency	Pre-test probability %	Sensitivity % (95% CI)	Specificity % (95% CI)	Quality
						in very experienced K=.75, mod experienced K=.61 and inexperienced K=.57.			
FDG-PET									
2 [Na, Ka]	39 and 106 (46 and 106)	VS[8]	NS	NS	S[3]	Range: 0.25 to 0.39	Range: 81 to 100	93	VERY LOW
SINGLE TEST – SINGLE STUDY									
Anti-granulocyte Fab' fragment antibody scintigraphy (LeukoScan)									
1 [Ru] 4 hours	78	S[9]	NS	S[10]	NA	0.79	92 (82 to 97)	75 (62 to 98)	LOW
1 [Ru] 24 hours	78	S[9]	NS	S[10]	NA	0.79	92 (82 to 97)	88 (48 to 93)	LOW
99mTc-labelled monoclonal antigranulocyte antibody (Moab)									
1 [Pa]	25	S[11]	NS	S[10]	NA	0.40	90 (55 to 100)	67 (38 to 88)	LOW
DI SPECT/CT v Bone and tissue culture / histology or clinical examination + other imaging									
Heiba (2010) ID806	213 (213)	VS[12]	S[13]	NS	NA	0.49	95 (89 to 98)	94 (87 to 97)	VERY LOW
BS SPECT/CT v Bone and tissue culture / histology or clinical examination + other imaging									
Heiba (2010) ID806	213 (213)	VS[12]	S[13]	NS	NA	0.49	94 (88 to 98)	47 (37 to 57)	VERY LOW
WBCS SPECT/CT v Bone and tissue culture / histology or clinical examination + other imaging									
Heiba (2010) ID806	213 (213)	VS[12]	S[13]	NS	NA	0.49	87 (78 to 92)	68 (58 to 77)	VERY LOW
DI planar v Bone and tissue culture / histology or clinical examination + other imaging									
Heiba (2010) ID806	213 (213)	VS[12]	S[13]	NS	NA	0.49	93 (87 to 97)	66 (56 to 75)	VERY LOW
DI SPECT v Bone and tissue culture / histology or clinical examination + other imaging									
Heiba (2010) ID806	213 (213)	VS[12]	S[13]	NS	NA	0.49	93 (87 to 97)	77 (68 to 85)	VERY LOW
DI SPECT/CT step 1 v Bone and tissue culture / histology or clinical examination + other imaging									
Heiba (2010) ID806	67 (67)	VS[12]	S[13]	NS	NA	0.54	94 (81 to 99)	58 (39 to 75)	VERY LOW
DI SPECT/CT step 2 v Bone and tissue culture / histology or clinical examination + other imaging									
Heiba (2010) ID806	67 (67)	VS[12]	S[13]	NS	NA	0.54	97 (85 to 100)	94 (79 to 99)	VERY LOW
5h 99mTc-IgC scintigraphy v clinical evaluation (MRI, culture histopathology and consensus)									

Study	Participants (wounds)	Risk of bias	Indirectness	Imprecision	Inconsistency	Pre-test probability %	Sensitivity % (95% CI)	Specificity % (95% CI)	Quality
Asli (2011) ID528	18 (23)	S[14]	S[13]	S[15]	NA	0.43	100 (69 to 100)	69 (39 to 91)	VERY LOW
24h 99mTc-IgC scintigraphy v clinical evaluation (MRI, culture histopathology and consensus)									
Asli (2011) ID528	18 (23)	S[14]	S[13]	S[15]	NA	0.43	60 (26 to 88)	77 (46 to 95)	VERY LOW
99mTc-UBI 29-41 scintigraphy v bone biopsy histopathology and culture or radiographic changes at follow up									
Saeed (2013) ID5205	*55*	*VS[16]*	*NS*	*S[10]*	*NA*	*0.67*	*100*	*100*	*VERY LOW*
COMBINATION TESTS									
99mTc-MDP + In-WBC									
2 [K, Pa]	25 & 39	S[17]	NS	S[2]	S[3]	0.40 & 0.38	Range: 80 to 100	Range: 79 to 80	VERY LOW
Moab + 99mTc-MDP									
1[Pa]	25	S[17]	NS	S[10]	NA	0.40	90 (55-100)	67 (38-88)	LOW
99mTc-MDP + 99Tc-HMPAO									
1[Po]	83	S[17]	NS	S[10]	NA	0.49	93 (80-96)	98 (87-100)	LOW
99mTc-MDP + Gallium 67 citrate									
1[We]	22	S[17]	NS	S[10]	NA	0.73	69 (41-89)	83 (36-100)	LOW

NOTE: for 95%CI for multiple studies, please see forest plots.

NS = No serious; S = serious; VS = very serious; NA = not applicable as single study.
[A] = Al-Khawari (2007): reference standard = histological analysis
[Al] = Alvaro-Alfonso (2013)
[As] = Asli (2011): reference standard = MRI, culture, histopathology, consensus
[B] = Beltran (1990): reference standard = aspiration/pathological examination/plain films
[C] = Croll (1996): reference standard = pathological specimen or bone culture
[D] = Devillers (1998): reference standard = radiographic/bacteriological/histological results/clinical follow-up
[E] = Ertugrul (2006): reference standard = histopathological analysis
[Hd] = Harwood (1999): reference standard = histological and/or microbiological cultures
[He] = Heiba (2010): reference standard = Bone and tissue culture / histology or clinical examination + other imaging
[Hy] = Harvey (1997): reference standard = histology, bone cultures and radiographic results
[K] = Keenan (1989): reference standard = culture and/or histological examination
[Ka] = Kagna (2012): reference standard = histological analysis of bone biopsy or clinical examination
[La] = Larcos (1991): reference standard = bone culture/biopsy/clinical follow-up
[L] = Levine (1994): reference standard = pathological/histological/surgical examination/clinical follow-up
[M] = Morrison (1995): reference standard = histological analysis or clinical and radiographic demonstration despite conservative antibiotic therapy

[Mo] = Morales Lozano (2010): reference standard = histological analysis of bone biopsy
[N] = Newman (1991): reference standard = bone biopsy and culture
[N1] = Newman (1991) (4 hours): reference standard = bone biopsy and culture
[N2] = Newman (1991) (24 hours): reference standard = bone biopsy and culture
[Na] = Nawaz (2010): reference standard = histological analysis of bone biopsy or clinical examination
[Pa] = Palestro (2003): reference standard = bone biopsy and culture/clinical follow-up
[Po] = Poirier (2002): reference standard = radiological examination or histopathological analysis
[R] = Rozzanigo (2009): reference standard = bacteriological and/or histological tests
[Ru] = Rubello (2004): reference standard = microbiological findings/CT scan/MRI/clinical follow-up
[S] = Shone (2006): reference standard = clinical signs of osteomyelitis, supported by MRI and microbiological analysis of deep tissue samples.
[S] = Saeed (2013): reference standard = bone biopsy histopathology and culture or radiographic changes at follow up
[W] = Wang (1990): reference standard = histological examination
[We] = Weinstein (1993): reference standard = histological examination
[Y] = Yuh (1989): reference standard = pathological tests
[1] *5 out of the 11 studies had no blinding; 4 out of the 11 studies with unclear selection criteria and baseline characteristics.*
[2] *Wide ranges of confidence intervals (see forest plot).*
[3] *Heterogeneity in reference standards being used.*
[4] *5 out of the 12 studies had no blinding, one study unclear whether recruitment was consecutive.*
[5] *2 out of the 3 studies had no blinding.*
[6] *4 out of the 8 studies had no blinding.*
[7] *5 out of the 10 studies had unclear patient selection (unsure it was consecutive), 2 studies had no blinding.*
[8] *All 3 studies had no blinding, a big proportion of patients in one study were already on antibiotics.*
[9] *Selection criteria, characteristics of patients not reported.*
[10] *Small sample size (<100).*
[11] *No blinding.*
[12] *Retrospective study, unclear time between tests, no blinding.*
[13] *Baseline characteristics of patients were not reported.*
[14] *Unclear patient selection (whether consecutive or not).*
[15] *Very small sample size (only 18).*
[16] *Unclear patient selection (whether consecutive or not), unclear blinding, patients with initial 99m-TC-MDP negative were excluded.*

I.7.6 Table 13: GRADE profile of Blood testing for osteomyelitis

No. of studies	No. of participants	Risk of bias	Indirectness	Imprecision	Inconsistency	Pre-test probability	Sensitivity (%)	Specificity (%)	GRADE quality
ESR ≥ 60 mm/h									
2 [E, K]	29 & 46	S[1]	NS	S[2]	S[3]	0.52 & 0.66	89 to 92	68 to 90	VERY LOW
ESR ≥ 65 mm/h									
2 [E, K]	29 & 46	S[1]	NS	S[2]	S[3]	0.52 & 0.66	88 to 89	73 to 90	VERY LOW

No. of studies	No. of participants	Risk of bias	Indirectness	Imprecision	Inconsistency	Pre-test probability	Sensitivity (%)	Specificity (%)	GRADE quality
ESR ≥ 70 mm/h									
2 [E, K]	29 & 46	S[1]	NS	S[2]	S[3]	0.52 & 0.66	83 to 89	77 to 100	VERY LOW
ESR > 70 mm/h									
2 [M, N]	28 & 43	S[1]	NS	S[2]	S[3]	0.51 & 0.64	28 to 91	95 to 100	VERY LOW
ESR ≥ 75 mm/h									
2 [E, K]	29 & 46	S[1]	NS	S[2]	S[3]	0.52 & 0.66	79 to 84	82 to 100	VERY LOW
ESR ≥ 80 mm/h									
2 [E, K]	29 & 46	S[1]	NS	S[2]	S[3]	0.52 & 0.66	71 to 79	91 to 90	VERY LOW
ESR > 100 mm/h									
1 [N]	39	S[1]	NS	S[4]	NA	0.67	23	100	LOW
Haematocrit > 36%									
1 [M]	43	S[1]	NS	S[4]	NA	0.51	95 (77 to 100)	86 (64 to 97)	LOW
Haemoglobin < 12 g/dL									
1 [M]	43	S[1]	NS	S[4]	NA	0.51	82 (60 to 95)	90 (70 to 99)	LOW
Platelet count > $400x10^9$/L									
1 [M]	43	S[1]	NS	S[4]	NA	0.51	45 (24 to 68)	95 (76 to 100)	LOW
Red cell distribution width > 14.5									
1 [M]	43	S[1]	NS	S[4]	NA	0.51	68 (45 to 86)	62 (38 to 82)	LOW
White cell count > $400x10^9$/L									
1 [M]	43	S[1]	NS	S[4]	NA	0.51	50 (28 to 72)	81 (58 to 95)	LOW
White cell count >$14x10^9$/L									
1 [Mi]	61	S[1]	NS	S[4]	NA	-	74 (57 to 91)	82 (69 to 95)	LOW
ESR >67 mm/h									
1 [Mi]	61	S[1]	NS	S[4]	NA	-	84 (70 to 98)	75 (60 to 90)	LOW
CRP >14 mg/L									
1 [Mi]	61	S[1]	NS	S[4]	NA	-	85 (72 to 98)	83 (70 to 96)	LOW

No. of studies	No. of participants	Risk of bias	Indirectness	Imprecision	Inconsistency	Pre-test probability	Sensitivity (%)	Specificity (%)	GRADE quality
Procalcitonin >0.30 ng/mL									
1 [Mi]	61	S[1]	NS	S[4]	NA	-	81 (66 to 96)	71 (56 to 86)	LOW

NS = No serious; S = serious; VS = very serious; NA = not applicable as single study.
[E] = Ertugrul (2009): reference standard = Histopathology/bone tissue culture/MRI conventional spin echo
[K] = Kaleta (2001): reference standard = Histological examination
[M] = Malabu (2001): reference standard = Bone scan/MRI/radiographs
[N] = Newman (1991): reference standard = Bone biopsy and culture
[Mi]= Michail (2013): reference standard= clinical examination(probe to bone)/X-ray/Scintigraphy/MRI
S = serious; NS = no serious; NA = not applicable as a single study
[1] Unclear blinding or selection criteria.
[2] Wide confidence intervals.
[3] Different reference standards being used.
[4] Small sample size (<100).

I.8 Review question 8 full GRADE profiles

Table 14: Warriner et al (2012) Routine care weekly versus routine care every other weekly

Quality assessment						Summary of findings				
						No of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Routine care weekly	Routine care every other weekly	Relative (95% CI)	Absolute	
Outcome: Closure of Diabetic foot ulcer[a]										
1	Retrospective cohort study[1]	serious[2]	no serious	no serious	no serious	63/101 (63.87%)	2/105 (2.0%)	[a] HR 0.048 (0.029-0.079) $p=8.0 \times 10^{-32}$		VERY LOW
Outcome: Median time to closure[a]										

1	Retrospective cohort study[1]	serious[2]	no serious	no serious	no serious	101	105	[a] Median time to DFU closure (days) Weekly group = 28 days Every other week group = 66 days $p=8.0 \times 10^{-41}$	VERY LOW

[1] Cohort study (downgrade 2 levels), [2] retrospective design & short follow-up
[a] Based upon cox proportional hazards regression (to adjust for confounds)

I.9 Review question 9 full GRADE profiles

I.9.1 Education and foot care programmes

Table 15: (Malone et al, 1989) Education programme vs. standard care

Quality assessment							Number of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Education programme	Standard care	Relative (95% CI)	Absolute	
Outcome: Number of healed ulcers[a] (follow-up 2 years)											
1	RCT	very serious[1,2]	no serious	no serious	no serious		160/177[b] (90.40%)	128/177[b] (72.32%)	RR 1.25 (1.13 to 1.39)	18 more per 100 (from 14 more to 23 more)	LOW
Outcome: Number of infected ulcers [a] (follow up 2 years)											
1	RCT	serious[1]	no serious	no serious	no serious		2/177[b] (1.12%)	2/177[b] (1.12%)	RR 1.00 (0.14 to 7.02)	0 more per 100 (from 14 more to 70 more)	LOW
Outcome Number of unhealed ulcers [a] (follow up 2 years)											
1	RCT	serious[1]	no serious	no serious	no serious		8/177[b]	26/177[b]	RR 0.31 (0.14 to 0.66)	10 fewer per 100 (from 13	LOW

Quality assessment							Number of patients		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Education programme	Standard care	Relative (95% CI)	Absolute	
										fewer to 1 fewer)	
	Outcome Total number of amputations [a] (follow up 2 years)										
1	RCT	serious[1]	no serious	no serious	no serious		7/177[b]	21/177[b]	RR 0.32 (0.15 to 0.76)	8 fewer per 100 (from 11 fewer to 1 fewer)	LOW
	Outcome: Number of minor amputations [c] (follow up 2 years)										
1	RCT	serious[1]	no serious	no serious	no serious		2/7[d]	3/21[d]	RR 2.00 (0.42 to 9.63)	8 fewer per 100 (from 11 fewer to 1 fewer)	LOW
	Outcome: Number of major amputations [c] (follow up 2 years)										
1	RCT	serious[1]	no serious	no serious	no serious		5/7[d]	18/21[d]	RR 0.83 (0.51 to 1.37)	14 fewer per 100 (from 48 fewer to 20 more)	LOW
	Outcome: Mortality (follow up varied)										
1	RCT	serious[1]	no serious	no serious	no serious		3/108 (2.77%)	4/100 (4.0%)	RR 0.69 (0.16 to 3.03)	1 fewer per 100 (from 4 fewer to 2 more)	LOW

[a] Healed ulcers classed as success rates infection, ulcer, amputation classed as failure rates; [b] Based on number of limbs; [c] Minor amputations: below ankle, major amputations: above ankle; [d] based on total number of amputations
[1]Randomisation method unsatisfactory;[2] Allocation concealment not reported

Table 16: Al-Wahabi et al (2010) Before and after establishing a foot care education and training programme

Quality assessment						Number of patients		Effect		Quality
No of studies	Design[1]	Risk of bias	Inconsistency	Indirectness	Imprecision	After programme	Before programme	Relative (95% CI)	Absolute	
Outcome: Total number of amputations										
1	Retrospective cohort	no serious	no serious	no serious	serious[2]	13/21 (61.9%)	14/20 (70%)	RR 0.88 (0.57 to 1.38)	8 fewer per 100 (from 30 fewer to 14 more)	VERY LOW

[1] Cohort design (downgrade 2 levels) [2] Small sample size

Table 17: Rerkasem et al (2007) Diabetic foot care programme versus standard care

Quality assessment						Number of patients		Effect		Quality
No of studies	Design[1 2]	Risk of bias	Inconsistency	Indirectness	Imprecision	Diabetic foot protocol	Standard care	Relative (95% CI)	Absolute	
Outcome: Total number of amputations										
1	Retrospective cohort	no serious	no serious	no serious	no serious	4/61 (6.5%)	30/110 (27.2%)	RR 0.24 (0.09 to 0.65)	21 fewer per 100 (from 27 fewer to 14 fewer)	VERY LOW
Outcome: Number of minor amputations[a]										
1	Retrospective cohort	no serious	no serious	no serious	no serious	2/4 (50.0%)	14/30 (46.7%)	RR 1.07 (0.37 to 3.07)	3 fewer per 100 from 47 fewer to 53 more)	VERY LOW
Outcome: Number of major amputations[a]										
1	Retrospective cohort	no serious	no serious	no serious	no serious	2/4 (50.0%)	16/30 (53.3%)	RR 0.94 (0.33 to 2.64)	3 fewer per 100 from 53	VERY LOW

Quality assessment						Number of patients		Effect		Quality
No of studies	Design[1 2]	Risk of bias	Inconsistency	Indirectness	Imprecision	Diabetic foot protocol	Standard care	Relative (95% CI)	Absolute	
									fewer to 47 more)	

[1] Cohort study design (downgrade 2 levels); [2] Retrospective design

Table 18: Weck et al (2013) Structured foot care programme versus standard care

Quality assessment						Number of patients		Effect		Quality
No of studies	Design[1]	Risk of bias	Inconsistency	Indirectness	Imprecision	Structured programme	Standard care	Relative (95% CI)	Absolute	
Outcome: Number of healed ulcers (follow up 2 years)										
1	Prospective cohort	serious[2]	no serious	no serious	no serious	194/684 (28.3%)	117/508 (23.0%)	RR 1.23 (1.01 to 1.50)	5 more per 100 (from 2 more to 9 more)	VERY LOW
Outcome: Number of ulcers improved[a] (follow up 2 years)										
1	Prospective cohort	serious[2]	no serious	no serious	no serious	352/684 (51.5%)	253/508 (49.8%)	RR 1.03 (0.92 to 1.16)	2 more per 100 (from 2 fewer to 6 more)	VERY LOW
Outcome: Number of major amputations[a]										
1	Prospective cohort	serious[2]	no serious	no serious	no serious	32/684 (4.7%)	110/508 (21.7%)	RR 0.22 (0.15 to 0.32)	17 fewer per 100 (from 19 fewer to 15 fewer)	VERY LOW
Outcome: Mortality rate (follow up 2 years)										
1	Prospective cohort	serious[2]	no serious	no serious	no serious	17/684 (2.5%)	48/508 (9.4%)	RR 0.26 (0.15 to 0.45)	7 fewer per 100 from 8 fewer to	VERY LOW

Quality assessment						Number of patients		Effect		Quality
No of studies	Design[1]	Risk of bias	Inconsistency	Indirectness	Imprecision	Structured programme	Standard care	Relative (95% CI)	Absolute	
									6 fewer	

I.9.2 Blood glucose control

Table 19: Aragon-Sanchez et al (2011) HBA1c values and ulcer healing time

Quality assessment						Number of patients		Effect		Quality
No of studies	Design [1]	Risk of bias	Inconsistency	Indirectness	Imprecision	HBA1c 5.3% 7.3%-	HBA1c7.4%-14%	Relative (95% CI)	Absolute	
Outcome: Number of amputations										
1	Prospective cohort	no serious	no serious	no serious	serious[2]	7/21 (33.3%)	26/60 (43.3%)	RR 0.77 (0.39 to 1.50)	10 fewer per 100 (from 31 fewer to 11 more)	VERY LOW
Outcome: Time to healing (in days)										
1	Prospective cohort	no serious	no serious	no serious	serious[2]	21	60	Median time to healing (range) HBA1c 5.3%-7.3%= 92 (52.5 to 152) HBA1c 7.4%-14%= 60 (34 to 120) p=0.26		VERY LOW
Outcome: Length of hospital stay (in days)										
1	Prospective cohort	no serious	no serious	no serious	serious[2]	21	60	Median length of stay (range) HBA1c 5.3%-7.3%= 40 (8 to 45.5) HBA1c 7.4%-14%= 29 (16 to 48) p=0.66		VERY LOW

Quality assessment						Number of patients		Effect		Quality
No of studies	Design [1]	Risk of bias	Inconsistency	Indirectness	Imprecision	HBA1c 5.3% 7.3%-	HBA1c7.4%-14%	Relative (95% CI)	Absolute	
Outcome: Mortality rate *(follow up 2 years)*										
1	Prospective Cohort	no serious	no serious	no serious	serious[2]	3/21 (14.3%) (2.5%)	2/60 (3.3%)	RR 4.29 (0.77 to 23.91)	11 more per 100 from 4 fewer to 26 more	VERY LOW

1 Cohort study design (downgrade 2 levels); 2Small sample size

Table 20: Markuson (2009) HBA1c values and ulcer healing time

Quality assessment						Number of patients		Effect		Quality
No of studies	Design [1 2]	Risk of bias	Inconsistency	Indirectness[3]	Imprecision	HBA1c 4% to 7%	HBA1c 7.1%-10%	Relative (95% CI)	Absolute	
Outcome: Number of ulcers healed										
1	Retrospective cohort	no serious	no serious	no serious	no serious	9/16[a] (56.3%)	13/20[a] (65.0%)	RR 0.87 (0.51 to 1.49)	9 fewer per 100 (from 34 fewer to 17 more)	VERY LOW
Outcome: Time to healing (in days)										
1	Retrospective cohort	no serious	no serious	no serious	no serious	16	20	<u>Mean time to healing (SD)</u> HBA1c 4%-7%= 85 (80.34) HBA1c 7.1%-10%= 123.63 (135.11)		VERY LOW

I.9.3 Other interventions: management of cardiovascular risk

Table 21: Young et al (2008) Patients receiving cardiovascular risk management programme versus standard care

Quality assessment						Number of patients		Effect		Quality
No of studies	Design [1 2]	Risk of bias[3]	Inconsistency	Indirectness	Imprecision	After programme introduced	Before programme introduced	Relative (95% CI)	Absolute	
Outcome: Mortality[a] (follow up 5 years)										
1	Retrospective cohort	serious	no serious	no serious	no serious	63/87[a] (72.4%)	194/285[a] (68.1%)	RR 1.06 (0.91 to 1.24)	4 more per 100 (from 5 fewer to 14 more)	VERY LOW
Outcome: Mortality rate[b]										
1	Retrospective cohort	serious	no serious	no serious	no serious	67/251 (26.8%)	193/404 (48.0%)	RR 0.56 (0.44 to 0.73)	21 fewer per 100 (from 27 fewer to 17 fewer)	VERY LOW

a Based on total number of deaths to date; b Based on estimated 5 year mortality rate (from survival analysis).: Survival measured at time of first ulceration to death

1 Cohort study design (downgrade 2 levels) 2 Retrospective design; 3Selective reporting of survival analysis results

I.9.4 Other interventions: exercise programmes

Table 22: Flahr et al (2010) Patients receiving foot care exercise intervention versus standard care

Quality assessment						Exercise programme		Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Exercise programme	Standard care	Relative (95% CI)	Absolute	
Outcome: Numbers of ulcers healed (follow up 12 weeks)										
1	RCT	serious[1]	no serious	no serious	serious[2]	3/10 (30.0%)	3/9 (33.3%)	RR 0.90 (0.24 to 3.38)	3 fewer per 100 (from 34 fewer to	VERY LOW

Quality assessment						Exercise programme		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Exercise programme	Standard care	Relative (95% CI)	Absolute	Quality
									27 more)	

[1] Pilot study short follow up period [2] Low number of events

I.9.5 Other interventions: Shellac for dry gangrene

Table 23: Alzahrani et al (2013) Patients receiving shellac for dry gangrene versus standard care

Quality assessment						Exercise programme		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Shellac group	Standard care (10% povidone-iodine)	Relative (95% CI)	Absolute	Quality
Outcome: Major Amputation at 12 months										
1	RCT	Very serious[1,3,4,5]	no serious	no serious	serious[2]	3/13 (23.1%)	3/10 (30%)	RR 1.10 (0.66 to 1.82)	3 more per 100 (from 10 fewer to 25 more)	VERY LOW
Outcome: All amputations at 12 months										
1	RCT	Very serious[1,3,4,5]	no serious	no serious	serious[2]	6/13 (46.2%)	6/10 (60%)	RR 1.35 (0.54 to 3.35)	21 more per 100 (from 28 fewer to 100 more)	VERY LOW

[1] Poor method of randomisation (not true randomisation)
[2] Low number of events
[3] Unlikely allocation concealment
[4] No blinding
[5] Unclear if patients equally compliant between groups

I.10 Review question 10 full GRADE profiles

I.10.1 Surgical versus non-surgical debridement

Table 24: Surgical debridement vs conventional non-surgical management (Piaggesi et al, 1998)

Quality assessment						Number of patients		Effect		Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Surgical debridement	Conventional non-surgical debridement[a]	Relative (95% CI)	Absolute (95% CI)	
Number of ulcers completely healed (follow-up 6 months)										
1	RCT	serious[1]	no serious	no serious	serious[2]	21/22 (95.5%)	19/24 (79.2%)	RR 1.21 (0.96 to 1.51)	166 more per 1000 (from 32 fewer to 404 more)	Low
Ulcers recurrence rates (follow-up 6 months)										
1	RCT	serious[1]	no serious	no serious	serious[2]	3/22 (13.6%)	8/24 (33.3%)	RR 0.41 (0.12 to 1.35)	196 fewer per 1000 (from 293 fewer to 117 more)	Low
Number of adverse events (follow-up 6 months)										
1	RCT	serious[1]	no serious	no serious	serious[2]	1/22 (4.5%)	3/24 (12.5%)	RR 0.36 (0.03 to 2.65)	80 fewer per 1000 (from 121 fewer to 206 more)	Low

[a] Conventional non-surgical management consisting of weight-bearing relief and regular dressings.
[1] unclear who conducted outcome assessment and hence unclear of assessor blinding (it was acceptable that blinding on participants and researchers were impossible to achieve); also loss to follow-up not reported.
[2] small study sample

I.10.2 Alginate dressings versus control dressing

Table 25: Alginate dressing versus Polyurethene foam dressing (Foster et al 1994)

Quality assessment						Number of patients		Effect		Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Alginate	Polyurethane	Relative (95% CI)	Absolute (95% CI)	
Complete wound healing (8 weeks)										
1	RCT	serious[1]	no serious	no serious	serious[2]	8/15 (53.3%)	9/15 (60%)	RR 0.89 (0.47 to 1.67)	67 fewer per 100 (from 34 fewer to 20 more)	LOW

[1] No allocation concealment, assessor not blinded.
[2] Total no. of events < 300.

I.10.3 Hydrocolloid dressings versus control dressing

Table 26: Hydrogel wound dressing versus saline gauze (SG) dressing (Jensen, 1997)

Quality assessment						Number of patients		Effect		Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Hydrogel	SG	Relative (95% CI)	Absolute (95% CI)	
Wound closure (follow up 16 weeks)										
1	RCT	serious[1]	no serious	serious[2]	serious[3]	11/13 (84.6%)	6/13 (46.1%)	RR 1.83 (0.98 to 3.45)	38 more per 100 (from 1 fewer to 100 more)	VERY LOW
Average time to close (weeks)										
1	RCT	serious[1]	no serious	serious[2]	serious[3]	13	13	Hydrogel = 10.30 weeks SG= 11.69 weeks		VERY LOW
Adverse events (follow up 16 weeks)										
1	RCT	serious[1]	no serious	serious[2]	serious[3]	2/13 (15.4%)	11/13 (53.9%)	RR 0.18 (0.05 to 0.66)	69 fewer per 100 (from 90 fewer to 49 fewer)	VERY LOW

[1] Randomisation method not reported
[2] Downgrade for indirect comparison- use of saline gauze
[3] Total no. of events < 300.

Table 27: Hydrofiber dressing vs Saline moistened gauze (SMG; Piaggesi et al , 2001)

Quality assessment	Number of patients	Effect	Quality

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	hydrofiber	SMG	Relative (95% CI)	Absolute (95% CI)	
Mean healing time (days)										
1	RCT	serious[1]	no serious	serious[2]	serious[3]	10	10	Mean healing time (days) (SD): Hydrofiber = 127 (46); SMG = 234 (61), p < 0.001		VERY LOW
Complication (infection) (8 weeks)										
1	RCT	serious[1]	no serious	serious[2]	serious[3]	1/10 (10%)	3/10 (30%)	RR 0.33 (0.04 to 2.69)	20 fewer per 100 (from 29 fewer to 51 more)	VERY LOW

[1] No allocation concealment;
[2] Downgrade for indirect comparison- use of saline gauze
[3]Total no. of events < 300.

I.10.4 Hydrocolloid dressings versus Alginate dressing

Table 28: Hydrofiber dressing vs CA (calcium alginate; Jude et al 2007)

Quality assessment						Number of patients		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Hydrofiber	CA	Relative (95% CI)	Absolute (95% CI)	Quality
Complete wound healing (follow up 8 weeks)										
1	RCT	serious[1]	no serious	no serious	serious[2]	21/67 (31.3%)	15/67 (22.4%)	RR 1.40 (0.79 to 2.47)	9 more per 100 (from 5 fewer to 33 more)	LOW
Wound surface reduction (%) (follow up 8 weeks)										
1	RCT	serious[1]	no serious	no serious	Serious[3]	67	67	Mean wound surface reduction (SD): Hydrofiber = 58.1 (53.1); CA = 60.5 (42.7), p = 0.948		LOW
Mean healing time (days)										

Quality assessment						Number of patients		Effect		Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Hydrofiber	CA	Relative (95% CI)	Absolute (95% CI)	
1	RCT	serious[1]	no serious	no serious	Serious[2]	67	67	Mean healing time (days) (SD): hydrofiber = 52.6 (1.8); CA = 57.7 (1.7), p = 0.340		LOW
Withdrawal due to AEs (unspecified) (follow up 8 weeks)										
1	RCT	serious[1]	no serious	no serious	serious[2]	8/67 (11.9%)	13/67 (19.4%)	RR 0.61 (0.27 to 1.39)	8 fewer per 100 (from 14 fewer to 8 more)	LOW
Wound-related complications (follow up 8 weeks)										
1	RCT	serious[1]	no serious	no serious	serious[2]	23/67 (34.3%)	26/67 (38.8%)	RR 0.88 (0.57 to 1.38)	5 fewer per 100 (from 17 fewer to 15 more)	LOW
Treatment-related AEs (follow up 8 weeks)										
1	RCT	serious[1]	no serious	no serious	serious[2]	11/67 (16.4%)	9/67 (13.4%)	RR 1.22 (0.54 to 2.76)	3 more per 100 (from 6 fewer to 24 more)	LOW

1 Allocation concealment unclear, assessor not blinded.
2 Total no. of events < 300.

I.10.5 Hydroactive dressings versus Hydrophilic dressing

Table 29: Hydroactive versus hydrophilic dressing (Clever and Dreyer, 1996)

Quality assessment						Number of patients		Effect		Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Hydroactive dressing	Hydrophilic dressing	Relative (95% CI)	Absolute (95% CI)	
Time to wound healing (days)										
1	RCT	very serious[1]	no serious	no serious	serious[2]	18	16	Mean time to healing (SD)		VERY LOW

Quality assessment						Number of patients		Effect		Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Hydroactive dressing	Hydrophilic dressing	Relative (95% CI)	Absolute (95% CI)	
								Hydroactive = 25.9 (23.52)days Hydrophilic = 20.43 (14.74) days <u>Median time to healing</u> Hydroactive = 15.5 days (range = 4-76 days Hydrophilic = 16.5 days (range = 4-52 days)		
Mean reduction in wound size (follow up 4 weeks)										
1	RCT	very serious[1]	no serious	no serious	serious[2]	18	16	<u>Mean reduction of ulcer</u> Hydroactive = 172.72mm Hydrophilic = 174.37mm		VERY LOW

1 Randomisation method and allocation not reported ;
2 Total number of events<300

I.10.6 Collagen dressings versus control dressing

Table 30: Collagen dressing versus Saline moistened gauze (SMG; Tallis et al, 2013)

Quality assessment						Number of patients		Effect		Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Collagen dressing	SMG	Relative (95% CI)	Absolute (95% CI)	
Mean change in wound size (follow up 12 weeks)										
1	RCT	no serious	no serious	serious[1]	serious[2]	24	24	<u>Mean change of ulcer size (%)</u> Collagen dressing= -53.83% (p=0.012) SMG= + 8.13% (p>0.05)		LOW

1 Downgrade for indirect comparison- use of saline gauze

[2]Total number of events<300

Table 31: Collagen/oxidised regenerated cellulose (ORC)/ silver dressing vs control treatment (SMG; Veves et al, 2002. Gottrup et al, 2013)

Quality assessment						Number of patients		Effect		Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Collagen /ORC /Silver	SMG	Relative (95% CI)	Absolute (95% CI)	
Complete wound healing (follow up 12 weeks, 14 weeks) (Veves 2002, Gottrup 2013)										
2	RCT	serious[1, 4]	no serious	serious[2]	serious[3]	63/127 (49.5%)	43/97 (46.4%)	RR 1.11 (0.83 to 1.47)	5 more per 100 (from 8 fewer to 21 more)	VERY LOW
Wound surface reduction (%) (follow up 12 weeks) (Veves 2002)										
1	RCT	serious[1]	no serious	serious[2]	serious[3]	104	84	Mean wound surface reduction Collagen/ORC/silver = 64.5%; SMG = 63.8%, P > 0.05		VERY LOW
Wound-related serious Adverse events (follow up 12 weeks, 14 weeks) (Veves 2002, Gottrup 2013)										
2	RCT	serious[1, 4]	no serious	serious[2]	serious[3]	25/127 (19.6%)	40/97 (41.2%)	RR 0.26 (0.03 to 2.56)	31 fewer per 100 (from 40 fewer to 64 more)	VERY LOW

[1] No allocation concealment, assessor not blinded.
[2] Downgrade for indirect comparison- use of saline gauze in one study
[3]Total no. of events < 300.
[4] Inadequate randomisation method reported in one study

Table 32: Collagen-Alginate dressing versus gauze dressing (Donaghue et al, 2008)

Quality assessment	Number of patients	Effect	Quality

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Collagen-Alginate dressing	Gauze dressing	Relative (95% CI)	Absolute (95% CI)	
Complete wound healing (follow up 8 weeks)										
1	RCT	serious[1]	no serious	serious[2]	serious[3]	24/50 (48.0%)	9/25 (36.0%)	RR=1.33 (0.73 to 2.42)	12 more per 100 (from 2 fewer to 27 more)	VERY LOW
Mean time to complete healing (follow up 8 weeks)										
1	RCT	serious[1]	no serious	serious[2]	serious[3]	50	25	Mean time to healing (SD) Collagen-alginate = 6.2 (0.4) weeks Gauze = 5.8 (0.4) weeks		VERY LOW
Mean reduction in wound area (follow up 8 weeks)										
1	RCT	serious[1]	no serious	serious[2]	serious[3]	50	25	Reduction in wound area (%)(SD) Collagen-alginate = 80.6 (6) Gauze = 61.1 (26)		VERY LOW

[1] Randomisation method not reported.
[2] Downgrade for indirect comparison- use of saline gauze
[3] Total no. of events < 300.

I.10.7 Other dressing

Table 33: Hydrofiber dressing vs N-A (non-adherent, knitted, viscose filament gauze; Jeffcoate et al, 2009. Comparison 1)

Quality assessment						Number of patients		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Hydrofiber	N-A	Relative (95% CI)	Absolute (95% CI)	Quality
Complete wound healing (follow up 24 weeks)										
1	RCT	no serious	no serious	no serious	serious[1]	46/103 (44.7%)	41/106 (38.7%)	RR 1.15 (0.84 to 1.59)	6 more per 100 (from 6 fewer to 23	MODERATE

Quality assessment						Number of patients		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Hydrofiber	N-A	Relative (95% CI)	Absolute (95% CI)	Quality
									more)	
Mean healing time (days)										
1	RCT	no serious	no serious	no serious	serious[2]	103	106	Mean healing time (days) (SD): Hydrofiber = 130.7 (52.4); N-A = 125.8 (55.9), p > 0.05		MODERATE
Major and minor amputation (follow up 24 weeks)										
1	RCT	no serious	no serious	no serious	serious[1]	4/103 (3.9%)	2/106 (1.9%)	RR 2.06 (0.39 to 10.99)	2 more per 100 (from 1 fewer to 19 more)	MODERATE
Withdrawal due to Adverse events (follow up 24 weeks)										
1	RCT	no serious	no serious	no serious	serious[1]	11/103 (10.7%)	15/106 (14.2%)	RR 0.75 (0.36 to 1.56)	4 fewer per 100 (from 9 fewer to 8 more)	MODERATE

[1] Total no. of events < 300.
[2] Total no. of events < 400.

Table 34: Hydrofiber vs impregnated dressing (Jeffcoate et al, comparison 2)

Quality assessment						Number of patients		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Hydrofiber	impregnated dressing	Relative (95% CI)	Absolute (95% CI)	Quality
Complete wound healing (follow up 24 weeks)										
1	RCT	no serious	no serious	no serious	serious[1]	46/103 (44.7%)	48/108 (44.4%)	RR 1.00 (0.74 to 1.36)	0 fewer per 100 (from 12 fewer to 16 more)	MODERATE
Mean healing time (days)										

Quality assessment						Number of patients		Effect		Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Hydrofiber	impregnated dressing	Relative (95% CI)	Absolute (95% CI)	
1	RCT	no serious	no serious	no serious	serious[2]	103	108	Mean healing time (days) (SD): Hydrofiber= 130.7 (52.4); Impregnated dressing = 127.8 (54.2), p > 0.05		MODERATE
Major and minor amputation (follow up 24 weeks)										
1	RCT	no serious	no serious	no serious	serious[1]	4/103 (3.9%)	1/108 (0.9%)	RR 4.19 (0.48 to 36.91)	3 more per 100 (from 0 fewer to 32 more)	MODERATE
Withdrawal due to Adverse events (follow up 24 weeks)										
1	RCT	no serious	no serious	no serious	serious[1]	11/103 (10.7%)	9/108 (8.3%)	RR 1.28 (0.55 to 2.96)	2 more per 100 (from 4 fewer to 16 more)	MODERATE
Complication (infection) (follow up 24 weeks)										
1	RCT	no serious	no serious	no serious	serious[1]	9/103 (8.7%)	12/108 (11.1%)	RR 0.79 (0.36 to 1.79)	2 fewer per 100 (from 7 fewer to 9 more)	MODERATE

[1] Total no. of events < 300.
[2] Total no. of events < 400.

Table 35: N-A vs Impregnated dressing (Jeffcoate et al, 2009; comparison 3)

Quality assessment						Number of patients		Effect		Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	N-A	Impregnated dressing	Relative (95% CI)	Absolute (95% CI)	
Complete wound healing (follow up 24 weeks)										

Quality assessment						Number of patients		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	N-A	Impregnated dressing	Relative (95% CI)	Absolute (95% CI)	Quality
1	RCT	no serious	no serious	no serious	serious[1]	41/106 (38.7%)	48/108 (44.4%)	RR 0.87 (0.63 to 1.20)	6 fewer per 100 (from 16 fewer to 9 more)	MODERATE
Mean healing time (days)										
1	RCT	no serious	no serious	no serious	serious[2]	106	108	Mean healing time (days) (SD): N-A = 125.8 (55.9); Impregnated dressing = 127.8 (54.2), p > 0.05		MODERATE
Major and minor amputation (follow up 24 weeks)										
1	RCT	no serious	no serious	no serious	serious[1]	2/106 (1.9%)	1/108 (0.9%)	RR 2.04 (0.19 to 22.14)	1 more per 100 (from 1 fewer to 19 more)	MODERATE
Withdrawal due to Adverse events (follow up 24 weeks)										
1	RCT	no serious	no serious	no serious	serious[1]	15/106 (14.2%)	9/108 (8.3%)	RR 1.70 (0.78 to 3.71)	6 more per 100 (from 2 fewer to 22 more)	MODERATE
Complication (infection) (follow up 24 weeks)										
1	RCT	no serious	no serious	no serious	serious[1]	7/106 (6.6%)	12/108 (11.1%)	RR 0.59 (0.24 to 1.45)	5 fewer per 100 (from 8 fewer to 5 more)	MODERATE

[1] Total no. of events < 300.
[2] Total no. of events < 400.

Table 36: Soft silicone dressing vs Vaseline gauze dressing

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SC + SJ		Relative (95% CI)	Absolute		
Cure Rate at 12 weeks - Soft silicone dressing (Zhang 2014)												
1	randomised trials	no serious risk of bias[8]	no serious inconsistency[5]	no serious indirectness[3]	serious[4]	none	18/24 (75%)	16/26 (61.5%)	RR 1.22 (0.83 to 1.79)	135 more per 1000 (from 105 fewer to 486 more)	MODERATE	
Adverse events at 12 weeks - Soft silicone dressing (Zhang 2014)												
1	randomised trials	no serious risk of bias[8]	no serious inconsistency[5]	no serious indirectness[3]	very serious[7]	none	3/24 (12.5%)	4/26 (15.4%)	RR 0.81 (0.2 to 3.26)	29 fewer per 1000 (from 123 fewer to 348 more)	LOW	

[1] Serious risk of bias due to unclear method of randomisation and blinding
[2] Serious inconsistency (I-squared between 33% and 66%)
[3] Population, intervention, outcome as specified in the review protcol
[4] Confidence intervals around the point estimate cross the MID line (either 0.75 or 1.25)
[5] Single study analysis
[6] No explanation was provided
[7] Confidence intervals around the point estimate cross both MID lines (0.75 and 1.25)
[8] No apparent risk of bias
[9] No inconsistency (I-squared less than 33%)
[10] Confidence intervals around point estimate do not cross MID
[11] Confidence intervals around point estimate cross line of no effect
[12] No inconsistency (Test for heterogeneity not applicable)
[13] Very serious inconsistency (I-squared greater than 67%)
[14] No events reported

I.10.8 Irremovable versus removable off-loading devices

Table 37: Total contact cast (TCC) versus removable footwear (Van de Weg et al 2008, Caravaggi 2000)

Quality assessment						Number of patients		Effect		Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	TCC	CTF	Relative (95% CI)	Absolute (95% CI)	
Complete wound healing (follow-up 16 weeks, 30 days) (Van de Weg 2008, Caravaggi 2000)										

Quality assessment						Number of patients		Effect		Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	TCC	CTF	Relative (95% CI)	Absolute (95% CI)	
2	RCT	serious[1]	no serious	no serious	serious[2]	19/49 (39.8%)	11/44 (25%)	RR 1.48 (0.55 to 3.99)	12 more per 100 (from 11 fewer to 75 more)	LOW
Wound surface reduction (cm^2) (follow-up 16 weeks) (Van de Weg 2008)										
1	RCT	serious[1]	no serious	no serious	serious[2]	23	20	Mean reduction (cm^2) (SD): TCC = -2.88 (2.5); CTF = -2.16 (3.4) Adjusted mean difference: 0.10 (95%CI: -0.92 to 0.72), p = 0.81		LOW
Time to wound healing (days) (Van de Weg 2008)										
1	RCT	serious[1]	no serious	no serious	serious[2]	23	20	Median time to wound healing (days) TCC= 90 days; CTF= 52 days (p=0.02)		LOW

[1] Randomisation and/or allocation inadequately reported
[2] Total no. of events < 300.

Table 38: Total contact cast (TCC) versus removable cast walker (RCW; Armstrong et al 2001, Armstrong et al 2005, Faglia et al 2010, Gutekunst et al 2011, Caravaggi 2007)

Quality assessment						Number of patients		Effect		Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	TCC	RCW	Relative (95% CI)	Absolute (95% CI)	
Complete wound healing (follow-up 12 weeks, 12 weeks, 90 days, follow up not reported)										
5	RCT	serious[1,5]	no serious	serious[4]	serious[2,3]	86/105 (81.9%)	71/110 (64.5%)	RR (non-event) 0.54	17 fewer per 100 (from 9	VERY LOW

Quality assessment						Number of patients		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	TCC	RCW	Relative (95% CI)	Absolute (95% CI)	Quality
								(0.33 to 0.88)	fewer to 25 fewer)	
Mean healing time (days) (Armstrong 2001, Armstrong 2005, Getekunst 2011)										
3	RCT	serious[1]	no serious	serious[4]	Serious[2,3]	53	59	Std. Mean Difference (95% CI) -1.14 (-2.43 - 0.15)		VERY LOW
Mean reduction in ulcer size (follow up 90 days) (Faglia 2010)										
1	RCT	Serious[5]	no serious	no serious	serious[2]	23	22	Mean reduction (cm^2) TCC= 73.6%; 1.2 cm^2 Removable walker = 90%; 1.73 cm^2 (p= 0.321)		LOW

[1] No allocation concealment, assessor not blinded.
[2] Total no. of events < 300.
[3] Total no. of events < 400 in one study
[4] Patients were assessed barefoot in one study
[5] Randomisation method not reported in two studies

Table 39: Total contact cast (iTCC) versus healing sandles (Lavery et al, 2014)

Quality assessment						Number of patients		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	TCC	Healing sandles	Relative (95% CI)	Absolute (95% CI)	Quality
Complete wound healing (follow up 12 weeks)										
1	RCT	serious[2, 3, 4, 5]	no serious	no serious	serious[1]	16/23 (69.6%)	10/23 (43.5%)	RR=0.54 (0.26 to 1.10)	20 fewer per 1000 (32 fewer to 4 more)	LOW
Mean healing time (days)										
1	RCT	serious[2, 3, 4, 5]	no serious	no serious	serious[1]	23	23	Mean healing time (weeks) (SD)		LOW

Quality assessment						Number of patients		Effect		Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	TCC	Healing sandles	Relative (95% CI)	Absolute (95% CI)	
								TCC = 5.4 ± 2.9 Healing sandles = 8.9 ± 3.5 P=<0.001		

[1] Total no. of events < 300.
[2] Unclear if allocation concealed adequately
[3] Unclear if differences between groups for all parameters at baseline (ulcer/amputation history)
[4] Single blind only
[5] uneven loss to follow up

Table 40: Total contact cast (iTCC) versus shear reducing removable boot (Lavery et al, 2014)

Quality assessment						Number of patients		Effect		Quality
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	TCC	Healing sandles	Relative (95% CI)	Absolute (95% CI)	
Complete wound healing (follow up 12 weeks)										
1	RCT	serious[2, 3, 4, 5]	no serious	no serious	serious[1]	16/23 (69.6%)	6/27 (22.2%)	RR=0.39 (0.20 to 0.75)	14 fewer per 1000 (6 fewer to 18 fewer)	LOW
Mean healing time (days)										
1	RCT	serious[2, 3, 4, 5]	no serious	no serious	serious[1]	23	27	Mean healing time (weeks) (SD) TCC = 5.4 ± 2.9 Shear walker = 6.7 ± 4.3 P=0.22		LOW

[1] Total no. of events < 300.
[2] Unclear if allocation concealed adequately
[3] Unclear if differences between groups for all parameters at baseline (ulcer/amputation history)
[4] Single blind only
[5] uneven loss to follow up

I.10.9 Irremovable versus irremovable off-loading devices

Table 41: Total contact cast (TCC) versus instant total contact cast (iTCC; Piaggesi, 2007. Katz, 2005)

Quality assessment						Number of patients		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	TCC	iTCC	Relative (95% CI)	Absolute (95% CI)	Quality
Complete wound healing (12 weeks) (Katz 2005, Piaggesi 2007)										
2	RCT	serious[1]	no serious	no serious	serious[2]	34/40 (85%)	34/41 (83%)	RR 1.06 (0.88 to 1.27)	5 more per 100 (from 10 fewer to 22 more)	LOW
Mean healing time (weeks) (Piaggesi, 2007)										
1	RCT	serious[1]	no serious	no serious	serious[3]	20	20	Mean healing time (weeks) (SD): TCC = 6.5 (4.4); Instant casting = 6.7 (3.4), p = 0.874		LOW
Treatment related adverse events (follow up 12 weeks) (Katz, 2005, Piaggesi, 2007)										
2	RCT	serious[1]	no serious	no serious	serious[2]	17/40 (43%)	13/41 (32%)	RR 1.37 (0.69 to 2.72)	12 more per 100 (from 10 fewer to 55 more)	LOW

[1] No allocation concealment, assessor not blinded.
[2] Total no. of events < 300.
[3] Total no. of events < 400

I.10.10 Irremovable off-loading devices versus dressing

Table 42: Total contact cast (TCC) versus dressing (Mueller et al, 1989)

Quality assessment						Number of patients		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	TCC	dressing	Relative (95% CI)	Absolute (95% CI)	Quality

Quality assessment						Number of patients		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	TCC	dressing	Relative (95% CI)	Absolute (95% CI)	Quality
Complete wound healing (follow up 6 weeks)										
1	RCT	very serious[1]	no serious	no serious	serious[2]	19/21 (90.5%)	6/19 (31.6%)	RR 2.87 (1.46 to 5.63)	59 more per 100 (from 15 more to 100 more)	VERY LOW

[1] No mention of randomisation methods, no allocation concealment, assessor not blinded.
[2] Total no. of events < 300.

I.10.11 Padding versus conventional therapy

Table 43: Felted foam padding versus half shoes (Zimny et al, 2002)

Quality assessment						Number of patients		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Felted foam	Half shoes	Relative (95% CI)	Absolute (95% CI)	Quality
Mean healing time (days)										
1	RCT	serious[1]	no serious	no serious	serious[2]	24	30	Average healing time (95% CI) Felted foam = 75.2 (67-84 days) Half shoes = 85.2 (79-92 days) P=0.03		LOW
Mean wound surface reduction (% per week)										
1	RCT	serious[1]	no serious	no serious	serious[2]	24	30	Mean wound radius reduction (95%CI) Felted foam = 0.48 mm (0.42-0.56) per week Half shoes = 0.39 mm (0.35-0.42) per week P=0.06		LOW

[1] No mention of randomisation methods, no allocation concealment
[2] Total no. of events < 300.

I.10.12 Padding versus padding

Table 44: Felt deflective padding (to the skin) versus Felt deflective padding (in the shoe; Nube et al, 2006)

Quality assessment						Number of patients		Effect		
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision			Relative (95% CI)	Absolute (95% CI)	Quality
Wound surface reduction (%) (follow up 4 weeks)										
1	RCT	serious[1]	no serious	no serious	serious[2]	15	17	<u>Wound surface reduction (%):</u> Skin = 73%; Shoe = 74%, z = 0.02, p = 0.9		LOW

[1] No allocation concealment, assessor not blinded.
[2] Total no. of events < 400

I.11 Review question 11 full GRADE profiles

Broad spectrum antibiotics vs. Broad spectrum antibiotics

Table 45: Ureidopenicilin / beta lactam inhibitor vs. Carboxypenicilin / beta lactam inhibitor

Piperacillin/Tazobactam (IV) vs. Ticarcillin/clavulanate (IV) (Tan et al. 1993)

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Piperacillin/ Tazobactam (IV)	ticarcillin/ calvulanate (IV)	Relative (95% CI)	Absolute	Quality
Clinical outcome: cured[a] (follow-up 10-14 days)											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	7/18 (38.9%)	6/17 (35.3%)	RR 1.10 (0.46 to 2.62) NNTB = N/A	4 more per 100 (from 19 fewer to 57 more)	LOW

Dosage: Piperacillin/Tazobactam (3 g/375 mg) every 6 hours ; Ticarcillin/Clavulanate (3 g/100 mg) every 6 hours, for at least 5 days.

[a] Cured = resolution of signs and symptoms.

[1] Allocation concealment unclear, extracted subgroup data.

[2] Total no. of events <300.

Table 46: Carbapenem / beta lactam inhibitor vs. Ureidopenicillin / Clindamycin

Imipenem/ Cilastatin (IV) vs. Piperacilin/ Clindamycin (IV) (Paul-Bouter et al. 1996)

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Imipenem/ Cilastatin (IV)	piperacilin/ clindamycin (IV)	Relative (95% CI)	Absolute	Quality
Clinical outcome: cured[a] (follow-up 10 days)											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	4/21 (19%)	6/24 (25%)	RR 0.76 (0.25 to 2.34) NNTB = N/A	6 fewer per 100 (from 19 fewer to 33 more)	LOW
Microbiological outcome: patients achieved eradication of pathogen(s) (follow-up 10 days)											
1	RCT	serious[1]	no serious	no serious indirectness	serious[2]	none	9/20 (45%)	16/23 (69.6%)	RR 0.65 (0.37 to 1.13) NNTB = N/A	24 fewer per 100 (from 44 fewer to 9 more)	LOW
No. of patients experienced treatment-related AEs (follow-up 10 days)											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	18/21 (85.7%)	12/24 (50%)	RR 1.71 (1.11 to 2.65) NNTH = 3 (2 to 12)	36 more per 100 (from 6 more to 83 more)	LOW

Dosage: Piperacillin (3000 mg QID) + clindamycin (600 mg TID); Imipenem/Cilastatin (500 mg QID), for at least 10 days.

[a] Cured = resolution of signs and symptoms.

[1] Allocation concealment unclear.

[2] Total no. of events <300

Table 47: Carbapenem/ beta lactam inhibitor vs. Aminopenicillin/ beta lactam inhibitor

Imipenem/ Cilastatin (IV) vs. Amplicillin/Sulbactam (IV) (Grayson et al. 1994)

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Imipenem /Cilastatin (IV)	Amplicilin /Sulbactam (IV)	Relative (95% CI)	Absolute	Quality
Clinical outcome: cured[a] (unit: no. of infections) (follow-up 6 days[1])											
1	RCT	serious[2]	no serious	no serious	serious[3]	none	39/48 (81.3%)	41/48 (85.4%)	RR 0.95 (0.80 to 1.14) NNTB = N/A	4 fewer per 100 (from 17 fewer to 12 more)	LOW
Microbiological outcome: infections achieved eradiction of pathogen(s) (follow-up 6 days[1])											
1	RCT	serious[2]	no serious	no serious	serious[3]	none	32/48 (66.7%)	36/48 (75%)	RR 0.89 (0.69 to 1.15) NNTB = N/A	8 fewer per 100 (from 23 fewer to 11 more)	LOW
No. of patients experienced significant[b] AEs (follow-up 6 days[1])											
1	RCT	serious[2]	no serious	no serious	serious[3]	none	7/46 (15.2%)	9/47 (19.1%)	RR 0.79 (0.32 to 1.96) NNTH = N/A	4 fewer per 100 (from 13 fewer to 18 more)	LOW

Dosage: Imipenem/Cilastatin (500 mg) every 6 hours. Ampicillin/Sulbactam (3 g) every 6 hours.
[a] Cured = resolution of soft-tissue infection.
[b] Significant = a severe reaction necessitating withdrawal of the study treatment.
[1] 6 days or until therapy was completed.
[2] Allocation concealment unclear.
[3] Total no. of events <300.

Table 48: Ureidopenicillin/ beta lactam inhibitor vs. Aminopenicillin/ beta lactam inhibitor

Piperacillin/Tazobactam (IV) vs. Ampicillin/Sulbactam (IV) (Harkless et al. 2005)

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Piperacillin/ Tazobactam (IV)	amplicilin/ Sulbactam (IV)	Relative (95% CI)	Absolute	Quality
Clinical outcome: cured or improvement[a] (follow-up 14-21 days)											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	99/139 (71.2%)	100/150 (66.7%)	RR 1.07 (0.92 to 1.25) NNTB = N/A	5 more per 100 (from 5 fewer to 17 more)	LOW
Pathogen outcome: eradication of Gram+ aerobes (unit: patient) (follow-up 14-21 days)											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	51/65 (78.5%)	46/64 (71.9%)	RR 1.09 (0.89 to 1.33) NNTB = N/A	6 more per 100 (from 8 fewer to 24 more)	LOW
No. of patients experienced at least 1 treatment-related AEs (follow-up 14-21 days)											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	29/155 (18.7%)	21/159 (13.2%)	RR 1.42 (0.85 to 2.37) NNTH = N/A	6 more per 100 (from 2 fewer to 18 more)	LOW
Withdrawals due to treatment-related AEs (follow-up 14-21 days)											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	18/155 (11.6%)	13/159 (8.2%)	RR 1.42 (0.72 to 2.80) NNTH = N/A	3 more per 100 (from 2 fewer to 15 more)	LOW

Dosage: Piperacillin/Tazobactam (4 g/0.5 g q8h); Ampicillin/Sulbactam (2 g/1 g q6h), for 4 to 14 days.
[a] Cured or improvement = resolution of signs and symptoms, or sufficient clinical improvement that the majority of symptoms of infection had abated.
[1] Open-labelled trial, no blinding.
[2] Total no. of events <300.

Table 49: Cephalosporins vs. Cephalosporins

Cerftizoxime (IV) vs. Cefoxitin (IV) (Hughes et al. 1987)

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Cerftizoxime (IV)	cefoxitin (IV)	Relative (95% CI)	Absolute	
Clinical outcome: cured or improvement[a] (follow-up varied)											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	23/28 (82.1%)	17/26 (65.4%)	RR 1.21 (0.88 to 1.66) NNTB = N/A	14 more per 100 (from 8 fewer to 43 more)	LOW
No. of patients experienced treatment-related AEs (follow-up varied)											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	16/33 (48.5%)	19/30 (63.3%)	RR 0.77 (0.49 to 1.19) NNTH = N/A	15 fewer per 100 (from 32 fewer to 12 more)	LOW

Dosage: Ceftizoxime, up to 4 g IV every 8 hours. Cefoxitin, up to 2 g IV every 4 hours.

[a] Cured or improvement = resolution of all signs and symptoms or sufficient improvement such that additional antimicrobial therapy was not required.

[1] Allocation concealment unclear, blinding unclear.

[2] Total no. of events <300.

Table 50: Ureidopenicillin/ beta lactam inhibitor vs. Carbapenem

Piperacillin/Tazobactam (IV) vs. Ertapenem (IV) (Lipsky et al. 2005)

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Piperacillin/ Tazobactam (IV)	ertapenem (IV)	Relative (95% CI)	Absolute	

Clinical outcome: cured[a] (follow-up 5 days)											
1	RCT	serious[1]	no serious	no serious	no serious	none	202/219 (92.2%)	213/226 (94.2%)	RR 0.98 (0.93 to 1.03) NNTB = N/A	2 fewer per 100 (from 7 fewer to 3 more)	LOW
Pathogen outcome: eradication of Gram+ aerobes (unit: pathogen) (follow-up 5 days)											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	122/146 (83.6%)	135/151 (89.4%)	RR 0.93 (0.85 to 1.02) NNTB = N/A	6 fewer per 100 (from 13 fewer to 2 more)	LOW
Pathogen outcome: eradication of Gram- aerobes (unit: pathogen) (follow-up 5 days)											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	40/51 (78.4%)	62/67 (92.5%)	RR 0.85 (0.72 to 0.99) NNTB = 7 (4 to 62)	14 fewer per 100 (from 1 fewer to 26 fewer)	LOW
No. of patients experienced treatment-related AEs (follow-up 5 days)											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	57/291 (19.6%)	44/295 (14.9%)	RR 1.31 (0.92 to 1.88) NNTH = N/A	5 more per 100 (from 1 fewer to 13 more)	LOW
Withdrawals due to treatment-related AEs (follow-up 5 days)											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	6/291 (2.1%)	3/295 (1%)	RR 2.03 (0.51 to 8.03) NNTH = N/A	1 more per 100 (from 0 fewer to 7 more)	LOW

Dosage: Ertapenem (1g bolus, followed by a saline placebo every 6 hours for three additional doses, IV); Piperacillin/Tazobactam (3 to375 g every 6 hours, IV), for 5 days.
[a] Cured = resolution of all signs and symptoms.
[1] Open-labelled study, no blinding.
[2] Total no. of events <300.

Table 51: Ertapenem ± Vancomycin vs. Tigecycline

Ertapenem ± Vancomycin (IV) vs. Tigecycline (IV) (Lauf et al, 2013)

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Ertapenem ± Vancomycin (IV)	Tigecycline (IV)	Relative (95% CI)	Absolute	Quality
Clinical outcome: cured[a] (follow-up 12-92 days)											
1	RCT	serious[1]	no serious	no serious	no serious	None[2]	334/405 (82.5%)	316/408 (77.5%)	RR 1.06 (0.99 to 1.14) NNTB = N/A	46 more per 1000 (from 8 fewer to 108 more)	MODERATE
Clinical outcome: study withdrawal due to adverse events (follow-up 12-92 days)											
1	RCT	serious[1]	no serious	no serious	Serious[3]	None[2]	2/467 (0.4%)	10/477 (2.1%)	RR 0.20 (0.05 to 0.93) NNTH = N/A	17 fewer per 1000 (from 1 fewer to 20 fewer)	LOW
Clinical outcome: drug discontinuation due to adverse events (follow-up 12-92 days)											
1	RCT	serious[1]	no serious	no serious	Serious[3]	None[2]	27/467 (5.8%)	42/477 (8.8%)	RR 0.66 (0.41 to 1.05) NNTH = N/A	30 fewer per 1000 (from 52 fewer to 4 more)	LOW

Dosage: Ertapenem (1g in 100ml normal saline administered over 30 minutes every 24 hours, IV); Tigecycline (150 mg in 100ml of normal saline infused over 30 minutes every 24 hours, IV), for up to 28 days, or up to 42 days for osteomyelitis.
[a] Cured = resolution of all signs and symptoms such that no further antibiotic therapy required.
[1] Unclear allocation concealment, participants were taken from many different sites internationally unclear if standard of care was similar for all participants
[2] Industry funded
[3] Event number <300

Table 52: Ureidopenicillin/ beta lactam inhibitor vs. Carbapenem/ beta lactam inhibitor

Piperacillin/Tazobactam (IV) vs. Imipenem/Cilastatin (IV) Saltoglu et al (2010)

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Piperacillin/ Tazobactam (IV)	Imipenem/Cilastatin (IV)	Relative (95% CI)	Absolute	Quality
Clinical outcome: cured[a] (follow-up 5 days[1])											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	14/30 (46.7%)	9/32 (28.1%)	RR 1.66 (0.84 to 3.25)	19 more per 100 (from 5 fewer to 63 more)	LOW
Microbiological outcome: infections[b] achieved eradication of pathogen(s) (follow-up 6 days[1])											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	23/24 (95.8%)	24/25 (96%)	RR 1.00 (0.89 to 1.12)	0 fewer per 100 (from 8 fewer to 8 more)	LOW
Number of patients requiring amputations											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	18/30 (60%)	22/32 (68.8%)	RR 0.87 (0.60 to 1.27)	9 fewer per 100 (from 27 fewer to 10 more)	LOW
No. of patients experienced significant AEs											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	9/30 (30%)	3/32 (9.4%)	RR 3.20 (0.96 to 10.71)	21 more per 100 (from 4 more to 37 more)	LOW

Dosage: 4g Piperacillin/Tazobactam (IV) 3 times a day vs. 500mg imipenem/Cilastatin (IV) 4 times a day;
[a] Cured = successful clinical response.
[b] Microbiological outcome = no of patients with a positive culture
[1] Open label trial; [2] Total no. of events <300

Table 53: Cephalosporin vs. Aminopenicillin/ beta lactam inhibitor

Cefoxitin (IV) vs. Amplicilin/Sulbactam (IV) (Erstad et al. 1997)

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Cefoxitin (IV)	Amplicilin/ Sulbactam (IV)	Relative (95% CI)	Absolute	Quality
Clinical outcome: cured[a] (follow-up 5 days[1])											
1	RCT	serious[2]	no serious	no serious	serious[3]	none	7/18 (38.9%)	1/18 (5.6%)	RR 7.00 (0.95 to 51.25) NNTB = N/A	33 more per 100 (from 0 fewer to 279 more)	LOW
Clinical outcome: length of hospital stay (days)											
1	RCT	serious[2]	no serious y	no serious	serious[4]	none	18	18	Mean length of hospital stay (days) (range): Cefoxitin = 12.1 (4 to 39) Ampicillin/Sulbactam = 21.1 (6 to 58), p = 0.06		LOW
No. of patients experienced treatment- related AEs (follow-up 5 days[1])											
1	RCT	serious[2]	no serious	no serious	serious[3]	none	6/18 (33.3%)	7/18 (38.9%)	RR 0.86 (0.36 to 2.05) NNTH = N/A	5 fewer per 100 (from 25 fewer to 41 more)	LOW

Dosage: Cefoxitin 2 g every 6 hours; Ampicillin/Sulbactam 3 g every 6 hours, for at least 5 days.
[a] Cured = disappearance of all signs and symptoms associated with active infection.
[1] 5 days but could be more to the discretion of the attending surgeon.
[2] Allocation concealment unclear. [3] Total no. of event <300.
[4] Total no. of participants <400.

Table 54: Quinolone vs. Ureidopenicillin/ beta lactam inhibitor & Aminopenicillin/ beta lactam inhibitor

Moxifloxacin (IV or oral) vs. PiperacillinTazobactam (IV)& Amoxicillin/Clavulanate (oral) Schaper et al (2013)

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Moxifloxacin (IV or oral)	Piperacillin/ Tazobactam (IV) & Amdinocillin/ clavulanic acid (oral)	Relative (95% CI)	Absolute	Quality
Clinical outcome: cured[a] (follow-up 6 days)											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	84/110 (76.4%)	75/96 (78.1%)	RR 0.97 (0.84 to 1.13)	2 fewer per 100 (from 10 fewer to 6 more)	LOW
Clinical oucome: additional surgeries requiring amputation											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	23/110 (20.9%)	24/96 25%)	RR 0.80 (0.48 to 1.32)	1 fewer per 100 (from 13 fewer to 3 more)	LOW
Microbiological outcome: patients achieved eradication of pathogen(s) (follow-up 6 days)											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	66/92 (71.7%)	61/85 (71.8%)	1.00 (0.83 to 1.20)	0 fewer per 100 (from 9 fewer to 9 more)	LOW
No. of patients experienced significant Adverse Events [c] (follow-up 6 days)											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	38/123 (30.9%)	35/110 (31.8%)	0.97 (0.66 to 1.42)	1 fewer per 100 (from 9 fewer to 7 more)	LOW

Dosage: 4g/0.5g Piperacillin/Tazobactam (IV) 3 times a day followed by 875/125mg Amoxicillin/clavulanate twice a day (oral) vs. 400mg moxifloxacinn (IV/oral) once a day;
a Cured = disappearance of all signs and symptoms associated with active infection Based on PP population (patients who received drug for at least 7 days with clinical evaluation at test of cure)
b Bacteriological response based on MBV population (all PP patients for whom at least 1 causative organism could be cultured)
c Adverse Events based on ITT population (all patients who received 1 dose of study drug and had at least 1 observation after taking study medication)
[1]Allocation concealment unclear. 2 Total no. of events <300.

Table 55: Cephalosporin vs. Cephalosporin

Ceftriaxone (IV or IM) vs. Cefazolin (IV or IM) Bradsher & Snow (1984)

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Ceftriaxone (IV or IM)	Cefazolin (IV or IM)	Relative (95% CI)	Absolute	
Clinical outcome: cured[a] (follow-up 7 days)											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	21/42 (50.0%)	25/42 (60.0%)	RR 0.84 (0.57 to 1.24)	10 fewer per 100 (from 25 fewer to 6 more)	LOW
Microbiological outcome: patients achieved eradication of pathogen(s) (follow-up 7 days)[b]											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	6/10 (60.0%)	4/10 (40%)	RR 1.50 (0.60-3.37)	20 more per 100 (from 13 fewer to 52 more)	LOW
No. of patients experienced treatment-related adverse events (follow-up 7 days)											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	12/42 (28.5%)	13/42 (31%)	RR 0.92 (0.48 to 1.78)	2 fewer per 100 (from 17 fewer to 11 more)	LOW

No. of surgical procedures											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	15/42 (35.7%)	12/42 (28.5%)	RR 1.25 (0.67 to 2.34)	7 more per 100 (from 8 fewer to 22 more)	LOW

Dosage: 1g ceftriaxone (IV or IM) once a day vs. 1g ceftriaxone (IV or IM) every 6 to 8 hours
[a] Cured = disappearance of all signs and symptoms associated with active infection.
[b] Eradication of pathogens based on sub-population with Diabetic foot ulcers only
[1] Lack of allocation concealment; [2] Total no. of events <300.

Table 56: Quinolone vs. Aminopenicillin/ beta lactam inhibitor

Ofloxacin (IV to oral) vs. Ampicillin/Sulbactam (IV) Amoxicillin/Clavulanic acid (oral) (Lipsky et al. 1997)

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Ofloxacin (IV to oral)**	**Amplicilin/Sulbactam (IV) to amoxicillin/ clavulanic (oral)**	**Relative (95% CI)**	**Absolute**	**Quality**
Clinical outcome: cured[a] (follow-up 7 days)											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	40/47 (85.1%)	34/41 (82.9%)	RR 1.03 (0.85 to 1.23) NNTB = N/A	2 more per 100 (from 12 fewer to 19 more)	LOW
Microbiological outcome: patients achieved eradication of pathogen(s) (follow-up 7 days)											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	39/47 (83%)	36/41 (87.8%)	RR 0.95 (0.79 to 1.12) NNTB = N/A	4 fewer per 100 (from 18 fewer to 11 more)	LOW
Pathogen outcome: Eradication of Gram+ aerobes (unit: pathogen) (follow-up 7 days)											

1	RCT	serious[1]	no serious	no serious	serious[2]	none	33/47 (70.2%)	38/43 (88.4%)	RR 0.79 (0.64 to 0.99) NNTB = 6 (3 to 79)	19 fewer per 100 (from 1 fewer to 32 fewer)	LOW
Pathogen outcome: Eradication of Gram- aerobes (unit: pathogen) (follow-up 7 days)											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	18/19 (94.7%)	15/18 (83.3%)	RR 1.14 (0.90 to 1.43) NNTB = N/A	12 more per 100 (from 8 fewer to 36 more)	LOW
No. of patients experienced treatment-related adverse events (follow-up 7 days)											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	17/47 (36.2%)	9/41 (22%)	RR 1.65 (0.83 to 3.29) NNTH = N/A	14 more per 100 (from 4 fewer to 50 more)	LOW

Dosage: Ofloxacin 400 mg (IV and oral) every 12 hours. Ampicillin (1 to 2 g)/Sulbactam (0.5 to 1g) (IV) every 6 hours; then 500 mg of amoxicillin/125 mg of clavulanic acid orally every 8 hours.
[a] Cured = disappearance of all signs and symptoms associated with active infection.
[1] Allocation concealment unclear.
[2] Total no. of events <300.

Table 57: Quinoonle vs. Aminopenicillin/ beta lactam inhibitor

Moxifloxacin (IV to oral) vs. Amoxicillin/ Clavulanate (IV & oral) (Vick-Fragoso et al 2009)

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Moxifloxacin (IV to oral)	Amoxicillin/clavulanate (IV or oral)	Relative (95% CI)	Absolute	Quality
Clinical outcome: cured[a] (follow-up 14-28 days)											

1	RCT	serious[1]	no serious	serious[2]	no serious	none	254/315 (80.6%)	268/317 (84.5%)	RR 0.95 (0.88 to 1.02)	4 fewer per 100 (from 8 fewer to 1 more)	LOW
Mean duration of treatment (days)											
1	RCT	serious[1]	no serious	serious[2]	no serious	none	13.5	14.1	Mean (days) (SD) Mean difference = -0.60 (95%CI: -1.62 to 0.42)		LOW
Microbiological outcome: infections achieved eradication of pathogen(s)[b] ((follow-up 14-28 days)											
1	RCT	serious[1]	no serious	serious[2]	no serious	none	127/167 (76.0%)	140/172 (81.4%)	RR 0.93 (0.84 to 1.04)	5 fewer per 100 (from 2 fewer to 1 more)	LOW
No. of patients experienced significant AEs[c] (follow-up 14-28 days)											
1	RCT	serious[1]	no serious	serious[2]	no serious	none	211/406 (52.0%)	190/397 (47.9%)	RR 1.09 (0.95 to 1.25)	4 more per 100 (from 1 fewer to 9 more)	LOW

Dosage: 1000mg/200mg Amoxicillin/clavulanate three times a day (IV) followed by 500mg/125mg Amoxicillin/clavulanate (oral) vs. 400mg moxifloxacin (IV) once a day followed by 400mg moxifloxacin(oral) once a day

[a] Cured = disappearance of all signs and symptoms associated with active infection. Based on PP population (patients with at least 80% compliance)

[b] Bacteriological response based on MBV population (all PP patients for whom at least 1 causative organism isolated at baseline amd a microbiological evaluation at test of cure)

[c] Adverse events based on ITT/ safety population (all patients receiving at least one study drug)

[1] Open label trial; [2] Population includes all patients with a CSSI .

Table 58: Quinolone vs. Ureidopenicillin/ beta lactam inhibitor

Moxifloxacin (IV to oral) vs. Piperacillin/ Tazobactam (IV) to Amoxillin/Clavulanate (oral) (Lipsky et al. 2007)

Quality assessment	Summary of findings		
	No of patients	Effect	Quality

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Moxifloxacin (IV to oral)	Piperacillin/ Tazobactam (IV) to moxifloxin vs. amoxillin/ clavulanate (oral)	Relative (95% CI)	Absolute	
Clinical outcome: cured[a] (follow-up 10-42 days)											
1	RCT	no serious	no serious	no serious	serious[1]	none	28/63 (44.4%)	25/64 (39.1%)	RR 1.14 (0.75 to 1.72) NNTB = N/A	5 more per 100 (from 10 fewer to 28 more)	MODERATE
Pathogen outcome: eradication of Gram+ aerobes (unit: pathogen) (follow-up 10-42 days)											
1	RCT	no serious	no serious	no serious	serious[1]	none	24/37 (64.9%)	27/42 (64.3%)	RR 1.01 (0.73 to 1.40) NNTB = N/A	1 more per 100 (from 17 fewer to 26 more)	MODERATE
Pathogen outcome: eradication of Gram- aerobes (unit: pathogen) (follow-up 10-42 days)											
1	RCT	no serious	no serious	no serious	serious[1]	none	2/6 (33.3%)	7/12 (58.3%)	RR 0.57 (0.17 to 1.95) NNTB = N/A	25 fewer per 100 (from 48 fewer to 55 more)	MODERATE
No. of patients experienced treatment-related AEs (follow-up 10-42 days)											
1	RCT	no serious	no serious	no serious	serious[1]	none	20/63 (31.7%)	8/64 (12.5%)	RR 2.54 (1.21 to 5.34) NNTH = 5 (3 to 20)	19 more per 100 (from 3 more to 54 more)	MODERATE
Withdrawals due to treatment-related AEs (follow-up 10-42 days)											
1	RCT	no serious	no serious	no serious	serious[1]	none	15/63	15/64	RR 1.02 (0.54 to	0 more per 100	MODERATE

							(23.8%)	(23.4%)	1.90) NNTH = N/A	(from 11 fewer to 21 more)	

Dosage: Moxifioxacin (400 mg/day) (IV for at least 3 days), then 400 mg orally; Piperacillin/Tazobactam (3.0 g/0.375 g every 6 hours) for at least 3 days, then amoxicillin/clavulanate (800 mg every 12 hours orally), for total duration of 7 to 14 days.
[a] Cured = resolution of all signs and symptoms or sufficient improvement such that additional antimicrobial therapy was not required. [1] Total no. of events <300.

Table 59: Quinolone vs. Ureidopenicillin/ beta lactam inhibitor

Clinafloxacin (IV to oral) vs. Piperacillin/ Tazobactam (IV to oral) (Siami et al 2001)

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Clinafloxacin (IV to oral)	Piperacillin/ Tazobactam (IV to oral)	Relative (95% CI)	Absolute	Quality
Clinical outcome: cured or improvement[a] (follow-up 14 days)											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	15/29 (51.7)	12/25 (48.0)	RR 1.07 (0.63 to 1.85)	3 more per 100 (from 15 fewer to 23 more)	LOW
Microbiological outcome: patients achieved eradication of pathogen(s) (follow-up 14 days)											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	32/73 (43.8)	15/47 (31.9)	RR 1.37 (0.84 to 2.25)	11 more per 100 (from 0 fewer to 24 more)	LOW

Dosage: Clinafloxacin 200 mg (IV) every 12 hours switched after 3 days to Clinafloxacin 200mg (oral) every 12 hours; vs. 3.375g of Piperacillin/ Tazobactam (IV) every 6 hours switched after 3 days to 500mg Amoxicillin/ clavulanate (oral) every 8 hours.
[a] Cured = disappearance of all signs and symptoms associated with active infection. N. based on diabetic foot population only.
[1] Allocation concealment unclear. [2] Total no. of events <300.

Table 60: Quinolone & Gentamicin sponge dressing vs. Quinolone & placebo sponge dressing

Levofloxacin & Gentamicin collagen sponge (oral & topical) vs. Levofloxacin & placebo sponge (oral & topical) (Lipsky et al 2012)

Quality assessment	Summary of findings

							No of patients		Effect		
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Levofloxacin (Iv or oral) & gentamicin collagen sponge dressing (topical**	**Levofloxacin (Iv or oral) & placebo sponge dressinhg (topical)**	**Relative (95% CI)**	**Absolute**	**Quality**
Clinical outcome: cured or improvement[a] (follow-up varied)											
1	RCT	very serious[1,2]	no serious	no serious	Serious[3]	none	24/26 (92.3%)	7/10 (70%)	RR 1.32 (0.87 to 2.01)	23 more per 100 (from 10 more to 35 more)	VERY LOW
Microbiological outcome: patients achieved eradication of pathogen(s) (follow-up 3 days)											
1	RCT	very serious[1,2]	no serious	no serious	Serious[3]	none	20/26 (76.9%)	1/8 (12.5%)	RR 6.15 (0.97 to 38.96)	64 more per 100 (from 47 more to 82 more)	VERY LOW
No. of patients experienced significant AEs											
1	RCT	very serious[1,2]	no serious	no serious	Serious[3]	none	11/38 (28.9%)	5/18 (27.8%)	RR 1.04 (0.42 to 2.56)	1 more per 100 (from 14 fewer to 17 more) +	VERY LOW

Dosage: 750mg Levofloxacin (IV or oral) plus 50mg or 200mg gentamicin sulphate applied on a 5x5 cm or a 10x10cm dressing vs. 750mg Levofloxacin (IV or oral) once a day plus placebo sponge dressing

[a] Cured = clinical cure at end of treatment

[1] Lack of allocation concealment; [2] Pilot study [3]Total no. of events <300.

Broad spectrum & Broad spectrum vs. Broad spectrum

Table 61: Nitroimidazole & Cephalosporin vs. carboxypenicillin/ beta lactam inhibitor

Metronidazole & Ceftriaxone (IV) vs. Ticarcillin/ Clavulanate (IV) (Clay et al 2004)

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Metronidazole (IV) & ceftriaxone (IV)	Ticarcillin/ clavulanate (IV)	Relative (95% CI)	Absolute	Quality
Clinical outcome: cured[a] ((follow-up 4 days)											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	31/36 (86%)	28/34 (82%	RR 1.04 (0.85 to 1.28)	4 more per 100 (from 8 fewer to 16 more)	LOW
Mean duration of treatment (days)											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	6.7	6.1	Mean (days) (SD) Mean difference = -0.60 (95%CI: -1.20 to 2.40)		LOW

Dosage: 1g metronidazole (IV) & 1g ceftriaxone once a day vs. 3.1g ticarcillin/clavulanate (IV) once a day
[a] Cured = disappearance of all signs and symptoms associated with active infection.
[1] Open label trial; [2] Total no. of events <300.

Table 62: Lincosamide antibiotics vs. cephalosporins

Clindamycin (oral) vs. Cephalexin (oral) (Lipsky et al. 1990)

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	AB	control	Relative (95% CI)	Absolute	Quality
Clinical outcome: complete healing (follow-up 2 weeks)											

1	RCT	serious[1]	no serious	no serious	serious[2]	none	10/25 (40%)	9/27 (33.3%)	RR 1.20 (0.59 to 2.46) NNTB = N/A	7 more per 100 (from 14 fewer to 49 more)	LOW

Dosage: Clindamycin (300 mg orally), four times daily for 2 weeks. Cephalexin (500 mg orally), four times daily for 2 weeks.
[1] Blinding and allocation concealment unclear.
[2] Total no. of events <300.

Table 63: Oxazolidinone vs. Penicillin/ beta lactam inhibitor & Aminopenicillin/ beta lactam inhibitor

Linezolid (IV or oral) vs. Amplicillin/Sulbactam (IV) or Amoxicillin/Clavulanate (oral) (Lipsky et al. 2004)

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Linezolid (IV)	amplicillin/ Sulbactam (IV) or amoxicillin /clavulanate (oral)	Relative (95% CI)	Absolute	Quality
Clinical outcome: cured[a] (follow-up 15-21 days)											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	165/203 (81.3%)	77/108 (71.3%)	RR 1.14 (0.99 to 1.31) NNTB = N/A	10 more per 100 (from 1 fewer to 22 more)	LOW
Pathogen outcome: eradication of Gram+ aerobes (unit: patient) (follow-up 15-21 days)											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	143/185 (77.3%)	71/100 (71%)	RR 1.09 (0.94 to 1.26) NNTB = N/A	6 more per 100 (from 4 fewer to 18 more)	LOW
Pathogen outcome: eradication of Gram- aerobes (unit: patient) (follow-up 15-21 days)											

1	RCT	serious[1]	no serious	no serious	serious[2]	none	65/81 (80.2%)	23/34 (67.6%)	RR 1.19 (0.92 to 1.53) NNTB = N/A	13 more per 100 (from 5 fewer to 36 more)	LOW
No. of patients experienced treat-related AEs (follow-up 15-21 days)											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	64/241 (26.6%)	12/120 (10%)	RR 2.66 (1.49 to 4.73) NNTH = 6 (4 to 12)	17 more per 100 (from 5 more to 37 more)	LOW
Withdrawals due to treatment-related AEs (follow-up 15-21 days)											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	18/241 (7.5%)	4/120 (3.3%)	RR 2.24 (0.78 to 6.47) NNTH = N/A	4 more per 100 (from 1 fewer to 18 more)	LOW

Dosage: Linezolid (600 mg q12h either IV or per oral); ampicillin/sulbaclam (1.5 to 3 g q6h IV), or amoxicillin/clavulanate (500-875 mg every 8-12 hours orally), for 7 to 28 days.
[a] Cured = resolution of all signs and symptoms.
[1] Open-labelled study, no blinding.
[2] Total no. of events <300.

Narrow spectrum & Broad spectrum vs. Broad spectrum

Table 64: Penicillin plus Cephalosporin vs. Cephalosporin

Amdinocillin plus Cefoxitin (IV) vs. Cefoxitin (IV) (File & Tan 1983)

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Amdinocillin (IV) & cefoxitin (IV)	Cefoxitin (IV))	Relative (95% CI)	Absolute	Quality
Satisfactory clinical response[a] (follow up 6-20 days)											
1	RCT	Serious[1]	no serious	no serious	serious[2]	none	18/20 (90%)	15/21 (71.0%)	RR 1.26 (0.93 to 1.71)	19 more per 100 (from 5 more to 33 more)	LOW
Microbiological outcome: infections achieved eradication of pathogen(s)											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	33/40 (83.0%)	22/34 (65.0%)	RR 1.28 (0.96 to 1.70)	18 more per 100 (from 5 more to 30 more)	LOW
No of patients requiring amputation											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	2/20(1 0.0%)	4/21 (19.04%)	RR 0.53 (0.11 to 2.56)	9 fewer per 100 (from 23 fewer to 5 more)	LOW

Dosage: 1omg/kg amdinoillin (IV) every 4 to 6 hours plus 1 to2mg cefoxitin (IV) every 4 to 6 hours vs. 1 to 2g cefoxitin (IV) every 4 to 6 hours

[a b] Satisfactory symptomatic response = cure or improvement of presenting signs and symptoms

[1] Lack of allocation concealment; [2] Total no. of events <300.

Narrow spectrum & Narrow spectrum vs. Narrow spectrum & Narrow spectrum

Table 65: Lipopeptide & semi-synthetic penicillin vs. Glycopeptide & semi-synthetic penicillin

Daptomycin & Nafcillin or Oxacillin or Cloxacillin or Flucloxacillin (IV) vs. Vancomycin & Nafcillin or, Oxacillin or Cloxacillin or Flucloxacillin (Lipsky et al 2005)

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Daplomycin (IV)	nafcillin or cloxacillin or flucloxacillin (IV)	Relative (95% CI)	Absolute	Quality
Clinical outcome: cured[a] (follow-up 6-20 days)											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	16/25 (64%)	19/27 (70.4%)	RR 0.91 (0.62 to 1.33) NNTB = N/A	6 fewer per 100 (from 27 fewer to 23 more)	LOW

Dosage: Daptomycin (4 mg/kg every 24 hours IV over 30 mins) for 7 to 14 days; or a narrow-spectrum penicillin (nafcillin, oxacillin, cloxacillin or flucloxacillin, depending on the investigator's choice, given in equally divided doses totalling 4 to12 g/day IV).
[a] Cured = resolution of all signs and symptoms.
[1] Allocation concealment not clear.
[2] Total no. of events <300.

I.12 Review question 12 full GRADE profiles

I.12.1 Rate of cure of diabetic foot ulcers for adjunctive therapies vs standard care

Table 66: Cure rate at 12 weeks for adjunctive therapies vs standard care

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SC + SJ	SC	Relative (95% CI)	Absolute		
Cure Rate at 12 weeks – Platelet Growth factor (Agrawal 2009, Hardikar 2005, Jaiswal 2010, Robson 2005)												
4	randomised trials	serious[1,3]	Very serious [14]	no serious indirectness	serious[4]	reporting bias[5]	308/646 (47.7%)	132/351 (37.6%)	RR 1.38 (0.91 to 2.1)	143 more per 1000 (from 34 fewer to 414 more)	VERY LOW	
Cure Rate at 12 weeks - B2 Growth factor (Robson 1999)												
1	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	serious[4]	reporting bias[5]	77/131 (58.8%)	24/46 (52.2%)	RR 1.13 (0.82 to 1.54)	68 more per 1000 (from 94 fewer to 282 more)	VERY LOW	
Cure Rate at 12 weeks – Fibroblast Growth factor (Richard 1995, Uchi 2009)												
2	randomised trials	serious[1,7,8]	serious[9]	no serious indirectness	very serious	none[10]	60/101 (59.4%)	27/55 (49.1%)	RR 0.97 (0.42 to 2.26)	15 fewer per 1000 (from 285 fewer to 619 more)	VERY LOW	
Cure Rate at 12 weeks - CT-102 Growth factor (Steed 1992)												
1	randomised trials	serious[1,3]	no serious inconsistency	no serious indirectness	very serious[11]	none[10]	5/7 (71.4%)	1/6 (16.7%)	RR 4.29 (0.67 to 27.24)	548 more per 1000 (from 55 fewer to 1000 more)	VERY LOW	
Cure Rate at 12 weeks - GAM501 Growth factor (Blume 2011)												
1	randomised trials	very serious[1,3,12,13]	no serious inconsistency	no serious indirectness	very serious[11]	none[10]	27/66 (40.9%)	5/16 (31.3%)	RR 1.31 (0.6 to	97 more per 1000 (from 125 fewer to 581 more)	VERY LOW	

									2.86)			
Cure Rate at 12 weeks – VEGF Growth factor (Hanft 2008)												
1	randomised trials	no serious risk of bias[14]	no serious inconsistency	no serious indirectness	serious[4]	none[15]	15/29 (51.7%)	9/26 (34.6%)	RR 1.49 (0.79 to 2.82)	170 more per 1000 (from 73 fewer to 630 more)	MODERATE	
Cure Rate at 12 weeks – Incretin (Marfella 2012)												
1	randomised trials	serious[1,2,13]	no serious inconsistency	no serious indirectness	serious[4]	none	16/53 (30.2%)	8/53 (15.1%)	RR 2 (0.94 to 4.27)	151 more per 1000 (from 9 fewer to 494 more)	LOW	
Cure Rate at 12 weeks - autologous platelet-rich plasma gel (Driver 2006)												
1	randomised trials	serious[6,12]	no serious inconsistency	no serious indirectness	very serious[11]	none[10]	13/40 (32.5%)	9/32 (28.1%)	RR 1.16 (0.57 to 2.35)	45 more per 1000 (from 121 fewer to 380 more)	VERY LOW	
Cure Rate at 12 weeks - Amniotic Membrane Wound Graft (Zelen 2013)												
1	randomised trials	Very serious[1,2,13,16]	no serious inconsistency	no serious indirectness	no serious imprecision	none[15]	10/13 (76.9%)	0/12 (0%)	RR 19.5 (1.27 to 300.42)	-	LOW	
Cure Rate at 12 weeks - Hyalograft-3D followed by Laserskin autograft (Caravaggi 2003, Uccioli 2011)												
2	randomised trials	serious[1,2,16]	no serious inconsistency	no serious indirectness	serious[4]	reporting bias[5]	41/115 (35.7%)	30/106 (28.3%)	RR 1.20 (0.84 to 1.72)	57 more per 1000 (from 45 fewer to 204 more)	VERY LOW	
Cure Rate at 12 weeks – Graftskin (Veves 2001)												
1	randomised trials	very serious[2,7]	no serious inconsistency	no serious indirectness	serious[4]	none[10]	63/112 (56.3%)	36/96 (37.5%)	RR 1.5 (1.11 to 2.04)	188 more per 1000 (from 41 more to 390 more)	VERY LOW	
Cure Rate at 12 weeks – Dermagraft (Gentzkow 1996, Hanft 2002, Marston 2003)												
3	randomised trials	serious[1,2,6,14]	no serious inconsistency	no serious indirectness	no serious imprecision	none[10]	65/191 (34%)	28/150 (18.7%)	RR 1.86 (1.26 to 2.74)	161 more per 1000 (from 49 more to 325 more)	MODERATE	
Cure Rate at 12 weeks – GraftJacket (Brigido 2006, Reyzelman 2009)												
2	randomised trials	very	serious[9]	no serious	serious[4]	none[10]	44/60	22/53	RR 1.91 (1	378 more per 1000 (from 0		

		serious[1,6,13,16,17]		indirectness			(73.3%)	(41.5%)	to 3.65)	more to 1000 more)	VERY LOW	
Cure Rate at 12 weeks - Cultured Allogeneic Keratinocyte Sheet (You 2012)												
1	randomised trials	serious[2,3]	no serious inconsistency	no serious indirectness	serious[4]	none[10]	23/27 (85.2%)	19/32 (59.4%)	RR 1.43 (1.03 to 1.99)	255 more per 1000 (from 18 more to 588 more)	LOW	
Cure Rate at 12 weeks – Apligraf (Edmonds 2009)												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[4]	reporting bias[5]	17/33 (51.5%)	10/38 (26.3%)	RR 1.96 (1.05 to 3.66)	253 more per 1000 (from 13 more to 700 more)	VERY LOW	
Cure Rate at 12 weeks - Talactoferrin alpha (Lyons 2007)												
1	randomised trials	serious[6,7,8]	no serious inconsistency	no serious indirectness	very serious[11]	none[10]	6/30 (20%)	3/16 (18.8%)	RR 1.07 (0.31 to 3.71)	13 more per 1000 (from 129 fewer to 508 more)	VERY LOW	
Cure Rate at 12 weeks - Immunokine (WF10)												
0	No evidence available					none	-	-	not pooled	not pooled		
Cure Rate at 12 weeks - External shock wave therapy (Moretti 2007)												
1	randomised trials	very serious[1,2,8,16]	no serious inconsistency	no serious indirectness	very serious[11]	none	8/15 (53.3%)	5/15 (33.3%)	RR 1.6 (0.68 to 3.77)	200 more per 1000 (from 107 fewer to 923 more)	VERY LOW	
Cure Rate at 12 weeks - Thrombin peptide Chrysalin (Fife 2007)												
1	randomised trials	serious[1,7]	no serious inconsistency	no serious indirectness	very serious[11]	none[10]	22/38 (57.9%)	10/21 (47.6%)	RR 1.22 (0.72 to 2.05)	105 more per 1000 (from 133 fewer to 500 more)	VERY LOW	
Cure Rate at 12 weeks – Promogran (Gottrup 2013, Veves 2002)												
2	randomised trials	very serious[1,2,3,7,13]	no serious inconsistency	no serious indirectness	serious[4]	none[10]	63/161 (39.1%)	43/151 (28.5%)	RR 1.35 (0.98 to 1.86)	100 more per 1000 (from 6 fewer to 245 more)	VERY LOW	
Cure Rate at 12 weeks - Iamin Gel copper complex (Mulder 1994)												
1	randomised trials	very	no serious	no serious	serious[4]	none[10]	15/28	10/32	RR 1.71	222 more per 1000 (from 25		

		serious[1,2,8,13,16]	inconsistency	indirectness			(53.6%)	(31.3%)	(0.92 to 3.18)	fewer to 681 more)	VERY LOW	
Cure Rate at 12 weeks - ANGIPARS herbal (oral) (Bahrami 2008)												
1	randomised trials	very serious[1,2,3,8,13,16,17]	no serious inconsistency	no serious indirectness	serious[4]	none[15]	5/6 (83.3%)	2/9 (22.2%)	RR 3.75 (1.05 to 13.4)	611 more per 1000 (from 11 more to 1000 more)	VERY LOW	
Cure Rate at 12 weeks - ANGIPARS herbal (oral and topical) (Bahrami 2008)												
1	randomised trials	very serious[1,2,3,8,13,16,17]	no serious inconsistency	no serious indirectness	no serious imprecision	none[15]	6/6 (100%)	2/9 (22.2%)	RR 3.71 (1.25 to 11.08)	602 more per 1000 (from 56 more to 1000 more)	LOW	
Cure Rate at 12 weeks - ANGIPARS (intravenous)												
0	No evidence available					none	-	-	not pooled	not pooled		
Cure Rate at 1 year - Hyperbaric oxygen therapy (Abidia 2003, Ma 2013, Londahl 2010)												
3	randomised trials	serious[1,2,19]	no serious inconsistency	no serious indirectness	no serious imprecision	none[15]	11/65 (16.9%)	2/61 (3.3%)	RR 5.23 (1.28 to 21.33)	139 more per 1000 (from 9 more to 667 more)	MODERATE	
Cure Rate at 12 weeks - AQUACEL dressing (Jeffcoate 2009)												
1	randomised trials	serious[6,7]	no serious inconsistency	no serious indirectness	very serious[11]	none	29/103 (28.2%)	27/106 (25.5%)	RR 1.11 (0.71 to 1.73)	28 more per 1000 (from 74 fewer to 186 more)	VERY LOW	
Cure Rate at 12 weeks - Low level laser therapy (Kaviani 2011)												
1	randomised trials	serious[8,13]	no serious inconsistency	no serious indirectness	very serious[11]	none	8/13 (61.5%)	3/9 (33.3%)	RR 1.85 (0.67 to 5.11)	283 more per 1000 (from 110 fewer to 1000 more)	VERY LOW	
Cure Rate at 12 weeks - Electric stimulation (Peters 2001)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	13/20 (65%)	7/20 (35%)	RR 1.86 (0.94 to 3.66)	301 more per 1000 (from 21 fewer to 931 more)	MODERATE	
Cure Rate at 12 weeks - Non-contact normothermic wound therapy (Alvarez 2003)												

1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none[10]	7/10 (70%)	4/10 (40%)	RR 1.75 (0.74 to 4.14)	300 more per 1000 (from 104 fewer to 1000 more)	LOW	
Cure Rate at 12 weeks - Topical tretinoin (Tom 2005)												
1	randomised trials	no serious risk of bias[8]	no serious inconsistency	no serious indirectness	very serious[11]	none[15]	6/13 (46.2%)	2/11 (18.2%)	RR 2.54 (0.64 to 10.13)	280 more per 1000 (from 65 fewer to 1000 more)	LOW	
Cure Rate at 12 weeks - Processed lipoaspirate cells (Han 2010)												
1	randomised trials	serious[3,6]	no serious inconsistency	no serious indirectness	serious[4]	none	26/26 (100%)	16/26 (61.5%)	RR 1.61 (1.18 to 2.18)	375 more per 1000 (from 111 more to 726 more)	LOW	
Cure Rate at 12 weeks - vacuum compression therapy												
0	No evidence available					none	-	-	not pooled	not pooled		
Cure Rate at 12 weeks - RGD peptide matrix (Steed 1995)												
1	randomised trials	serious[1,8]	no serious inconsistency	no serious indirectness	serious[4]	none[10]	14/40 (35%)	2/25 (8%)	RR 4.38 (1.08 to 17.65)	270 more per 1000 (from 6 more to 1000 more)	LOW	
Cure Rate at 12 weeks - Collagenase debridement												
0	No evidence available					none	-	-	not pooled	not pooled		
Cure Rate at 12 weeks - Achilles tendon lengthening (Mueller 2003)												
1	randomised trials	Serious[2, 17]	no serious inconsistency	no serious indirectness	Serious[4]	none	33/33 (100%)	29/33 (87.9%)	RR 1.14 (0.99 to 1.3)	123 more per 1000 (from 9 fewer to 264 more)	LOW	CRITICAL
Cure Rate at 12 weeks - Negative pressure wound therapy (Blume 2008, Armstrong 2005)												
2	randomised trials	Very serious[2,5,7,14]	no serious inconsistency	no serious indirectness	Serious[4]	Serious[5]	116/246 (47.2%)	81/251 (32.3%)	RR 1.47 (1.18 to 1.84)	15 more per 100 (from 6 more to 27 more)	Very LOW	CRITICAL
Cure Rate at 12 weeks – Resveratrol (Bashmakov 2014)												

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[11]	none	5/14 (35.7%)	1/10 (10%)	RR 3.57 (0.49 to 26.07)	257 more per 1000 (from 51 fewer to 1000 more)	LOW	
Cure Rate at 12 weeks - Royal Jelly (Siavash 2013)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	30/32 (93.8%)	29/32 (90.6%)	RR 1.03 (0.9 to 1.19)	27 more per 1000 (from 91 fewer to 172 more)	MODERATE	
Cure Rate at 12 weeks – Grafix (Lavery 2014)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	31/50 (62%)	10/47 (21.3%)	RR 2.91 (1.61 to 5.26)	406 more per 1000 (from 130 more to 906 more)	HIGH	
Cure Rate at 12 weeks – rhEGF (Gomez-villa 2014)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[11]	none	4/17 (23.5%)	0/17 (0%)	RR 9 (0.52 to 155.24)	-	LOW	

[1] Unclear randomisation in some of the trials, unclear if allocation was concealed
[2] Unblinding present in some of the trials
[3] Groups were not clearly balanced in terms of baseline characteristics
[4] Confidence intervals cross over one line of minimal important difference
[5] Heavy industry infiltration, evidence of sponsor influence such as the termination of a trial early or control of randomisation
[6] Blinding was inadequate
[7] significant attrition
[8] Unclear definition of outcome
[9] Heterogeneity between studies was greater than 33%
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[14] Unclear method of randomisation however no evidence of differences in group characteristics at baseline
[15] Unclear source of funding
[16] many important variables non-reported at baseline
[17] Inappropriate length of follow up chosen for one of the studies
[18] Standard care wasnt described in detail however this was a recent UK based study
[20] Unclear if reliable methods of determining outcome were used
[21] Heterogeneity greater than 66%

[22] Standard care wasnt described in detail

I.12.2 Amputation outcomes for adjunctive therapies vs standard care

Table 67: Amputation at 12 weeks for adjunctive therapies vs standard care

Amputation at 12 weeks – Graftskin (Veves 2001)											
1	randomised trials	very serious[2,7]	no serious inconsistency	no serious indirectness	serious[4]	none[10]	7/112 (6.3%)	15/96 (15.6%)	OR 0.36 (0.14 to 0.92)	94 fewer per 1000 (from 11 fewer to 131 fewer)	VERY LOW
Amputation at 12 weeks – Incretin (Marfella 2012)											
1	randomised trials	serious[1,2,13]	no serious inconsistency	no serious indirectness	serious[4]	none	1/53 (1.9%)	2/53 (3.8%)	OR 0.49 (0.04 to 5.58)	19 fewer per 1000 (from 36 fewer to 142 more)	LOW
Amputation at 12 weeks - Immunokine (WF10) (Yingsakmongkol 2011)											
1	randomised trials	no serious risk of bias[8]				none[10]	0/20 (0%)	0/20 (0%)	not pooled	not pooled	
Amputation at 1 year - Hyperbaric oxygen therapy (Faglia 1996, Abidia 2003, Ma 2013, Londahl 2010)											
4	randomised trials	serious[1,2,8]	serious[9]	no serious indirectness	serious[4]	none[10]	17/100 (17.0%)	21/94 (22.3%)	OR 0.70 (0.34 to 1.45)	56 fewer per 1000 (from 134 fewer to 71 more)	VERY LOW
Amputation at 12 weeks - AQUACEL dressing (Jeffcoate 2009)											
1	randomised trials	serious[2,7]	no serious inconsistency	no serious indirectness	very serious[11]	none	4/103 (3.9%)	2/106 (1.9%)	OR 2.1 (0.38 to 11.73)	20 more per 1000 (from 12 fewer to 165 more)	VERY LOW
Amputation at 12 weeks - Low level laser therapy (Kaviani 2011)											
1	randomised trials	serious[8,13]	no serious inconsistency	no serious indirectness	very serious[11]	none	0/13 (0%)	2/13 (15.4%)	OR 0.17 (0.01 to 3.92)	124 fewer per 1000 (from 152 fewer to 262 more)	VERY LOW
Amputation at 12 weeks - Electric stimulation (Peters 2001)											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[11]	none	0/20 (0%)	1/20 (5%)	OR 0.32 (0.01 to 8.26)	33 fewer per 1000 (from 49 fewer to 253 more)	LOW

Amputation at 12 weeks - Achilles tendon lengthening (Mueller 2003)												
1	randomised trials	Serious[2, 17]	no serious inconsistency	no serious indirectness	Very serious[11]	none	0/33 (0%)	1/33 (3%)	RR 0.33 (0.01 to 7.9)	20 fewer per 1000 (from 30 fewer to 209 more)	VERY LOW	CRITICAL
Amputation at 12 weeks - Negative pressure wound therapy (Blume 2008, Armstrong 2005)												
2	randomised trials	Very Serious[2, 1, 14, 7,]	no serious inconsistency	no serious indirectness	No serious imprecision	Serious[5]	9/246 (3.7%)	26/251 (10.4%)	RR 0.35 (0.17 to 0.74)	7 fewer per 100 (from 3 fewer to -9 fewer)	Very LOW	CRITICAL
Amputation at 12 weeks – Grafix (Lavery 2014)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[11]	none	0/50 (0%)	1/47 (2.1%)	RR 0.31 (0.01 to 7.52)	15 fewer per 1000 (from 21 fewer to 139 more)	LOW	

[1] Unclear randomisation in some of the trials, unclear if allocation was concealed
[2] Unblinding present in some of the trials
[3] Groups were not clearly balanced in terms of baseline characteristics
[4] Confidence intervals cross over one line of minimal important difference
[5] Heavy industry infiltration, evidence of sponsor influence such as the termination of a trial early or control of randomisation
[6] Blinding was inadequate
[7] significant attrition
[8] Unclear definition of outcome
[9] Heterogeneity between studies was greater than 33%
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[15] Unclear source of funding
[16] many important variables non-reported at baseline
[17] Inappropriate length of follow up chosen for one of the studies
[18] Standard care wasnt described in detail however this was a recent UK based study
[20] Unclear if reliable methods of determining outcome were used
[21] Heterogeneity greater than 66%

I.12.3 Length of hospital stay for adjunctive therapies vs standard care

Table 68: Length of hospital stay for adjunctive therapies vs standard care

Length of stay - Hyperbaric oxygen therapy (Better indicated by lower values) (Faglia 1996)												
1	randomised trials	very serious[1,2,20]	no serious inconsistency	no serious indirectness	very serious[11]	none[15]	35	33	-	not pooled	VERY LOW	

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[2] Unblinding present in some of the trials
[3] Groups were not clearly balanced in terms of baseline characteristics
[4] Confidence intervals cross over one line of minimal important difference
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[15] Unclear source of funding
[16] many important variables non-reported at baseline
[17] Inappropriate length of follow up chosen for one of the studies
[18] Standard care wasn't described in detail however this was a recent UK based study
[20] Unclear if reliable methods of determining

I.12.4 Adverse events for adjunctive therapies vs standard care

Table 69: Adverse events at 12 weeks for adjunctive therapies vs standard care

Adverse events at 12 weeks – Platelet (Bhansali 2009, Hardikar 2005, Jaiswal 2010, Robson 2005)											
3	randomised trials	serious[1,2,8,20]	no serious inconsistency	no serious indirectness	serious[4]	reporting bias[5]	98/442 (22.2%)	53/225 (23.6%)	OR 0.82 (0.56 to 1.21)	34 fewer per 1000 (from 88 fewer to 36 more)	VERY LOW
Adverse events at 12 weeks – Fibroblast (Uchi 2009)											
1	randomised trials	serious[1,2,8]	no serious inconsistency	no serious indirectness	serious[4]	none[10]	4/92 (4.3%)	3/47 (6.4%)	OR 0.67 (0.14 to 3.11)	20 fewer per 1000 (from 54 fewer to 111 more)	LOW
Adverse events at 12 weeks - GAM501 (Blume 2011)											

1	randomised trials	very serious[2,3,12,13]	no serious inconsistency	no serious indirectness		none[10]	0/66 (0%)	0/16 (0%)	not pooled	not pooled	
Adverse events at 12 weeks – VEGF (Hanft 2008)											
1	randomised trials	no serious risk of bias[14]	no serious inconsistency	no serious indirectness	very serious[11]	none[15]	19/29 (65.5%)	19/26 (73.1%)	OR 0.70 (0.22 to 2.22)	76 fewer per 1000 (from 357 fewer to 127 more)	LOW
Adverse events at 12 weeks – Incretin (Marfella 2012)											
1	randomised trials	serious[1,2,13]	no serious inconsistency	no serious indirectness	serious[4]	none	6/53 (11.3%)	16/53 (30.2%)	OR 0.3 (0.11 to 0.83)	187 fewer per 1000 (from 38 fewer to 256 fewer)	LOW
Adverse events at 12 weeks - autologous platelet-rich plasma gel (Driver 2006)											
1	randomised trials	serious[6,12]	no serious inconsistency	no serious indirectness	no serious imprecision	none[10]	6/40 (15%)	17/32 (53.1%)	OR 0.16 (0.05 to 0.47)	378 fewer per 1000 (from 184 fewer to 478 fewer)	MODERATE
Adverse events at 12 weeks - Amniotic Membrane Wound Graft (Zelen 2013)											
1	randomised trials	Very serious[1,2,13]	no serious inconsistency	no serious indirectness	very serious[11]	none[15]	1/13 (7.7%)	4/12 (33.3%)	OR 0.17 (0.02 to 1.78)	255 fewer per 1000 (from 323 fewer to 138 more)	VERY LOW
Adverse events at 12 weeks - Hyalograft-3D followed by Laserskin autograft (Caravaggi 2003, Ucioli 2011)											
2	randomised trials	serious[1,2,16]	very serious[21]	no serious indirectness	very serious[11]	reporting bias[5]	14/127 (11%)	12/123 (9.8%)	OR 1.06 (0.46 to 2.43)	5 more per 1000 (from 50 fewer to 110 more)	VERY LOW
Adverse events at 12 weeks – Dermagraft (Hanft 2002)											
1	randomised trials	serious[1,8,14]	no serious inconsistency	no serious indirectness	very serious[11]	none[15]	14/24 (58.3%)	16/22 (72.7%)	OR 0.52 (0.15 to 1.82)	146 fewer per 1000 (from 442 fewer to 102 more)	VERY LOW
Adverse events at 12 weeks – GraftJacket (Brigido 2004, Reyzelman 2009)											
2	randomised trials	very serious[1,6,13,16,17]	no serious inconsistency	no serious indirectness	very serious[11]	none[10]	4/66 (6.1%)	2/59 (3.4%)	OR 1.76 (0.3 to 10.18)	24 more per 1000 (from 23 fewer to 229 more)	VERY LOW
Adverse events at 12 weeks - Cultured Allogeneic Keratinocyte Sheet (You 2012)											
1	randomised trials	serious[2,3]	no serious inconsistency	no serious indirectness	very serious[11]	none[10]	6/20 (30%)	5/26 (19.2%)	OR 1.8 (0.46 to 7.06)	108 more per 1000 (from 94 fewer to 435 more)	VERY LOW
Adverse events at 12 weeks - Apligraf- living keratinocytes, living fibroblasts (Edmonds 2009)											

1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[11]	reporting bias[5]	8/33 (24.2%)	8/38 (21.1%)	OR 1.2 (0.39 to 3.66)	32 more per 1000 (from 116 fewer to 283 more)	VERY LOW
Adverse events at 12 weeks - Talactoferrin alpha (Lyons 2007)											
1	randomised trials	serious[6,7,8]	no serious inconsistency	no serious indirectness	very serious[11]	none[10]	56/30 (186.7%)	26/16 (162.5%)	not pooled	not pooled	VERY LOW
Adverse events at 12 weeks – Promogran (Gottrup 2013, Veves 2002)											
2	randomised trials	very serious[1,2,3,7,13]	very serious[21]	no serious indirectness	serious[4]	none	25/161 (15.5%)	40/151 (26.5%)	OR 0.53 (0.31 to 0.92)	105 fewer per 1000 (from 16 fewer to 164 fewer)	VERY LOW
Adverse events at 12 weeks - ANGIPARS herbal (oral) (Bahrami 2008)											
1	randomised trials	very serious[1,2,3,8,13,16,17]	no serious inconsistency	no serious indirectness		none[15]	0/6 (0%)	0/9 (0%)	not pooled	not pooled	
Adverse events at 12 weeks - ANGIPARS herbal (oral and topical) (Bahrami 2008)											
1	randomised trials	very serious[1,2,3,8,13,16,17]	no serious inconsistency	no serious indirectness		none[15]	0/6 (0%)	0/9 (0%)	not pooled	not pooled	
Adverse events at 12 weeks - ANGIPARS (intravenous) (Larijami 2008)											
1	no methodology chosen					none	0/16 (0%)	0/9 (0%)	not pooled	not pooled	
Adverse events at 1 year - Hyperbaric oxygen therapy (Ma 2013)											
2	randomised trials	serious[1,2]	no serious inconsistency	no serious indirectness		none[15]	0/8 (0%)	0/8 (0%)	not pooled	not pooled	
Adverse events at 12 weeks - AQUACEL dressing (Jeffcoate 2009)											
1	randomised trials	serious[6,7]	no serious inconsistency	no serious indirectness	very serious[11]	none	28/103 (27.2%)	35/106 (33%)	OR 0.76 (0.42 to 1.37)	58 fewer per 1000 (from 159 fewer to 73 more)	VERY LOW
Adverse events at 12 weeks - Low level laser therapy (Kaviani 2011)											
1	randomised trials	serious[8,13]	no serious inconsistency	no serious indirectness	very serious[11]	none	2/13 (15.4%)	3/10 (30%)	OR 0.42 (0.06 to 3.21)	147 fewer per 1000 (from 275 fewer to 279 more)	VERY LOW
Adverse events at 12 weeks - Electric stimulation (Peters 2001)											

1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[11]	none	2/20 (10%)	2/20 (10%)	OR 1 (0.13 to 7.89)	0 fewer per 1000 (from 86 fewer to 367 more)	LOW
Adverse events at 12 weeks - Non-contact normothermic wound therapy (Alvarez 2003)											
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness		none[10]	0/10 (0%)	0/10 (0%)	not pooled	not pooled	
Adverse events at 12 weeks - Processed lipoaspirate cells (Han 2010)											
1	randomised trials	serious[3,6]	no serious inconsistency	no serious indirectness		none	0/26 (0%)	0/26 (0%)	not pooled	not pooled	
Adverse events at 12 weeks - vacuum compression therapy (Akbari 2007)											
1	no methodology chosen					none	0/9 (0%)	0/9 (0%)	not pooled	not pooled	
Adverse events at 12 weeks - RGD peptide matrix (Steed 1995)											
1	randomised trials	serious[1,8]	no serious inconsistency	no serious indirectness	very serious[11]	none[10]	3/40 (7.5%)	4/25 (16%)	OR 0.43 (0.09 to 2.09)	84 fewer per 1000 (from 143 fewer to 125 more)	VERY LOW
Adverse events at 12 weeks - Collagenase debridement (Tallis 2013)											
1	no methodology chosen					none	0/24 (0%)	0/24 (0%)	not pooled	not pooled	

Adverse events at 12 weeks - Negative pressure wound therapy (Armstrong 2005)											
1	randomised trials	Very Serious[1,6, 14, 7]	no serious inconsistency	no serious indirectness	very serious[11]	Serious[5]	9/77 (11.7%)	11/85 (12.9%)	RR 0.90 (0.40 to 2.06)	1 fewer per 100 (from 8 fewer to 14 more)	VERY LOW

[1] Unclear randomisation in some of the trials, unclear if allocation was concealed
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[9] Heterogeneity between studies was greater than 33%
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[20] Unclear if reliable methods of determining outcome were used
[21] Heterogeneity greater than 66%

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**SC + SJ**		**Relative (95% CI)**	**Absolute**		
Adverse events at 12 weeks – Grafix (Lavery 2014)												
1	randomised trials	no serious risk of bias[8]	no serious inconsistency[5]	no serious indirectness[3]	serious[4]	none	22/50 (44%)	31/47 (66%)	RR 0.67 (0.46 to 0.97)	218 fewer per 1000 (from 20 fewer to 356 fewer)	MODERATE	
Adverse events at 12 weeks – rhEGF (Gomez-Villa 2014)												
1	randomised trials	no serious risk of bias[8]	no serious inconsistency[5]	no serious indirectness[3]	very serious[7]	none	2/17 (11.8%)	1/17 (5.9%)	RR 2 (0.2 to 20.04)	59 more per 1000 (from 47 fewer to 1000 more)	LOW	

[1] Serious risk of bias due to unclear method of randomisation and blinding
[2] Serious inconsistency (I-squared between 33% and 66%)
[3] Population, intervention, outcome as specified in the review protocol
[4] Confidence intervals around the point estimate cross the MID line (either 0.75 or 1.25)
[5] Single study analysis
[6] No explanation was provided
[7] Confidence intervals around the point estimate cross both MID lines (0.75 and 1.25)
[8] No apparent risk of bias
[9] No inconsistency (I-squared less than 33%)
[10] Confidence intervals around point estimate do not cross MID
[11] Confidence intervals around point estimate cross line of no effect
[12] No inconsistency (Test for heterogeneity not applicable)
[13] Very serious inconsistency (I-squared greater than 67%)
[14] No events reported

I.12.5 Infection outcomes for adjunctive therapies vs standard care

Table 70: Infection at 12 weeks for adjunctive therapies vs standard care

Infection at 12 weeks – Fibroblast (Richard 1995, Uchi 2009)											
2	randomised trials	serious[1,7,8]	no serious inconsistency	no serious indirectness	very serious[11]	none[10]	3/101 (3%)	3/55 (5.5%)	OR 0.7 (0.12 to 4.04)	16 fewer per 1000 (from 48 fewer to 134 more)	VERY LOW
Infection at 12 weeks – VEGF (Hanft 2008)											
1	randomised trials	no serious risk of bias[14]	no serious inconsistency	no serious indirectness	very serious[11]	none[15]	4/29 (13.8%)	5/26 (19.2%)	OR 0.67 (0.16 to 2.83)	55 fewer per 1000 (from 156 fewer to 210 more)	LOW
Infection at 12 weeks - Hyalograft-3D followed by Laserskin autograft (Uccioli 2011)											
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[11]	none[10]	13/84 (15.5%)	10/87 (11.5%)	OR 1.41 (0.58 to 3.42)	40 more per 1000 (from 45 fewer to 193 more)	VERY LOW
Infection at 12 weeks – Graftskin (Veves 2001)											
1	randomised trials	very serious[2,7]	no serious inconsistency	no serious indirectness	very serious[11]	none[10]	12/112 (10.7%)	13/96 (13.5%)	OR 0.77 (0.33 to 1.77)	28 fewer per 1000 (from 86 fewer to 82 more)	VERY LOW
Infection at 12 weeks – Dermagraft (Gentzkow 1996, Hanft 2002, Marston 2003)											
3	randomised trials	serious[1,2,6,14]	no serious inconsistency	no serious indirectness	serious[4]	none[10]	27/224 (12.1%)	32/186 (17.2%)	OR 0.59 (0.33 to 1.04)	63 fewer per 1000 (from 108 fewer to 6 more)	LOW
Infection at 12 weeks – GraftJacket (Brigido 2006)											
1	randomised trials	very serious[1,6,13,16]	no serious inconsistency	no serious indirectness	very serious[11]	none[10]	3/13 (23.1%)	5/14 (35.7%)	OR 0.54 (0.1 to 2.93)	126 fewer per 1000 (from 305 fewer to 262 more)	VERY LOW
Infection at 12 weeks - Cultured Allogeneic Keratinocyte Sheet (You 2012)											
1	randomised trials	serious[2,3]	no serious inconsistency	no serious indirectness	very serious[11]	none[10]	2/20 (10%)	3/26 (11.5%)	OR 0.85 (0.13 to 5.65)	16 fewer per 1000 (from 99 fewer to 309 more)	VERY LOW
Infection at 12 weeks - External shock wave therapy (Moretti 2009)											

1	randomised trials	very serious[1,2,8,16]	no serious inconsistency	no serious indirectness	very serious[11]	none	1/15 (6.7%)	5/15 (33.3%)	OR 0.14 (0.01 to 1.42)	268 fewer per 1000 (from 328 fewer to 82 more)	VERY LOW
Infection at 12 weeks - Thrombin peptide Chrysalin (Fife 2007)											
1	randomised trials	serious[1,7]	no serious inconsistency	no serious indirectness	very serious[11]	none[10]	2/38 (5.3%)	1/21 (4.8%)	OR 1.11 (0.09 to 13.03)	5 more per 1000 (from 43 fewer to 347 more)	VERY LOW
Infection at 12 weeks – Promogran (Gottrup 2013, Veves 2002)											
2	randomised trials	very serious[1,2,3,7,13]	very serious[21]	no serious indirectness	serious[4]	none[10]	25/161 (15.5%)	39/151 (25.8%)	OR 0.55 (0.32 to 0.96)	98 fewer per 1000 (from 8 fewer to 158 fewer)	VERY LOW
Infection at 12 weeks - Iamin Gel copper complex (Mulder 1994)											
1	randomised trials	very serious[1,2,8,13,16]	no serious inconsistency	no serious indirectness	no serious imprecision	none[10]	3/40 (7.5%)	14/42 (33.3%)	OR 0.23 (0.07 to 0.72)	230 more per 1000 (from 69 more to 300 more)	LOW
Infection at 12 weeks - AQUACEL dressing (Jeffcoate 2009)											
1	randomised trials	serious[6,7]	no serious inconsistency	no serious indirectness	serious[4]	none	54/103 (52.4%)	48/106 (45.3%)	OR 1.33 (0.77 to 2.29)	71 more per 1000 (from 64 fewer to 202 more)	LOW
Infection at 12 weeks - Low level laser therapy (Kaviani 2011)											
1	randomised trials	serious[8,13]	no serious inconsistency	no serious indirectness	very serious[11]	none	1/13 (7.7%)	0/10 (0%)	OR 2.52 (0.09 to 68.6)	-	VERY LOW
Infection at 12 weeks - Electric stimulation (Peters 2001)											
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[11]	none	2/20 (10%)	2/20 (10%)	OR 1 (0.13 to 7.89)	0 fewer per 1000 (from 86 fewer to 367 more)	LOW

Infection at 12 weeks - Negative pressure wound therapy (Blume 2008)											
1	randomised trials	Serious[2]	no serious inconsistency	no serious indirectness	very serious[11]	None[10]	4/169 (2.4%)	1/166 (0.6%)	RR 3.93 (0.44 to 34.79)	18 more per 1000 (from 3 fewer to 204 more)	VERY LOW	CRITICAL

[1] Unclear randomisation in some of the trials, unclear if allocation was concealed
[2] Unblinding present in some of the trials
[3] Groups were not clearly balanced in terms of baseline characteristics
[4] Confidence intervals cross over one line of minimal important difference
[5] Heavy industry infiltration, evidence of sponsor influence such as the termination of a trial early or control of randomisation
[6] Blinding was inadequate
[7] significant attrition
[8] Unclear definition of outcome
[9] Heterogeneity between studies was greater than 33%
[10] industry funded however no other clear evidence of influence
[11] Confidence intervals cross two lines of minimum effect
[12] Protocol not adhered to
[13] evidence of variance in care within groups
[14] Unclear method of randomisation however no evidence of differences in group characteristics at baseline
[15] Unclear source of funding
[16] many important variables non-reported at baseline
[17] Inappropriate length of follow up chosen for one of the studies
[18] Standard care wasn't described in detail however this was a recent UK based study
[20] Unclear if reliable methods of determining outcome were used
[21] Heterogeneity greater than 66%

I.12.6 Quality of life for adjunctive therapies vs standard care

Three studies (Abidia 2003, Londahl 2010, 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). The results of these studies separated for type of adjunctive therapy can be seen below. 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.

Quality assessment							Summary of results	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Quality of life- Hyperbaric oxygen therapy (Abidia 2003)									
1	randomised trials	No serious	no serious inconsistency	no serious indirectness	No serious	Serious[23]	Health related quality of life: Depression score as defined by the HAD scale: Improvement in the depression score was significant in both groups Hyperbaric treatment group: P=0.011 Control group: P= 0.023 Only the control group had significant improvement in anxiety score: P=0.042	MODERATE	IMPORTANT

<table>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>General health and vitality as defined by the SF–36 score:
Hyperbaric treatment group: P=0.012
Control group: P= 0.018
Significant improvement in both groups

Overall there were found to be no significant improvements in quality of life measures greater than those already seen in patients in the control group as measured by the SF–36 and HADS.</td><td></td><td></td></tr>
<tr><td colspan="9">Quality of life- Hyperbaric oxygen therapy (Londahl 2010)</td></tr>
<tr><td>1</td><td>randomised trials</td><td>No serious</td><td>no serious inconsistency</td><td>no serious indirectness</td><td>No serious</td><td>none</td><td>
<table>
<tr><td></td><td colspan="3">Treatment group (n=23)</td><td colspan="3">Placebo group (n=10</td></tr>
<tr><td>SF 36 domain</td><td>Baseline</td><td>12 month</td><td>P value</td><td>Baseline</td><td>Follow up</td><td>P value</td></tr>
<tr><td>Physical functioning</td><td>40 ± 5</td><td>41 ± 6</td><td>Ns</td><td>32 ± 9</td><td>50 ± 9</td><td>Ns</td></tr>
<tr><td>Bodily Pain</td><td>30 ± 8</td><td>61 ± 8</td><td><0.05</td><td>323 ± 14</td><td>70 ± 12</td><td>Ns</td></tr>
<tr><td>Role limitation due to physical health</td><td>62 ± 6</td><td>66 ± 5</td><td>Ns</td><td>48 ± 10</td><td>67 ± 10</td><td>Ns</td></tr>
<tr><td>General health</td><td>55 ± 4</td><td>54 ± 4</td><td>Ns</td><td>43 ± 6</td><td>46 ± 11</td><td>Ns</td></tr>
<tr><td>Vitality</td><td>55 ± 4</td><td>61 ± 4</td><td>Ns</td><td>52 ± 8</td><td>58 ± 10</td><td>Ns</td></tr>
<tr><td>Social function</td><td>72 ± 5</td><td>84 ± 4</td><td>Ns</td><td>66 ± 6</td><td>81 ± 10</td><td>Ns</td></tr>
<tr><td>Role limitation due to emotional health</td><td>65 ± 8</td><td>87 ± 6</td><td><0.05</td><td>53 ± 16</td><td>67 ± 14</td><td>Ns</td></tr>
<tr><td>Role limitation due to mental health</td><td>78 ± 4</td><td>80 ± 3</td><td>Ns</td><td>66 ± 6</td><td>71 ± 9</td><td>Ns</td></tr>
<tr><td>Physical health summary score</td><td>31 ± 2</td><td>33 ± 2</td><td>Ns</td><td>30 ± 4</td><td>38 ± 4</td><td>Ns</td></tr>
<tr><td>Mental health</td><td>50 ± 3</td><td>55 ± 2</td><td>Ns</td><td>47 ± 3</td><td>48 ± 5</td><td>Ns</td></tr>
</table>
</td><td>HIGH</td><td>IMPORTANT</td></tr>
</table>

							summary score							
Quality of life- AQUACEL dressing (Jeffcoate 2009)														
1	randomised trials	Serious[22,6]	no serious inconsistency	no serious indirectness	No serious	none	Health reported quality of life Self-reported Quality of life at baseline, 12 weeks or 24 weeks SF-36 Data tables provided in paper There was no differences observed between any of the groups across any of the domains at any of the time points Self-reported Quality of life at baseline, 12 weeks or 24 weeks SF-6D Data tables provided in paper There was no differences observed between any of the groups across any of the domains at any of the time points Self-reported Quality of life at baseline, 12 weeks or 24 weeks CWIS- Cardiff Wound impact Schedule Data tables provided in paper for Physical Functioning, Social Functioning, Well being There was no differences observed between any of the groups across any of the domains at any of the time points							MODERATE	IMPORTANT

[1] Unclear randomisation in some of the trials, unclear if allocation was concealed
[2] Unblinding present in some of the trials
[3] Groups were not clearly balanced in terms of baseline characteristics
[4] Confidence intervals cross over one line of minimal important difference
[5] Heavy industry infiltration, evidence of sponsor influence such as the termination of a trial early or control of randomisation
[6] Blinding was inadequate
[7] significant attrition
[8] Unclear definition of outcome
[9] Heterogeneity between studies was greater than 33%
[10] industry funded however no other clear evidence of influence
[11] Confidence intervals cross two lines of minimum effect
[12] Protocol not adhered to
[13] evidence of variance in care within groups
[14] Unclear method of randomisation however no evidence of differences in group characteristics at baseline
[15] Unclear source of funding
[16] many important variables non-reported at baseline
[17] Inappropriate length of follow up chosen for one of the studies
[18] Standard care wasn't described in detail however this was a recent UK based study
[20] Unclear if reliable methods of determining outcome were used
[21] Heterogeneity greater than 66%

[22] Variance in loss to follow up chosen between groups
[23] No further data on quality of life scores provided in study

I.13 Review question 13 full GRADE profiles

Table 71:

Author(s): Stuck (2008), Ross et al (2013)
Question: Does greater age increase the odds of Charcot foot?
Settings: USA

Quality assessment							Adjusted Odds Ratio	95% Confidence Interval	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations				
Age (assessed with: data taken from clinical records), years										
1	observational studies[1]	serious[2]	serious[3]	no serious indirectness	serious[4]	none[5]	**mean age, y** 0.99	0.94-1.07	VERY LOW	CRITICAL
1	observational studies[1]	serious[2,7]	serious[3]	no serious indirectness	no serious imprecision	none[5]	**Age, y** <**55** - 1.00 **55-64** – 1.37 **65-74** – 0.73 **75-84** – 0.48 **85**+ - 0.57	- 1.13–1.66 0.57–0.93 0.37–0.63 0.29–1.10	VERY LOW	CRITICAL

[1] case-control
[2] retrospective studies with data taken from clinical records.
[3] Two papers are not in agreement with regard to the effect of age on the development of Charcot foot
[4] Low number of participants (below 400)

[5] Unclear source of funding
[7] patients with missing BMI values were found to be younger, this may introduce bias

Table 72:

Author(s): Ross et al (2013)
Question: Does diagnosis of type 1 diabetes mellitus increase the odds of Charcot foot?
Settings: USA

Quality assessment							Adjusted Odds Ratio	95% Confidence Interval	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations				
Type 1 diabetes (assessed with: data was taken from clinical records)										
1	observational studies[1]	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none[4]	3.90	1.08 – 14.13	VERY LOW	CRITICAL

[1] case-control
[2] data was taken retrospectively from clinical records
[3] low number of participants (less than 400)
[4] unclear source of funding

Table 73:

Author(s): Stuck (2008), Ross et al (2013)
Question: Does greater body mass index increase the odds of developing Charcot foot?
Settings: USA

Quality assessment							Adjusted Odds ratio	95% Confidence Interval	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations				
Body mass index (≥25) (assessed with: data taken from clinical records)										
1	observational studies[1]	very serious[2,3]	serious[4]	no serious indirectness	serious[5]	none[6]	1.05	0.95 – 1.15	VERY LOW	CRITICAL

Obesity (BMI≥30) (assessed with: Body mass index, taken retrospectively)										
1	observational studies[1]	serious[8]	serious[9]	no serious indirectness	no serious imprecision	none[6]	1.589	1.152 – 2.191	VERY LOW	CRITICAL

[1] case-control
[2] data taken retrospectively via clinical records
[3] Patients self-reported height and weight values
[4] results are in disagreement with another study that found a significant effect of weight on the development of Charcot foot
[5] low number of participants
[6] unclear source of funding
[8] data taken retrospectively via clinical database
[9] results are in disagreement with another study that found no significant effect of a participants body mass index

Table 74:

Author(s): Stuck (2008)
Question: Should Race be used for the prediction of the development of Charcot foot?
Settings: USA

Quality assessment							Adjusted Odds ratio	95% Confidence Interval	Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**				
Race										
1	observational studies[1]	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none[3]	**White-** 1.00 **African American-** 0.614 **Hispanic** 0.855 **Other** 1.485 **Unknown**	- 0.501 – 0.752 0.465 – 1.572 0.868 – 2.543	VERY LOW	CRITICAL

							0.699	0.545 – 0.898		

[1] Case control
[2] Data was collected retrospectively from a clinical database
[3] unclear source of funding

Table 75:

Author(s): Stuck (2008)
Question: Should duration of diabetes be used for prediction of the development of Charcot foot?
Settings: USA

Quality assessment							Adjusted Odds ratio	95% Confidence Interval	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations				
Diabetes duration greater than or equal to 6 years (assessed with: data from clinical records)										
1	observational studies[1]	serious[2,3,4,5]	no serious inconsistency	no serious indirectness	no serious imprecision	none[6]	1.26	1.033 – 1.537	VERY LOW	CRITICAL

[1] Case control
[2] Data was collected retrospectively from a clinical database
[3] definition of a patient with diabetes is possibly not reliable and depends on a patient having used a diabetic drug, or having been hospitalised/seen in an outpatient clinic.
[4] data gives only the HbA1c and duration of diabetic diagnosis, which may not be the most accurate measure of diabetes severity.
[5] uncertain how patient compliance to therapy may have affected the participants within this study
[6] unclear source of funding

Table 76:

Author(s): Stuck (2008)
Question: Should HbA1c be used for prediction of the development of Charcot foot ?
Settings: USA

Quality assessment			Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Adjusted Odds Ratio	95% Confidence Interval		
HbA1c (assessed with: data taken retrospectively from clinical database)										
1	observational studies[1]	serious[2,3,4]	no serious inconsistency	no serious indirectness	no serious imprecision	none[5]	**<7%-** 1.00 **7 – 9%-** 1.33 **>9%-** 1.35 **Not measured-** 1.01	- 1.06 – 1.68 1.06 – 1.74 0.80 – 1.29	VERY LOW	CRITICAL

[1] Case control
[2] Data was drawn retrospectively from a database
[3] No explanation was provided
[4] The definition of a patient with diabetes depends on a patient having used a diabetic drug, or have been hospitalised/seen in an outpatient clinic which may exclude many diabetics who are on diet control.
[5] Unclear source of funding

Table 77:

Author(s): Stuck (2008)
Question: Should Peripheral neuropathy be used for the suspicion of developing Charcot foot?
Settings: USA

Quality assessment							Adjusted Odds Ratio	95% Confidence Interval	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations				
Peripheral neuropathy (assessed with: data taken retrospectively from clinical records)										

1	observational studies[1]	serious[2,3]	no serious inconsistency	no serious indirectness	no serious imprecision	none[4]	13.970	9.500–20.545	VERY LOW	CRITICAL

[1] Case control
[2] data taken retrospectively from clinical database
[3] Patient conditions used in the study were detected from diagnostic codes in the Veteran Affairs administrative files, these may not accurately represent a patient's clinical status
[4] Unclear source of funding

Table 78:

Author(s): Stuck (2008)
Question: Should presence of renal failure be used for suspicion of developing Charcot foot?
Settings: USA

Quality assessment							Adjusted Odds Ratio	95% Confidence Interval	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations				
Renal failure (assessed with: data taken retrospectively from clinical database)										
1	observational studies[9]	serious[2,10]	no serious inconsistency	serious[6]	no serious imprecision	none[8]	2.092	1.663–2.632	VERY LOW	CRITICAL

[2] Retrospective data
[8] unclear source of funding
[9] case control
[10] Patient conditions used in the study were detected from diagnostic codes in the Veteran Affairs administrative files, these may not accurately represent a patient's clinical status

Table 79:

Author(s): Stuck (2008)
Question: Should presence of rheumatoid arthritis be used for prediction of the development of Charcot foot?
Settings: USA

Quality assessment							Adjusted Odds Ratio	95% Confidence Interval	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations				

Rheumatoid arthritis (assessed with: data taken retrospectively from clinical database)										
1	observational studies[1]	serious[2,3]	no serious inconsistency	no serious indirectness	no serious imprecision	none[4]	1.905	1.138–3.189	VERY LOW	CRITICAL

[1] Case control
[2] Patient conditions used in the study were detected from diagnostic codes in the Veteran Affairs administrative files, these may not accurately represent a patient's clinical status
[3] data was taken retrospectively
[4] unclear source of funding

Table 80:

Author(s): Stuck (2008)
Question: Should deficiency anaemia be used for the prediction of developing Charcot foot?
Settings: USA

Quality assessment							Adjusted Odds Ratio	95% Confidence Interval	Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**				
Deficiency anaemia (assessed with: data taken retrospectively from clinical database)										
1	observational studies[1]	serious[2,3]	no serious inconsistency	no serious indirectness	no serious imprecision	none[4]	1.80	1.50–2.16	VERY LOW	CRITICAL

[1] Case control
[2] Data taken retrospectively
[3] Patient conditions used in the study were detected from diagnostic codes in the Veteran Affairs administrative files, these may not accurately represent a patient's clinical status
[4] unclear source of funding

Table 81:

Author(s): Foltz et al
Question: Should superficial pain sensation be used for suspicion of Charcot foot?
Settings: USA

Quality assessment							Results	Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			

Superficial pain sensation (assessed with: thermometer)												
1	observational studies[1]	serious[2]	no serious inconsistency	serious	serious[4]	none		Charcot Group (18)	Control group (41)	P value	VERY LOW	IMPORTANT
							Superficial pain sensation present, L	4	32	<0.001		
							Superficial pain sensation present, R	4	30	<0.001		

[1] case-control
[2] Other than the diagnosis of diabetes it is unclear if any attempt were made to match cases and controls for confounding factors. The Charcot disease group were found to be younger and have more type 1 diabetes. Unclear if knowledge of any primary exposure could have influenced case ascertainment.
[4] low number of participants (less than 400)

Table 82:

Author(s): Foltz et al
Question: Should vibrational sensation be used for suspicion of Charcot foot?
Settings: USA

Quality assessment							Results				Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**						
Vibrational sensation (assessed with: tuning fork examination)												
1	observational studies[1]	serious[2]	no serious inconsistency	serious	serious[4]	none	128-Hz Tuning fork	Charcot group	Control group	P value	VERY LOW	IMPORTANT
							L missed (0/8)	2	32	<0.001		
							R missed (0/8)	2	30	<0.001		
							L missed (2/8)	3	0	<0.001		
							R missed (2/8)	0	1	<0.001		
							L missed (4/8)	0	2	<0.001		
							R missed (4/8)	0	4	<0.001		
							L missed (6/8)	5	3	<0.001		
							R missed (6/8)	4	2	<0.001		
							L missed (8/8)	7	3	<0.001		
							R missed (8/8)	12	2	<0.001		

[1] case-control
[2] Other than the diagnosis of diabetes it is unclear if any attempt were made to match cases and controls for confounding factors. The Charcot disease group were found to be younger and have more type 1 diabetes. Unclear if knowledge of any primary exposure could have influenced case ascertainment.
[4] low number of participants (less than 400)

Table 83:

Author(s): Foltz et al
Question: Should fine touch sensation be used for suspicion of Charcot foot?
Settings: USA

Quality assessment							Results						Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations								
Fine touch examination (assessed with: Semmes-Weinstein monofilament)														
1	observational studies[1]	serious[2]	no serious inconsistency	serious	serious[4]	none	Filament size	Force (g)	Charcot group	Control group	Standard deviation	P value	VERY LOW	IMPORTANT
							2.83, L	0.07	0	1.38	2.10	0.008		
							2.83, R	0.07	0.06	1.26	2.00	0.013		
							3.61, L	0.40	0.56	4.44	3.50	<0.001		
							3.61, R	0.40	0.5	4.62	3.50	<0.001		
							4.31, L	2.00	1.39	6.49	3.60	<0.001		
							4.31, R	2.00	1.39	6.44	3.70	<0.001		
							4.56, L	4.00	1.44	7.36	3.40	<0.001		
							4.56, R	4.00	1.33	7.56	3.50	<0.001		
							5.07, L	10.00	2.17	8.31	3.90	<0.001		
							5.07, R	10.00	2.33	8.21	3.00	<0.001		
							6.65, L	300.00	3.11	9.05	2.30	<0.001		
							6.65, R	300.00	3.56	9.08	2.30	<0.001		

[1] case-control
[2] Other than the diagnosis of diabetes it is unclear if any attempt were made to match cases and controls for confounding factors. The Charcot disease group were found to be younger and have more type 1 diabetes. Unclear if knowledge of any primary exposure could have influenced case ascertainment.
[4] low number of participants (less than 400)

Table 84:

Author(s): Foltz et al
Question: Should deep tendon reflexes be used for suspicion of Charcot foot?
Settings: USA

Quality assessment							Results				Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations						
Deep tendon reflexes (assessed with: tendon hammer)												
1	observational studies[1]	serious[2]	no serious inconsistency	serious	serious[4]	none	Reflex Graded (0/4)	Charcot group	Control group	P value	VERY LOW	IMPORTANT
							Quadriceps reflex L (0)	8	6	0.008		
							Quadriceps reflex R (0)	8	6	0.027		
							Quadriceps reflex L (1)	8	12	0.008		
							Quadriceps reflex R (1)	7	11	0.027		
							Quadriceps reflex L (2)	1	18	0.008		
							Quadriceps reflex R (2)	2	17	0.027		
							Quadriceps reflex L (3)	1	5	0.008		
							Quadriceps reflex R (3)	1	5	0.027		
							Gastrosoleus reflex L (0)	15	12	0.002		
							Gastrosoleus reflex R (0)	15	11	0.001		
							Gastrosoleus reflex L (1)	2	13	0.002		
							Gastrosoleus reflex R (1)	2	12	0.001		
							Gastrosoleus reflex L (2)	1	12	0.002		
							Gastrosoleus reflex R (2)	1	12	0.001		
							Gastrosoleus reflex L (3)	0	4	0.002		
							Gastrosoleus reflex R (3)	0	4	0.001		

[1] case-control
[2] Other than the diagnosis of diabetes it is unclear if any attempt were made to match cases and controls for confounding factors. The Charcot disease group were found to be younger and have more type 1 diabetes. Unclear if knowledge of any primary exposure could have influenced case ascertainment.
[4] low number of participants (less than 400)

I.14 Review question 14 full GRADE profiles

1.1.1.7 Rates (and recurrent rates) of foot ulceration, infection and gangrene resulting from diabetes

Quality assessment							No of patients	Effect Rates of foot ulceration, infection and gangrene	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	consideration	Intervention			
Ulceration										
Weck 2013	Observational prospective	No serious imprecision	no serious inconsistency	no serious inconsistency	very serious[2,3,4, 5, 6, 7, 9, 11]	none	684 patients hospitalized because of diabetic foot ulceration 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 therapeutic algorithms. 684 diabetic patients with diabetic foot ulceration 508 controls	Rates (and recurrent rates) of foot ulceration, infection and gangrene resulting from diabetes The structured health care group had a significantly lower level of ulcer severity at discharge compared to controls after adjustment for age, ulcer severity, peripheral arterial disease, coronary heart disease, hypertension, smoking and MA. P=0.001 i.e. significant difference	VERY LOW	IMPORTANT
Larsson 1995	Observational	No serious imprecision	no serious inconsistency	no serious inconsistency	very serious [2, 4, 5, 7, 9, 11,	none	294 patients with known diabetes mellitus had 387 primary amputations. 71% of the amputations were precipitated by foot ulcer. 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. (Established in 1983.)	Rates (and recurrent rates) of foot ulceration, infection and gangrene resulting from diabetes In 195 patients (50% of total), a minor or major gangrene was present at the time of amputation and this proportion decreased from 53 to 36% (p<0.05) between the first and last 3 year period (data not provided)	VERY LOW	IMPORTANT

<table>
<tr>
<td>Yesil 2009</td>
<td>Observational prospective</td>
<td>No serious imprecision</td>
<td>no serious inconsistency</td>
<td>no serious inconsistency</td>
<td>very serious [2, 4, 5, 6, 7]</td>
<td>none</td>
<td>The management of 437 patients with diabetic foot ulceration. Data taken from between January 1999 and January 2008 with the clinic established in 2002.

Before Diabetic foot team (n=137)
After Diabetic foot team (n=437)

A diabetic foot care team was established consisting of endocrinologists, orthopaedist, plastic and vascular surgeons, infectious disease specialists, radiologists, rehabilitation specialists, diabetes education and wound-care nurses and footwear technician</td>
<td>Rates (and recurrent rates) of foot ulceration, infection and gangrene resulting from diabetes
<table>
<tr><th></th><th>Before Diabetic foot team (n=137)</th><th>After Diabetic foot team (n=437)</th><th>P value</th></tr>
<tr><td>Unhealed ulcers (n, %)</td><td>22 (16.1%)</td><td>59 (13.5%)</td><td>0.293</td></tr>
<tr><td>Healed ulcers (n,%) (without amputation)</td><td>60 (43.8%)</td><td>220 (50.3%)</td><td>0.203</td></tr>
</table>
</td>
<td>VERY LOW</td>
<td>IMPORTANT</td>
</tr>
</table>

[1]Unclear if the reason for allocation was or was not related to any other confounding factors. It is unclear if groups were comparable at baseline including all major confounding factors as such data was not provided per group. Unclear if the comparison groups received the same care. Participants were not blinded to intervention allocation. Individuals administering care were not blinded to intervention allocation. Unclear if groups were comparable for compliance or intervention completion. Unclear if groups were comparable for availability of outcome data. A valid and reliable method may not have been used

[2] Non Randomised

[3]Unclear if groups were comparable at baseline for all prognostic factors, no attempt to balance groups for confounding factors. Or groups not comparable for all confounding factors.

[4]Unclear if comparison group received the same care apart from intervention studied

[5]Non Blinded

[6]Only crude incidence rates recorded, no analysis to adjust for confounding factors

[7]Unclear if groups were comparable for adherence, clinic attendance or treatment completion

[8]Unclear if groups were comparable for outcome data available or loss to follow up

[9]Groups were not comparable for length of observation or unclear if patients were followed up for a similar amount of time (or adjustments not made)

[10]No precise definition of outcome

[11]Method of determination of outcome not valid or reliable or unclear (for example; retrospective or administrative data set)

[12]Length of follow up/observation inappropriate/unclear

1.1.1.8 Resource use and costs (including referral rates)

Quality assessment							No of patients	Effect Resource use and cost (results)	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	consideration	Intervention			

Resource use and costs										
Nather 2010	Observational retrospective	No serious imprecision	no serious inconsistency	no serious inconsistency	very serious [2,3,4,5,6,7,9,11]	none	939 patients with diabetic foot problems. Patients with Kings college classification stages 3-5 were placed on Part 1 of the clinical pathway (n=777) while those diagnosed with stage 6 were put on part 2 of the pathway (n=162) Before team formation= 61 After established=878 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.	Resource use and costs (including referral rates) Mean hospitalisation cost per patient 2002: $8,847.17 - 2003: $9,935.59 NS 2004: $7,659.55 NS 2005: $6,195.77 NS 2006: $6,320.19 NS 2007: $6,383.79 NS	VERY LOW	IMPORTANT

[1]Unclear if the reason for allocation was or was not related to any other confounding factors. It is unclear if groups were comparable at baseline including all major confounding factors as such data was not provided per group. Unclear if the comparison groups received the same care. Participants were not blinded to intervention allocation. Individuals administering care were not blinded to intervention allocation. Unclear if groups were comparable for compliance or intervention completion. Unclear if groups were comparable for availability of outcome data. A valid and reliable method may not have been used

[2] Non Randomised

[3]Unclear if groups were comparable at baseline for all prognostic factors, no attempt to balance groups for confounding factors. Or groups not comparable for all confounding factors.

[4]Unclear if comparison group received the same care apart from intervention studied

[5]Non Blinded

[6]Only crude incidence rates recorded, no analysis to adjust for confounding factors

[7]Unclear if groups were comparable for adherence, clinic attendance or treatment completion

[8]Unclear if groups were comparable for outcome data available or loss to follow up

[9]Groups were not comparable for length of observation or unclear if patients were followed up for a similar amount of time (or adjustments not made)

[10]No precise definition of outcome

[11]Method of determination of outcome not valid or reliable or unclear (for example; retrospective or administrative data set)

[12]Length of follow up/observation inappropriate/unclear

1.1.1.9 Rates of hospital admission for foot problems resulting from diabetes

Quality assessment	No of patients	Effect Rates of hospital admission (results)	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	consideration	Intervention			
Rates of hospital admission										

<table>
<tr>
<td>Williams 2012</td>
<td>Observational prospective</td>
<td>No serious imprecision</td>
<td>no serious inconsistency</td>
<td>no serious inconsistency</td>
<td>very serious[2,3,5,6,7,8,9,11]</td>
<td>none</td>
<td>diabetic patients in whom critical peripheral arterial disease is suspected. Amputation rates were based on the 9,328 people diagnosed with diabetes in the region.

Intervention: 1) 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 (see paper for details) 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

Established in 2006.</td>
<td>Admissions to vascular ward for patients with diabetes and lower limb disease
<table>
<tr><td></td><td>2004/2005</td><td>2005/2006</td><td>2006/2007</td><td>2007/2008</td><td>2008/2009</td><td>2009/2010</td></tr>
<tr><td>Number</td><td>36</td><td>63</td><td>59</td><td>58</td><td>47</td><td>34</td></tr>
</table>
</td>
<td>VERY LOW</td>
<td>IMPORTANT</td>
</tr>
</table>

<table>
<tr>
<td>Nather 2010</td>
<td>Observational retrospective</td>
<td>No serious imprecision</td>
<td>no serious inconsistency</td>
<td>no serious inconsistency</td>
<td>very serious [2, 3, 4, , 5, 6, 7, 9, 11,</td>
<td>none</td>
<td>939 patients with diabetic foot problems. Patients with Kings college classification stages 3-5 were placed on Part 1 of the clinical pathway (n=777) while those diagnosed with stage 6 were put on part 2 of the pathway (n=162)

Before team formation= 61
After established=878

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.</td>
<td>Rates of hospital admission for foot problems resulting from diabetes
Readmission rate
<table>
<tr><th></th><th>Readmission rate</th><th>P value</th></tr>
<tr><td>2002</td><td>13.11%</td><td>-</td></tr>
<tr><td>2003</td><td>7.14%</td><td>NS</td></tr>
<tr><td>2004</td><td>6.76%</td><td>NS</td></tr>
<tr><td>2005</td><td>7.22%</td><td>NS</td></tr>
<tr><td>2006</td><td>5.34%</td><td>NS</td></tr>
<tr><td>2007</td><td>8.26%</td><td>NS</td></tr>
</table>
</td>
<td>VERY LOW</td>
<td>IMPORTANT</td>
</tr>
</table>

[1]Unclear if the reason for allocation was or was not related to any other confounding factors. It is unclear if groups were comparable at baseline including all major confounding factors as such data was not provided per group. Unclear if the comparison groups received the same care. Participants were not blinded to intervention allocation. Individuals administering care were not blinded to intervention allocation. Unclear if groups were comparable for compliance or intervention completion. Unclear if groups were comparable for availability of outcome data. A valid and reliable method may not have been used

[2] Non Randomised

[3]Unclear if groups were comparable at baseline for all prognostic factors, no attempt to balance groups for confounding factors. Or groups not comparable for all confounding factors.

[4]Unclear if comparison group received the same care apart from intervention studied

[5]Non Blinded

[6]Only crude incidence rates recorded, no analysis to adjust for confounding factors

[7]Unclear if groups were comparable for adherence, clinic attendance or treatment completion

[8]Unclear if groups were comparable for outcome data available or loss to follow up

[9]Groups were not comparable for length of observation or unclear if patients were followed up for a similar amount of time (or adjustments not made)

[10]No precise definition of outcome

[11]Method of determination of outcome not valid or reliable or unclear (for example; retrospective or administrative data set)

[12]Length of follow up/observation inappropriate/unclear

1.1.1.10 Length of hospital stay

Quality assessment	No of patients	Effect Length of hospital stay (results	Quality	Importance

<table>
<tr><th>No of studies</th><th>Design</th><th>Risk of bias</th><th>Inconsistency</th><th>Indirectness</th><th>Imprecision</th><th>consideration</th><th>Intervention</th><th></th><th></th><th></th></tr>
<tr><td colspan="11">Length of hospital stay</td></tr>
<tr><td>Williams 2012</td><td>Observational prospective</td><td>No serious imprecision</td><td>no serious inconsistency</td><td>no serious inconsistency</td><td>very serious[2,3,5,6,7,8,9,11]</td><td>none</td><td>diabetic patients in whom critical peripheral arterial disease is suspected. Amputation rates were based on the 9,328 people diagnosed with diabetes in the region.

Intervention: 1) 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 (see paper for details) 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

Established in 2006.</td><td>Length of hospital stay

Median length of stay for patients with diabetic foot disease. No significant difference in the median length of stay was seen before and after the introduction of the foot service. (P= 0.422)

<table><tr><td></td><td>2004</td><td>2005</td><td>2006</td><td>2007</td><td>2008</td><td>2009</td></tr><tr><td>Length of stay (days)</td><td>16</td><td>18</td><td>17</td><td>13</td><td>14</td><td>15.5</td></tr></table></td><td>VERY LOW</td><td>IMPORTANT</td></tr>
<tr><td>Chiu 2011</td><td>Observational retrospective</td><td>No serious imprecision</td><td>no serious inconsistency</td><td>no serious inconsistency</td><td>very serious[3,4,5,7,8,11,]</td><td>none</td><td>Patients with infected diabetic foot ulcers.

Diabetic foot ulcer treatment programme = 350
Controls= 386

Surveillance and care by experienced specialists (endocrinologists, vascular surgeons and plastic surgeons with decision algorithm</td><td>Length of hospital stay

Length of hospital stay
Treatment programme group= 23.5 ± 5.8 days
Non-treatment programme group= 29.3 ± 17.9 days
P =0.188 i.e. not significant difference

Length of hospital stay in Stage D patients (ischaemic infected wounds)
Treatment programme group (n=162)= 24.5 ± 6.4 days
Non-treatment programme group (n=185)= 33.8 ± 19.9 days
P =0.014 i.e. significant difference</td><td>VERY LOW</td><td>IMPORTANT</td></tr>
</table>

<table>
<tr>
<td>Nather 2010</td>
<td>Observational retrospective</td>
<td>No serious imprecision</td>
<td>no serious inconsistency</td>
<td>no serious inconsistency</td>
<td>very serious [2, 3, 4, , 5, 6, 7, 9, 11,]</td>
<td>none</td>
<td>939 patients with diabetic foot problems. Patients with Kings college classification stages 3-5 were placed on Part 1 of the clinical pathway (n=777) while those diagnosed with stage 6 were put on part 2 of the pathway (n=162)

Before team formation= 61
After established=878

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.</td>
<td>Length of hospital stay
<table>
<tr><th></th><th>Average length of stay (days)</th><th>P value</th></tr>
<tr><td>2002</td><td>20.36</td><td>-</td></tr>
<tr><td>2003</td><td>19.03</td><td>NS</td></tr>
<tr><td>2004</td><td>13.74</td><td>0.0005</td></tr>
<tr><td>2005</td><td>10.81</td><td><0.0005</td></tr>
<tr><td>2006</td><td>11.67</td><td>0.0009</td></tr>
<tr><td>2007</td><td>12.2</td><td>0.0005</td></tr>
</table></td>
<td>VERY LOW</td>
<td>IMPORTANT</td>
</tr>
<tr>
<td>Yesil 2009</td>
<td>Observational prospective</td>
<td>No serious imprecision</td>
<td>no serious inconsistency</td>
<td>no serious inconsistency</td>
<td>very serious [2, 4, 5, 6, 7,]</td>
<td>none</td>
<td>The management of 437 patients with diabetic foot ulceration. Data taken from between January 1999 and January 2008 with the clinic established in 2002.

Before Diabetic foot team (n=137)
After Diabetic foot team (n=437)

A diabetic foot care team was established consisting of endocrinologists, orthopaedist, plastic and vascular surgeons, infectious disease specialists, radiologists, rehabilitation specialists, diabetes education and wound-care nurses and footwear technician</td>
<td>Rates (and recurrent rates) of foot ulceration, infection and gangrene resulting from diabetes

Length of hospital stay
<table>
<tr><th></th><th>Before Diabetic foot team</th><th>After Diabetic foot team</th><th>P value</th></tr>
<tr><td>Inpatient treatment (days)</td><td>39.47 ± 28.29</td><td>26.99 ± 21.27</td><td><0.001</td></tr>
</table></td>
<td>VERY LOW</td>
<td>IMPORTANT</td>
</tr>
</table>

[1]Unclear if the reason for allocation was or was not related to any other confounding factors. It is unclear if groups were comparable at baseline including all major confounding factors as such data was not provided per group. Unclear if the comparison groups received the same care. Participants were not blinded to intervention allocation. Individuals administering care were not blinded to intervention allocation. Unclear if groups were comparable for compliance or intervention completion. Unclear if groups were comparable for availability of outcome data. A valid and reliable method may not have been used

[2] Non Randomised

[3]Unclear if groups were comparable at baseline for all prognostic factors, no attempt to balance groups for confounding factors. Or groups not comparable for all confounding factors.

[4]Unclear if comparison group received the same care apart from intervention studied

[5]Non Blinded

[6]Only crude incidence rates recorded, no analysis to adjust for confounding factors

[7]Unclear if groups were comparable for adherence, clinic attendance or treatment completion

[8]Unclear if groups were comparable for outcome data available or loss to follow up

[9]Groups were not comparable for length of observation or unclear if patients were followed up for a similar amount of time (or adjustments not made)

[10]No precise definition of outcome

[11]Method of determination of outcome not valid or reliable or unclear (for example; retrospective or administrative data set)

[12]Length of follow up/observation inappropriate/unclear

1.1.1.11 Rates and extent of amputation

Quality assessment							No of patients	Effect Rates and extent of amputations (results)	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	consideration	Intervention			
Amputation										
Mills 1991	Observational case series	No serious imprecision	no serious inconsistency	no serious inconsistency	very serious[1]	none	Total participants= 55 Total limbs= 62	Narrative summary: A significant delay in referral for surgical care or inappropriate initial treatment was identified in 16 of the 55 participants. Reasons for delayed referral: Infection was either unrecognised or grossly under estimated= 10 participants Significant ischemia was not appreciated= 6 participants These delays led to more proximal amputation levels in 6 patients (seven limbs) including three below-knee amputations in patients with limbs that were initially salvageable.	VERY LOW	IMPORTANT
Alexandrescu 2008	Observational prospective	No serious imprecision	no serious inconsistency	no serious inconsistency	very serious[2,3,4,5,6,11]	none	A consecutive series of 163 patients with 183 limbs with diabetic ischaemic wounds treated by combined multi-level angioplasties. Multidisciplinary clinic period= 97 limbs Pre multidisciplinary clinic period= 86 limbs	Rates and extent of amputation Cumulative patency rates (SEM): pre and post operative care for these patients was optionally multidisciplinary 6 months= 76% (± 5.5) 12 months= 72% (± 6.1) 24 months= 66% (± 7.1) Cumulative patency rates: The implementation of multidisciplinary diabetic foot clinic and treatment algorithm 6 months= 80% (± 5,1) 12 months= 77% (±5.6) 24 months= 73% (±6.6) A significant difference was found between the two intervals for limb salvage rates (P=0.040) No significant statistical deviation was found in the results of the angioplasty alone (p=0.381)	VERY LOW	IMPORTANT

Rerkasem 2008	Observational prospective	No serious imprecision	no serious inconsistency	no serious inconsistency	very serious[2,4,5,6,9]	none	n= 183 patients with diabetic foot ulcer. Establishment of a multidisciplinary team and flow sheets based on foot protection algorithms 73 received diabetic foot protection 110 received preventive measures taken at the discretion of the physician and there were no detailed guidelines or flow sheets for specific services	4 years observation period, unclear individual length of follow up Rates and extent of amputation Number of major amputations Defined as either a below knee or above knee amputation Under diabetic foot protection period= 0 above knee amputations Control period= 3 above knee amputations P=0.28 i.e. not significant Under diabetic foot protection period= 3 below knee amputations Control period= 12 below knee amputations P=0.1 i.e. not significant The incidence of major amputations in the protocol and standard care group was 4.1% and 13.6% respectively (P=0.03 i.e. significant difference) Minor amputations The loss of any part of a lower limb (not including major amputations) Under diabetic foot protection period Toe- 4 amputations Transmetatarsal- 0 amputations Syme- 0 amputations Control period Toe- 10 amputations Transmetatarsal- 4 amputations Syme- 1 amputations	VERY LOW	IMPORTANT

Weck 2013	Observational prospective	No serious imprecision	no serious inconsistency	no serious inconsistency	very serious[2,3,4,5,6,7,9,11]	none	684 patients hospitalized because of diabetic foot ulceration 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 therapeutic algorithms. 684 diabetic patients with diabetic foot ulceration 508 controls	Rates and extent of amputation Major amputation Defined as amputation above the ankle Group treated by structured health care programme= 32 (4.7%) Control group= 110 cases (21.7%) P=<0.0001 (age adjusted) i.e. significant difference Minor amputations Group treated by structured health care programme= 215 of 684 participants Control group= 179 of 508 participants	VERY LOW	IMPORTANT

Edmonds 1986	Observational prospective	No serious imprecision	no serious inconsistency	no serious inconsistency	very serious[2,3,4, 5, 6,7,8, 9, 10, 11]	none	n= 239 diabetic patients with foot ulcers Unclear how many patients were treated in each period a specialised foot clinic for diabetic patients employing a chiropodist, shoe-fitter, nurse, physician and surgeon established	Rates and extent of amputation Major amputations: Two years before clinic was established: 11 and 12 major amputations yearly Three years following: 7, 7, and 5 amputations yearly The number of minor operations (drainage operations and “Ray” amputations) Two years before clinic was established: 27 and 29 major amputations yearly Three years following establishment of clinic: 16, 21, and 15 amputations yearly	VERY LOW	IMPORTANT

<table>
<tr>
<td>Williams 2012</td>
<td>Observational prospective</td>
<td>No serious imprecision</td>
<td>no serious inconsistency</td>
<td>no serious inconsistency</td>
<td>very serious[2,3,5,6,7,8,9,11]</td>
<td>none</td>
<td>diabetic patients in whom critical peripheral arterial disease is suspected. Amputation rates were based on the 9,328 people diagnosed with diabetes in the region.

Intervention: 1) 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 (see paper for details) 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</td>
<td>Rates and extent of amputation

Major amputations rate (above and below knee amputations)
<table>
<tr><td>Amputations</td><td>2004</td><td>2005</td><td>2006</td><td>2007</td><td>2008</td><td>2009</td><td>2004-2005</td><td>2006-2009</td></tr>
<tr><td>Major</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Diabetic</td><td>18</td><td>23</td><td>11</td><td>8</td><td>7</td><td>1</td><td>41</td><td>27</td></tr>
<tr><td>Non diabetic</td><td>7</td><td>12</td><td>5</td><td>7</td><td>8</td><td>3</td><td>19</td><td>23</td></tr>
<tr><td>Percent</td><td>72</td><td>66</td><td>69</td><td>53</td><td>47</td><td>25</td><td>68</td><td>54</td></tr>
</table>
A yearly major amputation rate that peaked in 2005 at 23 (24.7/10000) decreased in 2009 to 1 (1.07/10000).
Relative risk= 0.043 (95% CI 0.006-0.322) i.e. significant difference

Minor amputations rate (surgical debridements, partial foot amputations, toe amputations)
<table>
<tr><td>Amputations</td><td>2004</td><td>2005</td><td>2006</td><td>2007</td><td>2008</td><td>2009</td><td>2004-2005</td><td>2006-2009</td></tr>
<tr><td>Minor</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Diabetic</td><td>32</td><td>49</td><td>50</td><td>31</td><td>13</td><td>7</td><td>81</td><td>101</td></tr>
<tr><td>Non diabetic</td><td>2</td><td>3</td><td>5</td><td>6</td><td>10</td><td>6</td><td>5</td><td>27</td></tr>
<tr><td>Percent</td><td>94</td><td>94</td><td>91</td><td>84</td><td>57</td><td>54</td><td>91</td><td>79</td></tr>
</table>
</td>
<td>VERY LOW</td>
<td>IMPORTANT</td>
</tr>
</table>

<table>
<tr>
<td>Cahn 2014</td>
<td>Observational retrospective</td>
<td>No serious imprecision</td>
<td>no serious inconsistency</td>
<td>no serious inconsistency</td>
<td>very serious[2, 4, 5, 10, 11, 12]</td>
<td>none</td>
<td>Patient records with the diagnosis of diabetic foot or amputation who were hospitalised 2010-2011.

treated in 2010=93
treated in 2011= 103.

A diabetic foot unit within the orthopaedics department was gradually established allowing multidisciplinary team members 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. (2011)</td>
<td>Rates and extent of amputation
<table>
<tr><td></td><td>2010 (n=93)</td><td>2011 (n=101)</td><td>P value</td></tr>
<tr><td>Major amputations</td><td>34</td><td>19</td><td>0.03</td></tr>
<tr><td>Minor amputations</td><td>26</td><td>29</td><td>NS</td></tr>
<tr><td>Percentage amputations major (major/total)</td><td>56.7%</td><td>39.6%</td><td>0.0748</td></tr>
</table>
</td>
<td>VERY LOW</td>
<td>IMPORTANT</td>
</tr>
</table>

Chiu 2011	Observational retrospective	No serious imprecision	no serious inconsistency	no serious inconsistency	very serious [3, 4, 5, 7,8, 11,]	none	Patients with infected diabetic foot ulcers. Diabetic foot ulcer treatment programme = 350 Controls= 386 Surveillance and care by experienced specialists (endocrinologists, vascular surgeons and plastic surgeons with decision algorithm	Rates and extent of amputation The odds ratio for amputation when the diabetic foot ulcer treatment programme group was compared to the non treatment programme group was 2.89 (95% CI 1.28-6.53) i.e. significant difference. After stratification for stage D patients (ischaemic infected wounds): The odds ratio for amputation when the diabetic foot ulcer treatment programme group was compared to the non treatment programme group was 2.91 (95% CI 1.03-8.22) i.e. significant difference. A greater proportion of patients in the non-treatment programme group experienced amputation: Treatment programme group= 34 (9.7%) Non-treatment programme group= 91 (23.6%) P<0.001 i.e. significant difference Reamputation rate after 5 year follow up Treatment programme group= 11 of 350 patients (3.1%) Non-treatment programme group= 28 (7.3%) Odds ratio of likelihood of reamputation= 0.425 95% CI 0.11-1.65) P= 0.204 i.e. no significant difference Level of amputation Treatment programme group= toe 92%, below knee 7%, above knee 1% Non-treatment programme group= toe 63%, below knee 25%, above knee 12%	VERY LOW	IMPORTANT

<table>
<tr>
<td>Hedetoft 2009</td>
<td>Observational retrospective</td>
<td>No serious imprecision</td>
<td>no serious inconsistency</td>
<td>no serious inconsistency</td>
<td>very serious [2, 3, 4, 5, 7, 11]</td>
<td>none</td>
<td>All the clinical records of type 2 diabetic patients who had undergone leg amputation seen in the diabetic foot clinic in the observation period of 6 years were examined

The amputees were divided into two groups dependent of a regular review in in the clinic before and after the amputation (for more than 4 visits)= Group A
A regular review after the amputation or only briefly seen after the amputation= Group B.</td>
<td>Rates and extent of amputation

In the observation period of 6 years: 88 subjects underwent 142 amputations, 42 major amputations and 100 minor amputations. In the same period the number of type 2 diabetic patients with foot ulcers attending the clinic increased from 50 to nearly 200 and the number of patients with type 2 diabetes increased from 250 to 1217. There was no increase in the number of major amputations in this period
<table>
<tr><td></td><td colspan="2">Group A (n=28)</td><td colspan="2">Group B (n=60)</td><td colspan="2">P value</td></tr>
<tr><td></td><td>Major</td><td>Minor</td><td>Major</td><td>Minor</td><td>Major</td><td>Minor</td></tr>
<tr><td>Amputees</td><td>10</td><td>18</td><td>19</td><td>41</td><td>0.036</td><td>0.01</td></tr>
<tr><td>Amputations</td><td>14</td><td>44</td><td>28</td><td>56</td><td>0.046</td><td>NS</td></tr>
<tr><td>Reamputations</td><td colspan="2">21</td><td colspan="2">32</td><td colspan="2">NS</td></tr>
<tr><td>Foot ulcers (%)</td><td>100</td><td>100</td><td>100</td><td>100</td><td>NS</td><td>NS</td></tr>
</table>
</td>
<td>VERY LOW</td>
<td>IMPORTANT</td>
</tr>
</table>

<table>
<tr>
<td>Nather 2010</td>
<td>Observational retrospective</td>
<td>No serious imprecision</td>
<td>no serious inconsistency</td>
<td>no serious inconsistency</td>
<td>very serious [2, 3, 4, 5, 6, 7, 9, 11]</td>
<td>none</td>
<td>939 patients with diabetic foot problems. Patients with Kings college classification stages 3-5 were placed on Part 1 of the clinical pathway (n=777) while those diagnosed with stage 6 were put on part 2 of the pathway (n=162)

Before team formation= 61
After established=878

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.</td>
<td>Rates and extent of amputation
Major amputation rate (above or below knee)
<table>
<tr><th></th><th>Rate of major amputation</th><th>P value</th></tr>
<tr><td>2002</td><td>31.13%</td><td>_</td></tr>
<tr><td>2003</td><td>25.71%</td><td>NS</td></tr>
<tr><td>2004</td><td>19.59%</td><td>NS</td></tr>
<tr><td>2005</td><td>14.44%</td><td>0.004</td></tr>
<tr><td>2006</td><td>14.12%</td><td>0.002</td></tr>
<tr><td>2007</td><td>11.01%</td><td><0.0005</td></tr>
</table>
</td>
<td>VERY LOW</td>
<td>IMPORTANT</td>
</tr>
</table>

Larsson 1995 | Observational retrospective | No serious imprecision | no serious inconsistency | no serious inconsistency | very serious [2, 4, 5, 7, 9, 11] | none | 294 patients with known diabetes mellitus had 387 primary amputations. 71% of the amputations were precipitated by foot ulcer.

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. (Established in 1983.)

Rates and extent of amputation

	Through and above the knee	Below knee	Below ankle	Total
1982	12	20	6	38
1983	**8**	**19**	**12**	**39**
1984	4	18	13	35
1985	10	35	7	52
1986	9	17	10	36
1987	9	21	6	36
1988	9	10	15	34
1989	10	3	8	21
1990	8	7	9	24
1991	9	9	13	31
1992	4	4	12	20
1993	2	6	13	21
Total	94	169	124	387

Incidence of amputation in diabetic patients with or without vascular disease per 100000 inhabitants and year, according to age group.

	Amputation at all levels. Any age	Major amputations at any age	Major amputations <60 years	Major amputations 60-79 years	Major amputations ≥80 years
1982	19.1	16.1	0	50.6	272.0
1983	**19.5**	**13.3**	**0**	**43.3**	**219.2**
1984	17.4	10.9	0	43.1	137.5
1985	25.8	22.3	1.8	72.3	294.6
1986	17.6	12.7	1.2	49.0	128.0
1987	17.5	14.6	2.4	45.4	167.3
1988	16.3	9.1	1.2	38.8	67.1
1989	9.9	6.2	0	16.1	104.5
1990	11.2	7.0	0	19.3	115.1
1991	14.3	8.3	1.7	28.8	74.3
1992	9.1	3.6	0	19.1	24.2
1993	9.4	3.6	1.1	18.9	0

The total annual incidence of primary amputations decreased by 49%. The incidence of major amputations decreased by 78%
From 16.1 to 3.6/100000 inhabitants (p<0.001)
Calculated per 1000 diabetic subjects the total incidence of amputation decreased from 7.9 to 4.1 and the incidence of major amputations from 6.7 to 1.5.
The total reamputation rate decreased from 36 to 22% between the first and last 3 year period (P<0.05; data not provided)

VERY LOW | IMPORTANT

Faglia 1998	Observational retrospective	No serious imprecision	no serious inconsistency	no serious inconsistency	very serious [2, 3, 4, 5, 7, 9, 11, 12]	none	115 diabetic patients consecutively hospitalised for foot ulcer. Admitted 1986-1989= 78 Admitted 1990-1993= 115 Rates of amputation were compared with the previous two periods before criteria for admission to hospital and therapeutic-diagnostic protocol were established.	Rates and extent of amputation Major amputations (above or below the knee) Period from 1979 to 1981, patients admitted to general surgical department (n=42)= 17 major amputations 40.5% Period from 1986 to 1989, patients admitted to diabetology centre, processing stage of multidisciplinary protocol (n=78)= 26 major amputations 33.3% Period from 1990 to 1993, standardised application of multidisciplinary protocol (n=115)= 27 major amputations 23.5% Odds ratio (95% CI)= 0.66 (0.46-0.96) i.e. significant difference	VERY LOW	IMPORTANT

<table>
<tr>
<td>Yesil 2009</td>
<td>Observational prospective</td>
<td>No serious imprecision</td>
<td>no serious inconsistency</td>
<td>no serious inconsistency</td>
<td>very serious [2, 4, 5, 6, 7]</td>
<td>none</td>
<td>The management of 437 patients with diabetic foot ulceration. Data taken from between January 1999 and January 2008 with the clinic established in 2002.

Before Diabetic foot team (n=137)
After Diabetic foot team (n=437)

A diabetic foot care team was established consisting of endocrinologists, orthopaedist, plastic and vascular surgeons, infectious disease specialists, radiologists, rehabilitation specialists, diabetes education and wound-care nurses and footwear technician</td>
<td>Rates and extent of amputation
<table>
<tr><th></th><th>Before Diabetic foot team</th><th>After Diabetic foot team</th><th>P value</th></tr>
<tr><td>Overall amputations (n,%)</td><td>55 (40.1%)</td><td>158 (36.2%)</td><td>0.418</td></tr>
<tr><td>Minor amputations (n,%)</td><td>27 (19.7%)</td><td>103 (23.6%)</td><td>0.413</td></tr>
<tr><td>Major amputations (n,%)</td><td>28 (20.4%)</td><td>55 (12.6%)</td><td>0.026</td></tr>
</table>
</td>
<td>VERY LOW</td>
<td>IMPORTANT</td>
</tr>
</table>

Armstrong 2012	Observational prospective	No serious imprecision	no serious inconsistency	no serious inconsistency	very serious [2,3,4,5,6,7,11]	none	790 operations related to the treatment of diabetic foot complications requiring surgery or vascular intervention in 374 patients. Data taken from 24 months before and after integrating podiatric surgery with a vascular surgical limb-salvage service.	Rates and extent of amputation 790 operations were performed related to treatment of diabetic foot complications in 374 patients. 502 were classified as non-vascular diabetic foot surgery and 288 were vascular interventions. Surgery classified as urgent foot surgery Before team implementation= 77.7% After team implementation= 48.5% Odds ratio= 3.7 (95% CI 2.4-5.5) P<0.0001 i.e. significant difference. High/low amputation ratio Before team implementation= 0.35 After team implementation= 0.27 Mid foot amputations Before team implementation= 8.2% After team implementation= 26.1% Odds ratio= 4.0 (95% CI 2.0-83.3) P<0.0001 i.e. significant difference. A 37.5% reduction in below knee amputations was realised.	VERY LOW	IMPORTANT

<table>
<tr>
<td>Trautner 2007</td>
<td>Observational retrospective</td>
<td>No serious imprecision</td>
<td>no serious inconsistency</td>
<td>no serious inconsistency</td>
<td>very serious [2, 4, 5, 7, 8, 11]</td>
<td>none</td>
<td>501 patients had first non-traumatic lower-limb amputations in the three local hospitals during the defined period

Data given per 100,000 person years

An interdisciplinary ward for inpatient treatment including preoperative and post-operative care opened in 2001.</td>
<td>Rates and extent of amputation
<table>
<tr><th>Year</th><th>Incidence rate (95% CI) in diabetic population: Standard=total population (per 100,000 person years)</th><th>Incidence rate (95% CI) in diabetic population: Standard=diabetic population (per 100,000 person years)</th></tr>
<tr><td>1990</td><td>224 (136-311)</td><td>549 (382-715)</td></tr>
<tr><td>1991</td><td>143 (75-210)</td><td>356 (221-491)</td></tr>
<tr><td>1994</td><td>226 (141-312)</td><td>544 (383-705)</td></tr>
<tr><td>1995</td><td>175 (96-255)</td><td>386 (252-521)</td></tr>
<tr><td>1996</td><td>180 (101-259)</td><td>426 (286-566)</td></tr>
<tr><td>1997</td><td>455 (0-989)</td><td>433 (290-576)</td></tr>
<tr><td>1998</td><td>195 (113-278)</td><td>463 (316-611)</td></tr>
<tr><td>1999</td><td>191 (113-269)</td><td>474 (330-618)</td></tr>
<tr><td>2000</td><td>165 (93-237)</td><td>415 (282-549)</td></tr>
<tr><td>2001</td><td>78 (48-107)</td><td>304 (187-421)</td></tr>
<tr><td>2002</td><td>131 (67-195)</td><td>335 (218-451)</td></tr>
<tr><td>2003</td><td>119 (67-171)</td><td>360 (237-482)</td></tr>
<tr><td>2004</td><td>113 (52-174)</td><td>281 (173-389)</td></tr>
<tr><td>2005</td><td>235 (136-335)</td><td>428 (295-560)</td></tr>
</table>
Over 15 years an estimated reduction in amputations above the toe level by 37.1% (95% CI 12.3-54.8) results.

Estimated relative risk per calendar year was 0.976 (95% CI 0.958-0.996) P<0.0164 in the diabetic population
i.e. significant effect

Estimated relative risk per calendar year was 0.970 (95% CI 0.948-0.991) P<0.006 in the diabetic population when only all first amputations above the toe were included. (n=527)
i.e. significant effect

Estimated relative risk per calendar year was 0.970 (95% CI 0.943-0.997) P<0.0318 in the diabetic population when only all first amputations above the ankle were included. (n=352)
i.e. significant effect</td>
<td>VERY LOW</td>
<td>IMPORTANT</td>
</tr>
</table>

Setacci 2013	Observational retrospective	No serious imprecision	no serious inconsistency	no serious inconsistency	very serious [2,5,6,7,8,11]	none	375 patients with critical limb ischaemia and diabetic foot infection Intervention=183 Comparison=192 treated with delayed vascularisation (pre-protocol) application of new interdisciplinary shared protocol	Major amputation rate at 6 months Intervention group= 24.6% Comparison group= 39.6% Hazard ratio= 0.58, P value = 0.0024	VERY LOW	IMPORTANT
Elgzyri 2014	Observational retrospective	No serious imprecision	no serious inconsistency	no serious inconsistency	very serious [3,4,5,,7,8,9,11,13]	none	A series of 478 patients 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.	Survival analysis for factors affecting healing without major amputation Univariate analysis Time to revascularisation ≤8 weeks 1.96 (1.52-2.52) P value <0.001	VERY LOW	IMPORTANT

<table>
<tr>
<td>13 Rubio 2014</td>
<td>Observational retrospective</td>
<td>No serious imprecision</td>
<td>no serious inconsistency</td>
<td>no serious inconsistency</td>
<td>very serious[2,3,4, 5,8, 11]</td>
<td>none</td>
<td>374 amputations in people with diabetes were performed in the health care area during the period of study.

A multidisciplinary diabetic foot unit, team for the diagnosis and treatment of diabetic foot disease. Coordinated by an endocrinologist and a podiatrist. Introduced in march 2008.</td>
<td>Rates and extent of amputation
Incidence of lower extremity amputations in diabetic population per 100000 inhabitants and per year (mean (95% confidence interval))
<table>
<tr><td>Study period</td><td>All</td><td>Minor</td><td>Major</td></tr>
<tr><td>2001-2011 (total)</td><td>10.8 (9.1-12.5)</td><td>5.5 (4.2-6.7)</td><td>5.3 (4.3-6.3)</td></tr>
<tr><td>2001-2007 (pre MDT)</td><td>11.8 (9.3-14.3)</td><td>5.7 (3.9-7.5)</td><td>6.1 (4.9-7.2)</td></tr>
<tr><td>2008-2011 (post MDT)</td><td>9.1 (7.6-10.6)</td><td>5.0 (2.3-7.8)</td><td>4.0 (2.6-5.5)</td></tr>
<tr><td>P value</td><td>0.090</td><td>0.732</td><td>0.020</td></tr>
</table>
</td>
<td>VERY LOW</td>
<td>IMPORTANT</td>
</tr>
</table>

[1]Unclear if the reason for allocation was or was not related to any other confounding factors. It is unclear if groups were comparable at baseline including all major confounding factors as such data was not provided per group. Unclear if the comparison groups received the same care. Participants were not blinded to intervention allocation. Individuals administering care were not blinded to intervention allocation. Unclear if groups were comparable for compliance or intervention completion. Unclear if groups were comparable for availability of outcome data. A valid and reliable method may not have been used

[2] Non Randomised

[3]Unclear if groups were comparable at baseline for all prognostic factors, no attempt to balance groups for confounding factors. Or groups not comparable for all confounding factors.

[4]Unclear if comparison group received the same care apart from intervention studied

[5]Non Blinded

[6]Only crude incidence rates recorded, no analysis to adjust for confounding factors

[7]Unclear if groups were comparable for adherence, clinic attendance or treatment completion

[8]Unclear if groups were comparable for outcome data available or loss to follow up

[9]Groups were not comparable for length of observation or unclear if patients were followed up for a similar amount of time (or adjustments not made)

[10]No precise definition of outcome

[11]Method of determination of outcome not valid or reliable or unclear (for example; retrospective or administrative data set)

[12]Length of follow up/observation inappropriate/unclear

[13]Univariate analysis

1.1.1.12 Health related quality of life

Quality assessment							No of patients	Effect Health related quality of life (results)	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	consideration	Intervention			
Health related quality of life										
Rerkasem 2008	Observational prospective	No serious imprecision	no serious inconsistency	no serious inconsistency	very serious[2,4,5,6,9]	none	n= 183 patients with diabetic foot ulcer. Establishment of a multidisciplinary team and flow sheets based on foot protection algorithms 73 received diabetic foot protection 110 received preventive measures taken at the discretion of the physician and there were no detailed guidelines or flow sheets for specific services	In the second study 56 participants who received diabetic foot protection and 40 patients who received standard care respectively were recruited to provide information about quality of life using the short-form 36 questionnaire. Total SF-26 score Under diabetic foot protection period= 54.7 ± 21.6 Control period= 46.0 ± 16.5 P=0.03 i.e. significant	VERY LOW	IMPORTANT
Weck 2013	Observational prospective	No serious imprecision	no serious inconsistency	no serious inconsistency	very serious[2,3,4,5,6,7,9,11]	none	684 patients hospitalized because of diabetic foot ulceration 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 therapeutic algorithms. 684 diabetic patients with diabetic foot ulceration 508 controls	Health related quality of life Age adjusted mortality during initial hospitalisation (no follow up available for control group) Group treated by structured health care programme= 17 (2.5%) Control group= 48 (9.4%) P=<0.001 i.e. significant difference	VERY LOW	IMPORTANT

[1]Unclear if the reason for allocation was or was not related to any other confounding factors. It is unclear if groups were comparable at baseline including all major confounding factors as such data was not provided per group. Unclear if the comparison groups received the same care. Participants were not blinded to intervention allocation. Individuals administering care were not blinded to intervention allocation. Unclear if groups were comparable for compliance or intervention completion. Unclear if groups were comparable for availability of outcome data. A valid and reliable method may not have been used

[2] Non Randomised

[3]Unclear if groups were comparable at baseline for all prognostic factors, no attempt to balance groups for confounding factors. Or groups not comparable for all confounding factors.

[4]Unclear if comparison group received the same care apart from intervention studied

[5]Non Blinded

[6]Only crude incidence rates recorded, no analysis to adjust for confounding factors

[7]Unclear if groups were comparable for adherence, clinic attendance or treatment completion
[8]Unclear if groups were comparable for outcome data available or loss to follow up
[9]Groups were not comparable for length of observation or unclear if patients were followed up for a similar amount of time (or adjustments not made)
[10]No precise definition of outcome
[11]Method of determination of outcome not valid or reliable or unclear (for example; retrospective or administrative data set)
[12]Length of follow up/observation inappropriate/unclear

I.15 Review question 15 full GRADE profiles

Quality assessment							Outcomes of interest	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	n			
Magnetic resonance imaging vs X-ray cross checked by MRI or X-ray alone in the diagnosis of stage 0 Charcot foot (Chantelau 2013)									
1	observational studies	very serious[1,2,3,4,5,6,7,8]	no serious inconsistency	no serious indirectness	no serious imprecision	71 cases	Median time from symptom onset to treatment Received MRI investigation first= 1 month Received X-ray investigation cross-checked by MRI= 2.5 months Only X-ray investigation received= 4.5 months Detection of Stage 0 Charcot foot Received MRI investigation first= 19 of 19 cases detected Received X-ray investigation cross-checked by MRI= 8 of 8 cases detected Only X-ray investigation received= 0 of 8 cases detected Calculated accuracy measures for MRI: Sensitivity= 1.000 (0.974-1.000), Specificity= NA, Likelihood ratio+= 1.950 (1.772-2.146), Likelihood ratio-=0.050 (0.007-0.339), Positive predictive value= 1.000 (0.974-1.000), Negative predictive value= NA X-ray and MRI: Sensitivity= 1.000 (0.938-1.000), Specificity= NA, Likelihood ratio+= 1.889 (1.536-2.322), Likelihood ratio-=0.111 (0.017-0.713), Positive predictive value= 1.000 (0.938-1.000), Negative predictive value= NA X-ray investigation alone: Sensitivity= 0.000 (0.000-0.063), Specificity= NA, Likelihood ratio+= 0.111 (0.017-0.713) Likelihood ratio-=1.889 (1.536-2.322), Positive predictive value= NA, Negative predictive value= 0.000 (0.000-0.063) Median time from symptom onset to treatment (for stage 0 Charcot) Received MRI investigation first= 1 month Received X-ray investigation cross-checked by MRI= 0.5 months Only X-ray investigation received= 5 months Feet with skeletal deformities at institution of total contact casting (for stage 0 Charcot) Received MRI investigation first= 4 of 19 Received X-ray investigation cross-checked by MRI= 0 of 8 Only X-ray investigation received= 12 of 13	Very Low Quality	IMPORTANT
Magnetic resonance imaging vs X-ray in the assessment of Charcot foot (Chantelau 2006)									

1	observational studies	very serious[1,3,9,10,11,12,13]	no serious inconsistency	no serious indirectness	no serious imprecision[14]	20 participants	Detection of Stage 0 Charcot foot MRI investigation = 7 of 7 cases detected X-ray investigation= 0 of 7 cases detected Calculated accuracy measures for MRI: Sensitivity= 1.000 (0.929-1.000), Specificity= NA, Likelihood ratio+= 1.875 (1.488-2.362), Likelihood ratio-=0.125 (0.020-0.793), Positive predictive value= 1.000 (0.929-1.000), Negative predictive value= NA Calculated accuracy measures for X-ray: 0.000 (0.000-0.071), Specificity= NA, Likelihood ratio+= 0.125 (0.020-0.793) Likelihood ratio-=1.875 (1.488-2.362), Positive predictive value= NA, Negative predictive value= 0.000 (0.000-0.071) Detection of Stage I and II Charcot foot MRI investigation = 14 of 14 cases detected X-ray investigation= 14 of 14 cases detected Calculated accuracy measures for MRI or X-ray: Sensitivity= 1.000 (0.964-1.000), Specificity= NA, Likelihood ratio+= 1.933 (1.704-2.194), Likelihood ratio-=0.067 (0.010-0.445), Positive predictive value= 1.000 (0.964-1.000), Negative predictive value= NA	Very Low Quality	IMPORTANT
Early vs delayed diagnosis and treatment of Charcot foot (Chantelau 2005)									

1	observational studies	very serious[3,6,9,10,12,13]	no serious inconsistency	no serious indirectness	no serious imprecision[15]	24 participants	Number misdiagnosed prior to treatment Overt Charcot foot group= 13 of 13 participants Incipient Charcot foot= 6 of 11 participants Significant (P=0.013) Median time from onset of symptoms until application of total contact casting (range) Overt Charcot foot group= 3 (1-12) months Incipient Charcot foot= 1 (0.5-5) months Non-significant (P>0.05) Time from total contact casting to healing Overt Charcot foot group= 5.5 (2-12) months Incipient Charcot foot group= 3 (2-9) months Non-significant (P=>0.05) Progression to definite fractures of tarsometatarsal joints or talonavicular joint Overt Charcot foot group= 13 of 13 participants Incipient Charcot foot= 1 of 11 participants Significant (P=<0.001) Progression to gross foot deformity Plano-valgus-abductus foot, rocker bottom foot, extremely flat foot Overt Charcot foot group= 12 of 13 participants Incipient Charcot foot group=1 of 11 participants Significant (P=<0.001)	Very Low Quality	IMPORTANT
FDG PET vs MRI for the diagnosis of Charcot foot (Basu 2007)									
1	observational studies	very serious[1,9,12,13,16,17]	no serious inconsistency	no serious indirectness	no serious imprecision	22 participants	In those with either Osteomyelitis or Charcot foot FDG PET- 1.000 (0.969-1.000) sensitivity for Charcot foot 1.000 (0.917-1.000) specificity for Charcot foot MRI 0.688 (0.429-0.946) sensitivity for Charcot foot 1.000 (0.917-1.000) specificity for Charcot foot Accuracy measures were calculated from data provided in the study. FDG PET= 16 of 16 participants diagnosed with Charcot foot 6 of 6 participants diagnosed with osteomyelitis MRI= 11 of 16 participants diagnosed with Charcot foot 6 of 6 participants diagnosed with osteomyelitis	Very Low Quality	IMPORTANT
Foot skin temperature in the assessment of Charcot foot (Moura-Neto 2012)									

1	observation al studies	very serious[18]	no serious inconsistency	no serious indirectness	no serious imprecision	28 participants	Following use of temperature difference to diagnose remission and withdraw immobilisation Relapse after 1 year follow up= 0 of 25 participants	Very Low Quality	IMPORTANT
ring PET or hybrid PET vs MRI in the preoperative assessment of Charcot foot (Hopfner 2004)									
1	observational studies	very serious[1,9,10,12,19]	no serious inconsistency	no serious indirectness	no serious imprecision	16 participants	Diagnosis of lesions associated with Charcot neuroarthropathy Ring PET- 0.949 (0.867-1.000) sensitivity for Charcot lesion Hybrid PET- 0.769 (0.624-0.914) sensitivity for Charcot lesion MRI- 0.939 (0.843-1.000) sensitivity for Charcot lesion Accuracy measures calculated from data provided within the study Ring PET- 37 of 39 lesions detected Hybrid PET- 30 of 39 lesions detected MRI- 31 of 33 lesions detected (excluding those with extensive metal artifacts)	Very Low Quality	IMPORTANT
Magnetic resonance imaging vs X-ray in the diagnosis of acute Charcot foot (Beltran 1990)									
1	observational studies	very serious[1,3,9,10,12,13,19]	no serious inconsistency	no serious indirectness	no serious imprecision	14 participants	In a case series of participants with suspected foot infection and/or Charcot Plain radiograph Sensitivity- 0.400 (0.000-0.929) MRI Sensitivity- 1.000 (0.900-1.000) Accuracy measures calculated from data provided in the study Plain radiograph- 2 of 5 cases of Charcot foot detected MRI- 5 of 5 cases of Charcot foot detected	Very Low Quality	IMPORTANT

[1] Case series
[2] Unclear if groups comparable at baseline

[3] data taken retrospecitively
[4] no attempt to balance groups for confounders
[5] Unclear if groups received the same care
[6] no blinding
[7] Unclear if groups were comparable for availability of outcome data
[8] Unclear if groups were comparable for intervention completion
[9] Unrandomised
[10] Unclear if many participants were inappropriately excluded
[11] Unclear if investigators were unaware of findings of the comparator
[12] No threshold was pre-specified
[13] The results of the reference standard were not interpreted without knowledge of the index test
[14] Population did not include those with infected foot
[15] Only participants who had had undetectably fractures on X-ray after the onset of symptoms. Results therefore cannot give a true effect of the sensitivity of X-ray for early stage acute Charcot foot.
[16] Results not provided for many participants in other groups
[17] not all participants received the same reference standard

[18] Foot skin temperature was used both as an indicator of remission and as an measure of relapse, there is questionable theory behind using an experimental measure to record outcome
[19] unclear inclusion criteria

I.16 Review question 16 full GRADE profiles

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	considerations	Intervention	Comparator	Outcomes	Absolute effects		
Zoledronic acid vs placebo for the clinical resolution of Charcot Neuroarthropathy (Pakarinen 2011)												
Median time for total immobilisation												
1	randomised trials	very serious[1,2,3,4,5]	no serious	no serious	serious[6]	none	18	17	Treatment group= 27 weeks (range 10-62) Placebo group= 20 weeks (range 20-52)		VERY LOW	IMPORTANT
Relapse of Charcot												
1	randomised trials	very serious[1,2,3,]	no serious	no serious	serious[6]	none	1/18 (5.55%)	1/17 (5.88%)	Risk Ratio 0.94 (0.06-13.93)	4 fewer per 1000 (from 55 fewer to 761 more)	VERY LOW	IMPORTANT
Zoledronic acid vs once weekly Alendronate in the management of acute Charcot neuroarthropathy (Bahrath 2013)												
Mean time for complete clinical resolution of symptoms												
1	randomised trials	very serious[1,2,3,]	no serious	no serious	serious[6]	none	16	14	Zoledronic acid group= 126 ± 44.8 days (range 87-221) Alendronate group= 117 ± 29.1 days (range 70-182) Mean Difference 9.00 (-17.73- 35.73)	9 more days (17.73 fewer to 35.73 more)	VERY LOW	IMPORTANT
Combined magnetic field bone growth stimulation as an adjunct in the treatment of Charcot joint (Hanft 1998)												
Mean time to consolidation												
1	randomised trials	very serious[1,2,3,5,8]	no serious	no serious	serious[6]	none[9]	21	10	Treatment group= 11.1 ± 3.2 weeks Control group= 23.2 ± 7.7weeks Mean difference -12.10 (-17.06- 7.14)	12.10 fewer weeks (17.06 fewer to 7.14 more)	VERY LOW	IMPORTANT

Palliative radiotherapy as an adjunct to treatment of Charcot foot (Chantelau 1997)												
Median overall healing time (95% confidence interval)												
1	randomised trials	serious[1,2,10]	no serious	no serious	serious[6]	none[9]	6	6	Treatment group= 7 months (4-10) Placebo group= 9.7 months (4-15)		LOW	IMPORTANT
Uniplanar external fixator vs retrograde intramedullary nailing for ankle arthrodesis in Charcot neuroarthropathy (Shah 2011)												
Amputation rate												
1	observational studies	very serious[3,5,1]	no serious	no serious	serious[6,17]	none	1/6 (16.66%)	0/5 (0.00%)	Unadjusted risk ratio 2.57 (0.13-52.12)		VERY LOW	IMPORTANT
Number of participants achieving union within 30 weeks												
1	observational studies	very serious[3,5,1]	no serious	no serious	serious[6,17]	none	0/6 (0.00%)	5/5 (100.00%)	Unadjusted risk ratio 0.08 (0.01-1.14)	920 fewer per 1000 (from 990 fewer to 140 more)	VERY LOW	IMPORTANT
Number of participants achieving union within 40 weeks:												
1	observational studies	very serious[3,5,1]	no serious	no serious	serious[6,17]	none	1/6 (16.66%)	5/5 (100.00%)	Unadjusted risk ratio 0.23 (0.06-0.99)	770 fewer per 1000 (from 10 fewer to 940 fewer)	VERY LOW	IMPORTANT
Non-union within 40 weeks:												
1	observational studies	very serious[3,5,11,12,13,]	no serious	no serious	serious[6,17]	none	4/6 (66.66%)	0/5 (0.00%)	Unadjusted risk ratio 7.71 (0.51-116.01)		VERY LOW	IMPORTANT
Removable offloading vs non-removable offloading in the treatment of Charcot foot (Game 2012)												
Time to remission median (range)												
1	observational studies	very serious[3,4,5,6,7]	no serious	no serious	serious[6]	none	87	123	Initial offloading with non-removable device= 9 months (range 3-25) Never had non-removable cast = 12 months (range 3-36)		VERY LOW	IMPORTANT
Treatment with intravenous/oral bisphosphonates vs no bisphosphonates in the treatment of Charcot foot (Game 2012)												
Time to remission median (range)												

1	observational studies	very serious[3,4,5,6,7]	no serious	no serious	serious[6]	none	87	123	Treatment with intravenous/oral bisphosphonates= 12 months (range 3-39) No treatment with bisphosphonates = 10 months (range 2-29)		VERY LOW	IMPORTANT
	Cast and total non-weightbearing at initial presentation vs no cast and total non-weightbearing at initial presentation (Pakarinen 2002)											
Amputation (number requiring surgical treatment)												
1	observational studies	very serious[3,4,7,]	no serious	no serious	serious[17]	none	2/18 (11.11%)	8/18 (44.44%)	Unadjusted risk ratio 0.25 (0.06-1.02)	333 fewer per 1000 (from 418 fewer to 9 more)	VERY LOW	IMPORTANT
	Complete offloading within 2 months of symptoms vs weight-bearing treatment or short cast (Clohisy 1998)											
Number undergoing amputation (unclear definition)												
1	observational studies	very serious[3,4,7,8,]	no serious	no serious	serious[17]	none	0/7 (0.00%)	3/11 (27.27%)	Unadjusted risk ratio 0.21 (0.01-3.61)	215 fewer per 1000 (from 270 fewer to 712 more)	VERY LOW	IMPORTANT
Number who could not walk (unclear definition)												
1	observational studies	very serious[3,4,7,8,12,1]	no serious	no serious	serious[17]	none	0/7 (0.00%)	4/11 (36.36%)	Unadjusted risk ratio 0.17 (0.01-2.69)	302 fewer per 1000 (from 360 fewer to 615 more)	VERY LOW	IMPORTANT

[1] Unclear method of randomisation
[2] Unclear method of allocation concealment
[3] Unclear if/No blinding to treatment allocation for participants or those administering care
[4] Unclear if groups were comparable for availability of outcome data/loss to follow up
[5] Unclear if/No blinding of investigators to participant allocation or other confounding factors
[6] Number of participants less than 400 (continuous outcome)
[7] Unreliable method of determining outcome
[8] Unclear if groups were similar at baseline
[9] Unclear source of funding
[10] There were more participants who were "compliant" in the radiotherapy group than the sham radiotherapy group
[11] Unclear if method of allocation unrelated to potential confounding factors
[12] No attempts were made to balance groups for confounding factors
[13] Groups had differing exclusion criteria
[14] baseline characteristics were not reported
[15] data was gathered retrospectively
[16] no evidence of adjustment of analysis for certain dichotomous outcomes

[17] less than 300 events (dichotomous outcome)
[18] Both groups did not receive similar care apart from intervention studied
[19] Imprecise definition of outcome
[20] Non-randomised (cohort)
[21] Inappropriate length of follow up