NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology consultation supporting documentation

The enclosed documents were considered by the NICE medical technologies advisory committee (MTAC) alongside the assessment report and assessment report overview.

Documents included are:

1. Adoption scoping report – produced by the adoption team at NICE to provide a summary of levers and barriers to adoption of the technology within the NHS in England.

2. Sponsor submission of evidence – the evidence submitted to NICE by the notifying company.

3. Expert questionnaires – expert commentary gathered by the NICE team on the technology.

4. EAC correspondence log – a log of all correspondence between the external assessment centre (EAC) and the company and/or experts during the course of the development of the assessment report.

5. Company fact check comments – the manufacturer's response following a factual accuracy check of the assessment report.

Please use the bookmarks included in this PDF file to navigate to each of the above documents.

Medicines and Technologies Programme
Adoption Scoping Report MTG UrgoStart for chronic wounds

SUMMARY – for MTAC1 meeting

Adoption Levers

- Good evidence for the benefits of UrgoStart
- Having UrgoStart (or another dressing that inhibits protease activity) already on a local formulary
- Ease of use

Adoption Barriers

- Lack of continuity between healthcare professionals assessing and dressing a wound (in the absence of a structured care pathway)
- Clinician preferences
- Cost

1. Introduction

The Adoption team has collated information from healthcare professionals working within NHS organisations who have experience of using UrgoStart for the treatment of chronic wounds (such as leg ulcers, pressure ulcers or diabetic foot ulcers, as well as for non-healing acute wounds).

This adoption scoping report includes some of the benefits and difficulties that may be faced by organisations when planning to adopt the technology into routine NHS use.

2. Contributing organisations

The Adoption team engaged with the manufacturer and spoke to 4 NHS clinicians; 3 podiatrists and 1 tissue viability nurse.

3. Current context and use of UrgoStart in practice

There are a wide range of dressings for chronic wounds available. A NICE evidence summary (March 2016) on advanced wound dressings and antimicrobial dressings for chronic wounds found little good quality evidence from randomised controlled trials (RCTs) to support their use. NICE guidance and advice on care of chronic wounds does not make any recommendations about specific dressings to use. This makes evidence-based dressing selection difficult in practice.

There is agreement among the guidance and advice that dressing selection should be made after careful clinical assessment of the person's wound, their clinical condition, and their personal experience and preferences. If a specific dressing cannot be adequately justified on clinical grounds, it would seem appropriate for NHS healthcare professionals to routinely choose the least costly dressing of the type that meets the required characteristics appropriate for the type of wound and its stage of healing (for example, size, adhesion, conformability and fluid handling properties). The frequency of dressing change needs to be carefully considered and should be appropriate for the wound and dressing type.

Contributors reported using UrgoStart on a variety of leg and foot ulcers and wounds including diabetic foot ulcers (neuropathic and ischaemic), chronic non-healing foot and leg ulcers and traumatic wounds. All contributors used UrgoStart in a dedicated wound clinic setting.

The manufacturer reports that there are 6 ‘formats’ of UrgoStart: UrgoStart Contact Layer, UrgoStart Non-Adhesive, UrgoStart Plus Non-Adhesive, UrgoStart Plus Pad, UrgoStart Border and UrgoStart Plus Border. All contributors used the UrgoStart Contact and Border dressings.

4. Reported benefits

The benefits of adopting UrgoStart, as reported to the Adoption team by the healthcare professionals using the technology are reduced healing time leading to a reduction in;

- time spent re-dressing wounds
- patient visits for dressing changes

- risk of infection

5. Levers and barriers to adoption

The key considerations for adoption highlighted through discussions with contributors are:

Care pathway

Contributors reported that if there is no protocol or agreement in place for use of a selected dressing; different healthcare professionals reviewing and dressing a wound may choose a dressing according to their own preferences. This can result in a dressing being discontinued prematurely or not used consistently in which case clinicians will be unable to assess the efficacy of any particular dressing or its impact on wound healing. This is a barrier to sustained adoption and proper use of any dressing.

All contributors agreed that UrgoStart should be used as part of a structured care pathway. To provide continuity, one contributor has developed a leg ulcer care pathway which specifies when UrgoStart should be used. The new pathway is used in the leg ulcer clinic and by all district nurses. It ensures a consistent approach to treatment for all patients. The contributor reported a 44% improvement in leg ulcer healing times since implementing the pathway.

Based on the evidence for UrgoStart and their experiences with its benefits, all contributors said that they were using UrgoStart earlier in the care pathway than they had previously used other dressings which inhibit protease activity. Prior to the availability of dressings which inhibit protease activity one contributor reported that they had used simple foam with no additional benefits.

Patient Selection - wound assessment and preparation

All contributors agreed that UrgoStart should only be used after a thorough wound and patient assessment and interventions to control other modifiable factors have been implemented. This includes, for example, treating infection and reducing slough. For diabetic foot ulcers addressing glycaemic control, vascular assessment, pressure relief and debridement. For leg ulcers appropriate compression bandages or hosiery should be used.

The medtech innovation briefing on UrgoStart for chronic wounds states that the dressing is indicated for the treatment of both chronic and non-healing acute wounds. Contributors differed in their assessment of what constitutes a 'chronic' wound. One stated that they classed all diabetic foot ulcers as chronic on the day of presentation whilst another considered this to be non-healing after 4 weeks. Differing assessments on the appropriate point in the care pathway to treat a wound as 'chronic' may result in the most appropriate dressing not being applied at the correct time.

Contributors would not use UrgoStart on wounds with infection (or where they suspected infection), necrotic wounds and wounds with over 40% slough.

The specialist commentators for the MIB noted that an alternative protease inhibitor dressing, Promogran, is intended to be used only after the wound has been tested to identify raised protease activity. The UrgoStart manufacturer state this test is not needed for UrgoStart. None of the contributors used the Woundcheck Protease status test to guide their use of UrgoStart.

The NICE evidence summary and wound dressing section of the BNF provides further detail of the factors healthcare professionals would consider when assessing a wound and selecting a dressing.

Initiation and review

At all 4 sites wound care experts such as a podiatrist or tissue viability nurse choose UrogStart as part of the treatment plan and then re-dressed the wound weekly. At one site, where there is an agreed cross organisational leg ulcer care pathway, district nurses also start using UrgoStart in line with the care pathway. All

contributors work within multidisciplinary teams which include tissue viability and district nurses. Commonly district nurses will change dressings between the specialist clinic appointments, if required.

One contributor said they would formally review progress of UrgoStart after 4 weeks and if something had changed in the patient's clinical condition or healing was not as expected they may need to change the treatment plan. This is less than the 8 week treatment time recommended by the manufacturer and reflects comments from the MIB specialist commentators who queried whether UrgoStart would be used for 8 weeks. For context, in the National Diabetes Foot Care Audit 2014-2015, 50.8% of people still had a foot ulcer 12 weeks after the first foot ulcer assessment.

Usability and patient experience

Two podiatrists reported that UrgoStart border dressings used on the foot have to be cut to shape and can become loose.

The tissue viability nurse stated that if compression bandages for a pressure ulcer were being used they would select the contact dressing and where compression hosiery were being used they would select the border dressing.

One contributor said that the UrgoStart contact dressing was in the same form as many other types of contact dressing and so clinicians would be familiar with it. There were no usability issues or problems from a clinician or patient experience perspective reported by any of the contributors.

Clinician confidence / acceptance

Contributors agreed that clinician preference plays a major part in dressing choice and that clinician confidence in the technology could be a barrier to adoption. Three contributors commented on the strong evidence for UrgoStart and said this was unusual for dressings. They said these results would be a lever for adoption but acknowledged that some clinicians may still prefer other dressings.

One contributor highlighted that some services do not accurately record current service effectiveness and so may be unaware of any problems. This may influence clinicians' openness to adopting a new dressing.

Commissioning / Procurement / Resource Impact

For all of the contributors UrgoStart was on their formulary making it easy and accessible for them to use.

Where UrgoStart is not on a local formulary it may be a barrier to adoption. One contributor highlighted that if other more expensive protease inhibiting dressings are on the local formulary, the case for including UrgoStart would be easier to make.

Contributors reported the cost of UrgoStart compared to a standard dressing is a barrier for adoption, particularly if there are no clear pathways for its use which risks it being used inappropriately (for example it being stocked on inpatient wards and ward based nurses using it ad hoc). The case for adoption was strengthened by the clinical teams providing evidence of potential cost savings as part of a structured pathway for selected patients. This pathway should include agreement on review and for stopping it if there is no improvement.

In order to get UrgoStart onto their local formulary contributors worked with their local procurement teams following testing in practice and submission of information and patient case studies showing the impact of using UrgoStart.

Advice from the Wound Care Alliance UK on producing or reviewing a wound dressing's formulary can be found online.

Contributors order UrgoStart via a mixture of the formulary and their prescription system. One contributor described using a 'total purchase system'. This is an agreement between the CCG and shared business services. UrgoStart is on the formulary of this system and is ordered from the trust. The manufacturer said that the dressing can be purchased via NHS Supply Chain or via Community Wholesalers.

Training

Contributors reported that whilst no specific training on applying the dressing is required, training is required in suitable patient selection. The contributors said that the UrgoStart manufacturer provides on-site training to teams using the technology. The manufacturer has provided details of their training support which includes a clinical specialist team providing training to clinicians, regular contact with users and supporting educational literature.

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Medical Technologies Evaluation Programme

Sponsor submission of evidence
Evaluation title: UrgoStart for Chronic Wounds
Sponsor: Urgo Medical
Date sections A and B submitted: 09 April 2018
Date section C submitted: 08 May 2018

10 May 2018 v6.1

Contents

Instructions for sponsors

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the Medical Technologies Evaluation Programme process for developing NICE medical technologies guidance. Use of the submission template is mandatory.

The purpose of the submission is for the sponsor to collate, analyse and present all relevant evidence that supports the case for adoption of the technology into the NHS in England, within the scope defined by NICE. Failure to comply with the submission template and instructions could mean that the NICE cannot issue recommendations on use of the technology.

The submission should be completed after reading the 'Medical Technologies Evaluation Programme Methods guide' and the 'Medical Technologies Evaluation Programme Process guide' available at www.nice.org.uk/mt. After submission to, and acceptance by, NICE, the submission will be critically appraised by an External Assessment Centre appointed by NICE.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence'). When data are 'commercial in confidence' or 'academic in confidence', it is the sponsor's responsibility to highlight such data clearly. For further information on disclosure of information, submitting cost models and equality issues, users should see section 11 of this document 'Related procedures for evidence submission'.

The submission should be concise and informative. The main body of the submission should not exceed 100 pages (excluding the pages covered by the template and appendices). The submission should be sent to NICE electronically in Word or a compatible format, not as a PDF file.

The submission must be a stand-alone document. Additional appendices may only be used for supplementary explanatory information that exceeds the level

of detail requested, but that is considered to be relevant to the case for adoption. Appendices will not normally be presented to the Medical Technologies Advisory Committee when developing its recommendations. Any additional appendices should be clearly referenced in the body of the submission. Appendices should not be used for core information that has been requested in the specification. For example, it is not acceptable to attach a key study as an appendix and to complete the economic evidence section with 'see appendix X'.

All studies and data included in the submission must be referenced. Identify studies by the first author or trial ID, rather than by relying on numerical referencing alone (for example, 'Trial 123/Jones et al.[126], rather than 'one trial[126]').Please use a recognised referencing style, such as Harvard or Vancouver.

The sponsor should provide a PDF copy of full journal articles or reports – in electronic or hard copy form – included in the submission, if the sponsor is either the copyright owner or has adequate copyright clearance to permit the intended use by NICE. This clearance must be wide enough to allow NICE to make further copies, store the article electronically for a limited period of time on a shared drive to be accessed by a limited number of staff. Additionally, any full article obtained and submitted in electronic format must be done so in a manner compliant with the relevant contractual terms of use permitting the sponsor electronic access to the article. If the sponsor does not have sufficient copyright clearance, they are asked to submit references or links only, or details of contacts for unpublished research. NICE will then itself obtain full copies of all relevant papers or reports, paying a copyright fee where necessary. For unpublished studies for which a manuscript is not available, provide a structured abstract about future journal publication. If a structured abstract is not available, the sponsor must provide a statement from the authors to verify the data provided.

If a submission is based on preliminary regulatory recommendations, the sponsor must advise NICE immediately of any variation between the preliminary and final approval.

List of tables and figures

Section C – Economic evidence

Section C requires sponsors to present economic evidence for their technology.

All statements should be evidence-based and directly relevant to the decision problem.

The approach to the de novo cost analysis expected to be appropriate for most technologies is cost-consequence analysis. Sponsors should read section 7 of the Medical Technologies Evaluation Programme Methods guide on cost-consequences analysis, available from www.nice.org.uk/mt

Sponsors are requested to submit section C with the full submission. For details on timelines, see the NICE document 'Guide to the Medical Technologies Evaluation Programme process', available from www.nice.org.uk/mt

1 Existing economic evaluations

1.1 Identification of studies

1.1.1 Describe the strategies used to retrieve relevant health economics studies from the published literature and to identify all unpublished data. The search strategy used should be provided as in section 10, appendix 3.

A systematic literature review was undertaken. The PICOS methodology was used to derive search terms. The search was entered into the MMU library search as follows:

(UrgoStart or TLC-NOSF or KSOS) AND ((Resource AND (Use OR Utilisation)) OR Cost)

This tool searches multiple databases, including PubMed, Medline, Cochrane and Ovid.

1.1.2 Describe the inclusion and exclusion criteria used to select studies from the published and unpublished literature. Suggested headings

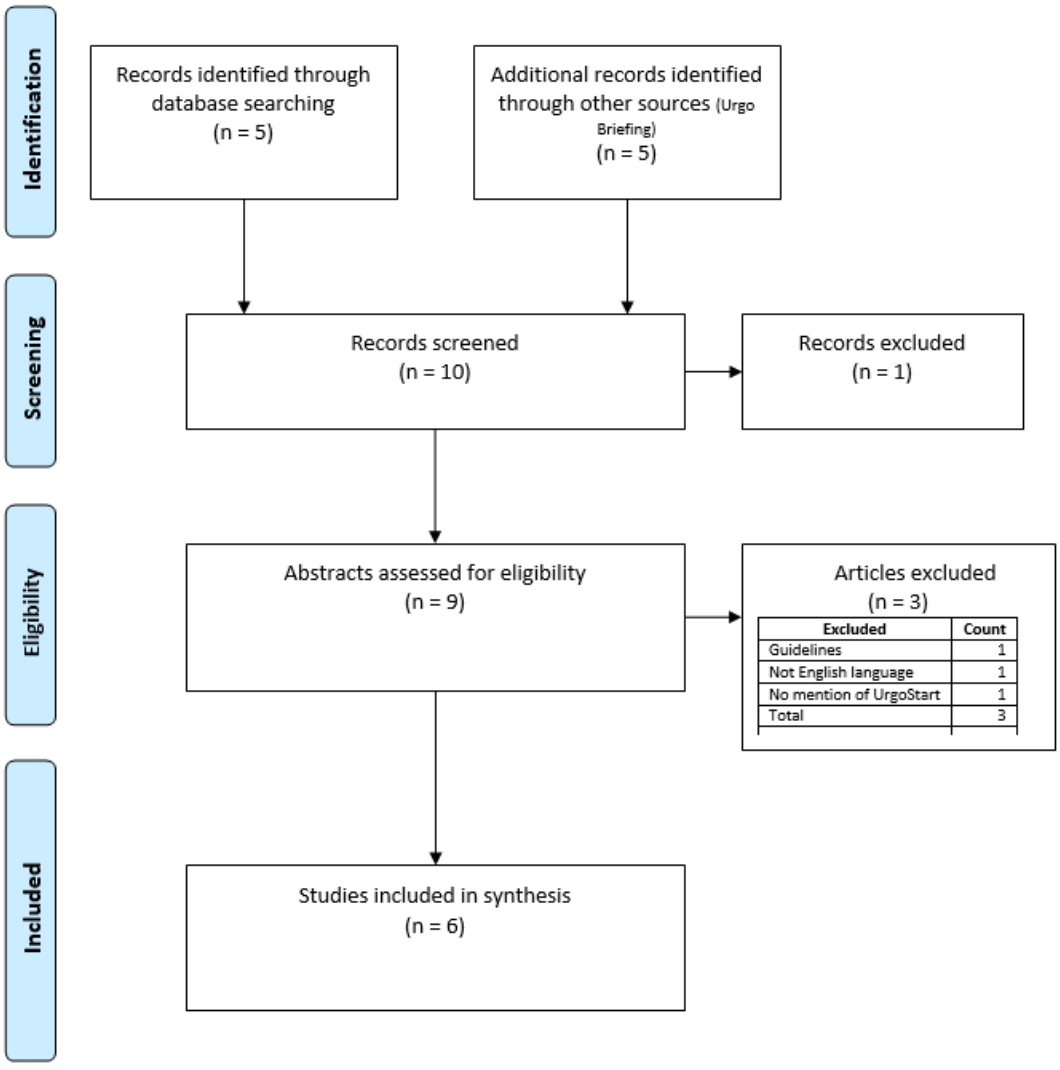
are listed in the table below. Other headings should be used if necessary.

Table 1 C1. Selection criteria used for health economic studies

Inclusion criteria	
Population	Leg Ulcer or Diabetic Foot Ulcer
Interventions	UrgoStart
Outcomes	Economic outcomes, resource use, cost, ICER, cost per patient
Study design	Modelling, economic studies
Language restrictions	English
Search dates	No restrictions
Exclusion criteria	
Population	Paediatrics (<18), Acute wounds (including Burns, Trauma, Surgery)
Interventions	Surgical Novel non-surgical (including electrical stimulation, hyperbaric treatment, vacuum therapy) Infection control measures (including silver, iodine or honey) Debridement (including, surgical, maggot) Bioengineered skin substitutes Offloading
Outcomes	No economic outcomes reported
Study design	In vitro studies, review or discussion articles
Language restrictions	Non-English Language
Search dates	N/A

1.1.3 Report the numbers of published studies included and excluded at each stage in an appropriate format.

Figure 1. PRISMA Diagram for included economic studies



1.2 Description of identified studies

1.2.1 Provide a brief review of each study, stating the methods, results and relevance to the scope. A suggested format is provided in table C2.

Table 2 C2.Summary list of all evaluations involving costs

Study name (year)	Location of study	Summary of model and comparators	Patient population	Costs	Patient outcomes	Results
Augustin et al, 2016	Germany	Decision tree design using Challenge study results; UrgoStart vs Neutral dressing	Leg ulcers	Direct medical costs included	Proportion of patients reaching a minimum of 40% wound size reduction at week 8. Rate was 65.6% for UrgoStart and 39.4% for neutral dressing	UrgoStart group had a saving of €485.64 over the 8-week period per responder. The cost per patient is greater than the comparator but the higher response rate results in a lower cost per responder.
Unpublished: Economic Assessment of UrgoStart for the Treatment of Chronic Leg Ulcers 2011	UK	One-year Markov model using Challenge study results. UrgoStart vs Neutral Foam Dressing.	Chronic Leg Ulcers	Direct medical costs included	Probability of wound closure at 20 weeks of 47.6% with UrgoStart and 29.8% with neutral dressing.	[redacted]
Unpublished: Maunoury et al. 2017. (Updated from Maunoury et al 2012)	France	Lifetime Markov Model using Challenge and Reality study results. UrgoStart vs Neutral dressing	Leg ulcers	Direct medical costs included	Wound area reduction of more than 40% was reported in 65.5% for patient receiving TLC-NOSF compared with 39.4% for neutral dressing at 8 weeks.	[redacted]
Unpublished: Maunoury et al. 2018	France	Lifetime Markov Model using Explorer study results. UrgoStart vs Neutral dressing	Diabetic foot ulcers	Direct medical costs included	Mean % reduction in wound surface area at 8 weeks. UrgoStart reaching 58% reduction and 32% with a neutral dressing.	[redacted]

Unpublished The impact of treating Diabetic Foot Ulcers with UrgoStart compared to a Neutral Dressing on the NHS budget over a 5 year time period. 2018	UK	Budget Impact Analysis using Explorer study results	Diabetic Foot Ulcers	Direct medical costs included	Time to wound closure 115 days for UrgoStart vs 135 days for neutral dressing	[redacted]
Unpublished The impact of treating Leg Ulcers with UrgoStart compared to a Neutral Dressing on the NHS budget over a 5 year time period. 2018	UK	Budget Impact Analysis using Reality study results	Leg ulcers	Direct medical costs included	Time to wound closure 112 days for UrgoStart vs 210 days for neutral dressing	[redacted]

1.2.2 Provide a complete quality assessment for each health economic study identified. A suggested format is shown in table C3.

Table 3. C3 Quality assessment of health economic studies

Study name Augustin et al 2016		
Study design	**Decision tree**	
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Yes	1. Can the additional use of NOSF technology in a hydro active foam dressing increase efficiency of leg ulcer treatment compared with a comparable foam dressing without NOSF technology? 2. In particular, how do UrgoStart and the neutral foam dressing compare regarding the cost-effectiveness under the conditions of the German health system?
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	Similar dressing without the NOSF technology
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	Challenge double blind randomised clinical trial
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	

10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	No	
13. Were the details of the subjects from whom valuations were obtained given?	Yes	
14. Were productivity changes (if included) reported separately?	N/A	Not included
15. Was the relevance of productivity changes to the study question discussed?	N/A	Not included
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	No	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	N/A	8 week model and no need for currency conversion
20. Were details of any model used given?	N/A	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	N/A	8 week model
24. Was the choice of rate justified?	N/A	8 week model
25. Was an explanation given if cost or benefits were not discounted?	N/A	8 week model

26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	N/A	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study name: Unpublished: Economic Assessment of UrgoStart for the Treatment of Chronic Leg Ulcers 2011		
Study design	**Markov model**	
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	NHS in England
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	Identical dressing without NOSF
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	Markov model
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	No	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	Total cost per patient; Total number of dressing changes; Total health benefits (e.g. quality-adjusted life years (QALYs)); Total nurse time (in hours) saved per patient.
12. Were the methods used to value health states and other benefits stated?	Yes	

13. Were the details of the subjects from whom valuations were obtained given?	Yes	
14. Were productivity changes (if included) reported separately?	N/A	Not included
15. Was the relevance of productivity changes to the study question discussed?	N/A	Not included
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	N/A	
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	
22. Was the time horizon of cost and benefits stated?	Yes	One year base case, but model was variable.
23. Was the discount rate stated?	Not clear	
24. Was the choice of rate justified?	No	
25. Was an explanation given if cost or benefits were not discounted?	No	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	N/A	
27. Was the approach to sensitivity analysis described?	Yes	One-way sensitivity analyses
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	

30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	No	
36. Were generalisability issues addressed?	No	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study name: Unpublished: Maunoury et al. 2017 (LU)		
Study design	**Markov model**	
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	To estimate the cost-effectiveness impact of treating French LU patients with TLC-NOSF
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	All-payers (collective) perspective
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	Identical dressing without NOSF
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	Lifetime Markov model
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	N/A	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Yes	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	Life-years without diabetic foot ulcer Secondary outcome: QALYs
12. Were the methods used to value health states and other benefits stated?	Yes	
13. Were the details of the subjects from whom valuations were obtained given?	Yes	

14. Were productivity changes (if included) reported separately?	N/A	Not included
15. Was the relevance of productivity changes to the study question discussed?	N/A	Not included
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	Yes	
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	
22. Was the time horizon of cost and benefits stated?	Yes	Lifetime horizon
23. Was the discount rate stated?	Yes	Discounted at 4% per year in the base case analysis to clinical and economic outcomes
24. Was the choice of rate justified?	Yes	
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	
27. Was the approach to sensitivity analysis described?	Yes	One-way sensitivity analyses and probabilistic sensitivity analysis
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	

30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study name: Unpublished: Maunoury et al. 2018 (DFU)		
Study design	**Markov model**	
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	To assess the cost-effectiveness of dressing with TLC-NOSF for treatment of patients with neuro-ischaemic diabetic foot ulcers
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	All-payers (collective) perspective
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	Identical dressing without NOSF
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	Lifetime Markov model
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	Life-years without diabetic foot ulcer Secondary outcome: QALYs
12. Were the methods used to value health states and other benefits stated?	Yes	

13. Were the details of the subjects from whom valuations were obtained given?	No	
14. Were productivity changes (if included) reported separately?	N/A	Not included
15. Was the relevance of productivity changes to the study question discussed?	N/A	Not included
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	Yes	Discounted at 4% per year in the base case analysis to clinical and economic outcomes
20. Were details of any model used given?	N/A	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	
22. Was the time horizon of cost and benefits stated?	Yes	
23. Was the discount rate stated?	Yes	
24. Was the choice of rate justified?	Yes	
25. Was an explanation given if cost or benefits were not discounted?	N/A	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	
27. Was the approach to sensitivity analysis described?	Yes	One-way sensitivity analyses and probabilistic sensitivity analysis
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	

30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study name: Unpublished. The impact of treating Diabetic Foot Ulcers with UrgoStart compared to a Neutral Dressing on the NHS budget over a 5 year time period. 2018		
Study design	**Markov model**	
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	N/A	No publication yet.
2. Was the economic importance of the research question stated?	N/A	No publication yet.
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	NHS perspective
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	Identical dressing without NOSF
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	Budget Impact Analysis
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	N/A	No publication yet.
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	N/A	No publication yet.
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	Based on 1 study
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	Cost per patient
12. Were the methods used to value health states and other benefits stated?	N/A	No health states

13. Were the details of the subjects from whom valuations were obtained given?	N/A	No publication yet.
14. Were productivity changes (if included) reported separately?	N/A	Not included
15. Was the relevance of productivity changes to the study question discussed?	N/A	Not included
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	No	N/A UK recent data
20. Were details of any model used given?	N/A	No publication yet.
21. Was there a justification for the choice of model used and the key parameters on which it was based?	N/A	No publication yet.
22. Was the time horizon of cost and benefits stated?	Yes	5 years
23. Was the discount rate stated?	N/A	Not used
24. Was the choice of rate justified?	N/A	Not used
25. Was an explanation given if cost or benefits were not discounted?	N/A	No publication yet.
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	N/A	No publication yet.
27. Was the approach to sensitivity analysis described?	N/A	No publication yet. Scenario analysis planned.
28. Was the choice of variables for sensitivity analysis justified?	N/A	No publication yet. Scenario analysis planned.
29. Were the ranges over which the parameters were varied stated?	N/A	No publication yet. Scenario analysis planned.

30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	N/A	No publication yet. Scenario analysis planned.
31. Was an incremental analysis reported?	N/A	No publication yet. Scenario analysis planned.
32. Were major outcomes presented in a disaggregated as well as aggregated form?	N/A	No publication yet.
33. Was the answer to the study question given?	N/A	No publication yet.
34. Did conclusions follow from the data reported?	N/A	No publication yet.
35. Were conclusions accompanied by the appropriate caveats?	N/A	No publication yet.
36. Were generalisability issues addressed?	N/A	No publication yet.
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Study name: Unpublished. The impact of treating Leg Ulcers with UrgoStart compared to a Neutral Dressing on the NHS budget over a 5 year time period. 2018		
Study design	**Markov model**	
Study question	**Response (yes/no/not clear/N/A)**	**Comments**
1. Was the research question stated?	N/A	No publication yet.
2. Was the economic importance of the research question stated?	N/A	No publication yet.
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	NHS perspective
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	Identical dressing without NOSF
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	Budget Impact Analysis
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	N/A	No publication yet.
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	N/A	No publication yet.
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	N/A	Based on 1 study
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	Cost per patient
12. Were the methods used to value health states and other benefits stated?	N/A	No health states

13. Were the details of the subjects from whom valuations were obtained given?	N/A	No publication yet.
14. Were productivity changes (if included) reported separately?	N/A	Not included
15. Was the relevance of productivity changes to the study question discussed?	N/A	Not included
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	No	N/A UK recent data
20. Were details of any model used given?	N/A	No publication yet.
21. Was there a justification for the choice of model used and the key parameters on which it was based?	N/A	No publication yet.
22. Was the time horizon of cost and benefits stated?	Yes	5 years
23. Was the discount rate stated?	N/A	Not used
24. Was the choice of rate justified?	N/A	Not used
25. Was an explanation given if cost or benefits were not discounted?	N/A	No publication yet.
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	N/A	No publication yet.
27. Was the approach to sensitivity analysis described?	N/A	No publication yet. Scenario analysis planned.
28. Was the choice of variables for sensitivity analysis justified?	N/A	No publication yet. Scenario analysis planned.
29. Were the ranges over which the parameters were varied stated?	N/A	No publication yet. Scenario analysis planned.

30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	N/A	No publication yet. Scenario analysis planned.
31. Was an incremental analysis reported?	N/A	No publication yet. Scenario analysis planned.
32. Were major outcomes presented in a disaggregated as well as aggregated form?	N/A	No publication yet.
33. Was the answer to the study question given?	N/A	No publication yet.
34. Did conclusions follow from the data reported?	N/A	No publication yet.
35. Were conclusions accompanied by the appropriate caveats?	N/A	No publication yet.
36. Were generalisability issues addressed?	N/A	No publication yet.
Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

2 De novo cost analysis

Section 9 requires the sponsor to provide information on the de novo cost analysis.

The de novo cost analysis developed should be relevant to the scope.

All costs resulting from or associated with the use of the technology should be estimated using processes relevant to the NHS and personal social services.

Note that NICE cites the price of the product used in the model in the Medical Technology guidance.

2.1 Description of the de novo cost analysis

2.1.1 Provide the rationale for undertaking further cost analysis in relation to the scope.

Current published cost analysis is only available for LU patients. New data for DFU full wound closure is available (Edmonds et al 2018), and utility scores for patients were also collected using EQ5D-5L in the Explorer study; a cost utility analysis is now achievable. For LU, new real world resource use data from the UK can be utilised in order to ensure up to date analysis that is relevant to the NHS.

The current standard care for DFU and LU have common components, including use of dressings, debridement and infection control, additionally LUs require compression and DFU management includes offloading. Regarding dressings, current guidance (NG19 DFU and SIGN 120 VLU) does not indicate a preferred dressing for patients with these wounds. Improved wound care management using UrgoStart is asserted to be cost saving due to increased efficacy and, in the case of DFU, fewer amputation events following complications such as infection or critical ischaemia. Additionally, patients could experience a quality of life benefit due to improved healing rates and reduced healing time.

Patients

2.1.2 What patient group(s) is (are) included in the cost analysis?

Patients with leg ulcers Patients with diabetic foot ulcers

Technology and comparator

2.1.3 Provide a justification if the comparator used in the cost analysis is different from the scope.

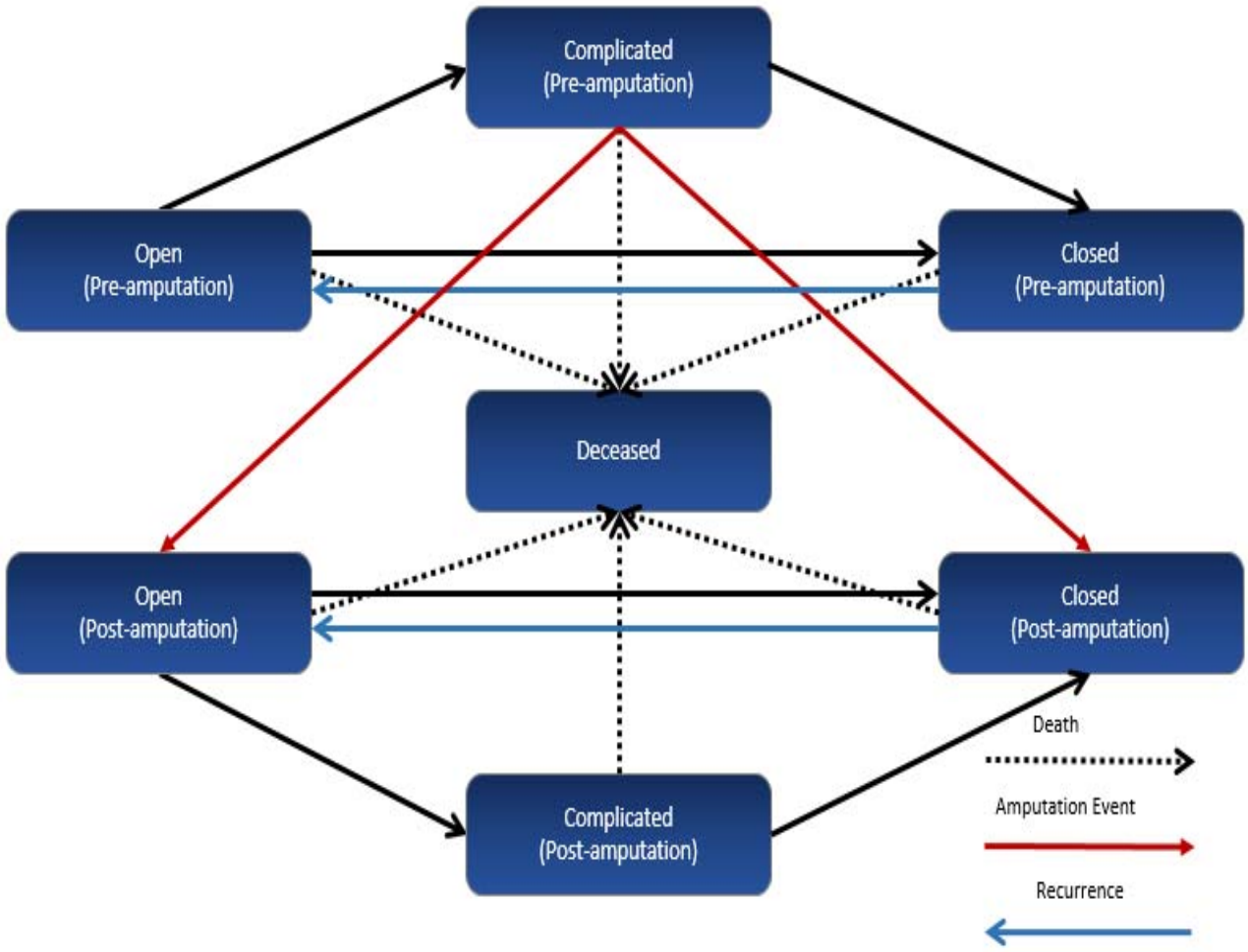
As per scope- other wound dressing, neutral dressing, and standard care for either LU or DFU.

Model structure

2.1.4 Provide a diagram of the model structure you have chosen.

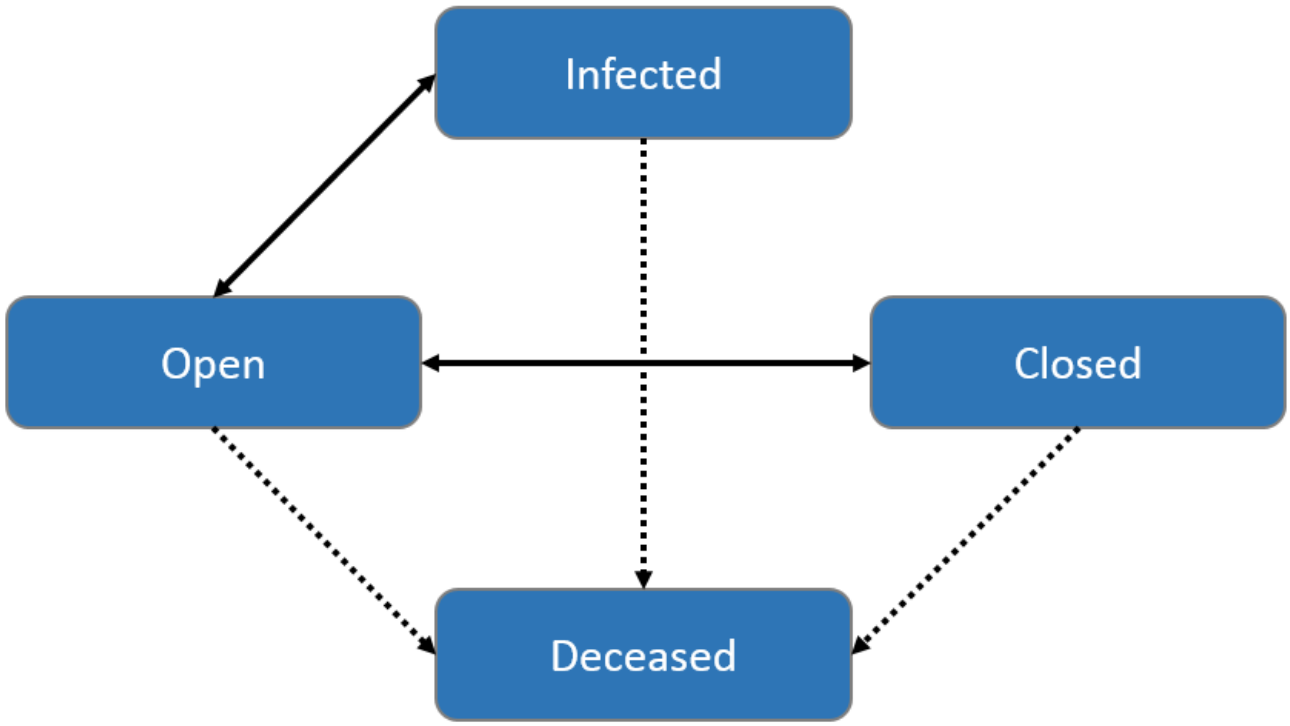
For the DFU model, the below structure:

Figure 2 DFU Model Structure



For the LU model, the below structure

Figure 3LU Model Structure



2.1.5 Justify the chosen structure in line with the clinical pathway of care identified in response to question 3.3.

DFU:

Diabetic foot ulcers have 3 core health states- open wound, closed wound and complicated wound. The model makes a distinction for wounds that have not been amputated (pre-amputation), versus patients who have an amputation (post amputation). Amputation is often a consequence of a persistent complicated and unhealed DFU. A patient starts with an open wound; and this wound can either close (heal), or become complicated and then the healing process will be delayed. Complicated wounds can also cause an amputation event, causing a patient to move to the post-amputation block. After amputation, patients have a closed wound (healing by primary intention, means closed at the operating room by the surgeon); or their wound persists as an open wound post amputation and will need to be healed in secondary intention and then could become complicated before healing. Closed health states have a risk of recurrence; this is higher post-amputation. In all health states, patients have a risk of death.

LU:

A leg ulcer can be open, infected or closed. Wounds that are infected incur higher costs to the healthcare system. A patient starts with an open wound; this wound can then become infected. The infection can be resolved and the wound is once again open. The wound can close and the patient is healed. Closed LUs can have a high chance of recurrence. In all health states, patients have a risk of death.

2.1.6 Provide a list of all assumptions in the cost model and a justification for each assumption.

Table 4Table of assumptions and justifications

Assumption	Justification
DFU: All patients who have an amputation were in the complicated health state	Validated by clinicians; wounds would not be amputated unless there was a persistent infection/critical ischaemia
DFU: An amputation can only occur once	Base case of 1 year; patient unlikely to be amputated twice within a year. This assumption also allowed for a simplification of the model structure.
Both: All patients begin with an open wound	Patients with a closed wound would not be treated.
DFU: All patients who have an amputation (minor or major) require physiotherapy	Validated by clinicians.
DFU: Prosthesis will only follow a major amputation	As per NICE costing report.
Both: The death health state does not incur any costs	Deceased patients require no treatment.
LU: Average infection lasts 2 to 4 weeks. 3 weeks used as base case infection duration.	Validated with clinicians.
DFU: A closed wound will have the same estimated resource use both pre and post amputation.	This is a conservative assumption, as no data available to support changing these health state costs.

2.1.7 Define what the model's health states are intended to capture.

The health states are intended to capture the varying costs and quality of life for patients with a DFU/LU. The core health states are open wound, closed wound and complicated/infected wound. A wound with clinical infection will require further treatment to resolve the wound, and, for a DFU, it is possible that this wound will then require an amputation. The DFU model used complicated as a health state, as this also includes other traits common to DFUs such as ischaemia. The LU model only uses infected, as this is the key complication for these wounds. The DFU model makes the distinction between patients who have not had an amputation, and those that have. Amputation is an event that incurs the cost of surgery, the cost of subsequent physiotherapy and a prosthesis, supplied to patients after a major amputation. Amputation is not such a risk factor for patients with LU, and as such, no distinction between pre and post amputation is made.

2.1.8 Describe any key features of the cost model not previously reported. A suggested format is presented below.

Table 5 C4 Key features of DFU and LU models not previously reported

Factor	Chosen values	Justification	Reference
Time horizon of model	1 year	1 year model to capture a wound episode, for DFU only once amputation. The model has the functionality for the user to choose to view either: 6 months, 1 year, 2 years, 5 years and 10 years to observe long-term health and cost consequences.	
Discount of 3.5% for costs	3.5% for both outcomes and costs		As per instruction from NICE
Perspective (NHS/PSS)	NHS perspective		As per NICE scope.
Cycle length	1 week		Informed by clinical practice
NHS, National Health Service; PSS, Personal Social Services			

2.2 Clinical parameters and variables

2.2.1 Describe how the data from the clinical evidence were used in the cost analysis.

Transition probabilities:

DFU: Transition probabilities were calculated using data from patients in the Explorer study. These patients also had a confirmed neuro-ischaemic diabetic foot ulcer, with no statistically significant differences to the treatment arm.

LU: Transition probabilities were calculated using data from patients in the Challenge study. These patients also had a leg ulcer with no statistically significant differences to the treatment arm.

Prior to calculating the transition probability, probability and hazard rates were estimated. This was calculated as below:

Rates= [-ln(1-P)]/t

P=probability, t=time

The weekly probability for each transition was then calculated as below:

7/365.25 Year Probability= 1-exp (-ru)

r=hazard rate, u=cycle length

The transition probabilities do not change over time; and are assumed to be representative of patients with wound of varying duration, as they included studies included wounds of varied duration (DFU: Mean 7.3 months with standard deviation of 6.5; LU: Mean 15.1 months with standard deviation of 8.7).

UrgoStart efficacy:

DFU: The Explorer study *(RCT 4 in Section B)* measured wound healing as the primary endpoint.

LU: The Challenge study *(RCT 1 in Section B)* did not measure wound healing as an endpoint of the study, and measured Relative Wound Area Reduction (RWAR) as a surrogate endpoint for healing rate. Using the formula below reported by Cardinal et al (2008); this has been transformed to provide a weekly healing rate.

Healing rate (%) = (LN(1 – Mean surface area reduction in %))/weeks)

Patient characteristics:

DFU: The Explorer study informed the patient characteristics with regards to age at inclusion, amputation history.

LU: The Challenge study informed the patient characteristics with regards to age at inclusion.

All-cause mortality:

DFU: All-cause mortality among diabetic foot patients was informed by data from the Third Annual Report of The National Diabetes Foot Care Audit. At 12 weeks, 520 patients were confirmed deceased from a cohort of 22,653. This data was transformed into weekly transition probabilities as per the above calculations.

LU: Patients with leg ulcers have not been shown to have a higher mortality rate when compared with control in a study by Nelzen et al (1997). In light of this; a weekly transition for age related mortality has been calculated for patients to move into the deceased health state.

Recurrence:
DFU: Dubsky et al (2012) carried out a prospective follow up of 73 patients with DFU, and during a 3 year period, 42 patients experienced a recurrent DFU.

LU: Clarke-Moloney et al (2012), provides recurrence data for 100 patients using compression stockings, as per the standard of care. At 12 months, 16.1% of patients had experienced a recurrent ulcer.

2.2.2 Are costs and clinical outcomes extrapolated beyond the study follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified?

The effectiveness of UrgoStart has been extrapolated beyond the study timeline. This is because patients with varying duration of wound were included into the Explorer and Challenge studies and as such UrgoStart can be assumed effective on wounds of varying duration.

2.2.3 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what

sources of evidence were used and what other evidence is there to support it?

DFU:

No surrogate endpoint- healing was the primary endpoint in the Explorer study and healing of either an open or complicated wound is included in the model.

LU:

The Challenge study *(RCT 1 in Section B)* did not measure wound healing as an endpoint of the study, and measured Relative Wound Area Reduction (RWAR) as a surrogate endpoint for healing. Using the formula below reported by Cardinal et al (2008); this has been transformed to provide a weekly healing rate.

Healing rate (%) = (LN(1 – Mean surface area reduction in %))/weeks)

2.2.4 Were adverse events such as those described in section 7.7 included in the cost analysis? If appropriate, provide a rationale for the calculation of the risk of each adverse event.

DFU: Infection and amputation were included in the cost analysis. The infection rate was calculated from the Explorer study and the amputation rate was drawn from the National Diabetes Foot Care Audit.

LU: Infection was included as an adverse event for these wounds. The rates of infection were calculated from the Challenge study. (UrgoStart = 7/93 Control= 6/94).

2.2.5 Provide details of the process used when the sponsor's clinical advisers assessed the applicability of available or estimated clinical model parameter and inputs used in the analysis.

We need to get clinicians to validate our clinical model parameters and inputs.

- (Internal) Martin Tadej- Clinical Specialist
- (Internal) Serge Bohbot- Medical Director
- Dave Russell – Consultant Vascular Surgeon
- Chris Manu – Consultant Diabetologist
- Experts were selected due to their knowledge of DFU and LU.
- 2 internal experts and 2 external experts were approached
- 2 internal experts and 2 external expert participated
- Martin Tadej and Serge Bohbot are employed by Urgo Medical.
- Explorer and Challenge were provided as background information.
- Use of questionnaire survey, self-administered.

2.2.6 Summarise all the variables included in the cost analysis. Provide cross-references to other parts of the submission. A suggested format is provided in table C5 below.

Table 6 C5a Summary of variables applied in the DFU cost model (Base

Case)

Variable	Value	Range or 95% CI	Source
Age	*65 years*		Explorer
Prior Amputation	*50%*		Explorer
Major Amputation	*24%*		*NICE Costing Document*
Minor Amputation	*76%*		*NICE Costing Document*
Proportion with prosthesis after major amputation	*86%*		*NICE Costing Document*
Neutral Dressing. Transition probability: open pre -> complicated pre	*0.018660468*		Explorer (comparator arm). Of 51 patients with open wound& no prior amputation 16 became infected over 20 weeks.
Neutral Dressing. Transition probability: open pre -> closed pre	*0.016694216*		Explorer (comparator arm). Of 35 patients with open wound& no prior amputation 10 healed by 20 weeks.
Neutral Dressing. Transition probability: open pre -> deceased	*0.001934667*		National Diabetes Foot Care Audit Third Annual Report, 2018. 520/22653 patients confirmed deceased at 12 weeks.
Neutral Dressing. Transition probability: complicated pre -> closed pre	*0.003223928*		Explorer (comparator arm). Of 16 patients with infected wound& no prior amputation 1 healed by 20 weeks.
Neutral Dressing. Transition probability: complicated pre -> open post	*0.003354487*		National Diabetes Foot Care Audit Third Annual Report, 2018. 1469/17514 patients amputations at 6 months
Neutral Dressing. Transition probability: complicated pre -> closed post	*0.003354487*		
Neutral Dressing. Transition probability: complicated pre -> deceased	*0.001934667*		National Diabetes Foot Care Audit Third Annual Report, 2018. 520/22653 patients confirmed deceased at 12 weeks.
Neutral Dressing. Transition probability: closed pre -> open pre	*0.005460204*		Dubsky et al, (2012), of 73 patients, 42 had a DFU recurrence within 3 years.
Neutral Dressing. Transition probability: closed pre -> deceased	*0.001934667*		National Diabetes Foot Care Audit Third Annual Report, 2018. 520/22653 patients confirmed deceased at 12 weeks.
Neutral Dressing. Transition probability: open post -> complicated post	*0.014552464*		Explorer (comparator arm). Of 63 patients with open wound with prior amputation, 16 became infected by 20 weeks.
Neutral Dressing. Transition probability: open post -> closed post	*0.025581983*		Explorer (comparator arm). Of 47 patients with open wound with prior amputation, 19 healed by 20 weeks.
Neutral Dressing. Transition probability: open post -> deceased	*0.001934667*		National Diabetes Foot Care Audit Third Annual Report, 2018. 520/22653 patients confirmed deceased at 12 weeks.
Neutral Dressing. Transition probability: complicated post -> closed post	*0.014290858*		Explorer (comparator arm). Of 16 patients with infected wound with prior amputation, 4 healed by 20 weeks.
Neutral Dressing. Transition probability: complicated post -> deceased	*0.001934667*		National Diabetes Foot Care Audit Third Annual Report, 2018. 520/22653 patients confirmed deceased at 12 weeks.
Neutral Dressing. Transition probability: closed post -> open post	*0.005460204*		Dubsky et al, 2012, of 73 patients, 42 had a DFU recurrence within 3 years.
Neutral Dressing. Transition probability: closed post -> deceased	*0.001934667*		National Diabetes Foot Care Audit Third Annual Report, 2018. 520/22653 patients confirmed deceased at 12 weeks.
UrgoStart. Transition probability: open pre -> complicated pre	*0.013513855*		Explorer (treatment arm). Of 42 patients with open wound& no prior amputation 10 became infected over 20 weeks.
UrgoStart. Transition probability: open pre -> closed pre	*0.037200636*		Explorer (treatment arm). Of 32 patients with open wound& no prior amputation 17 healed by 20 weeks.
UrgoStart. Transition probability: open pre -> deceased	*0.001934667*		National Diabetes Foot Care Audit Third Annual Report, 2018. 520/22653 patients confirmed deceased at 12 weeks.

UrgoStart. UrgoStart. Transition probability: complicated pre -> closed pre	*0.011102724*		Explorer (treatment arm). Of 10 patients with infected wound& no prior amputation 2 healed by 20 weeks.
UrgoStart. Transition probability: complicated pre -> open post	*0.003354487*		National Diabetes Foot Care Audit Third Annual Report, 2018. 1469/17514 patients amputations at 6 months
UrgoStart. Transition probability: complicated pre -> closed post	*0.003354487*		
UrgoStart. Transition probability: complicated pre -> deceased	*0.001934667*		National Diabetes Foot Care Audit Third Annual Report, 2018. 520/22653 patients confirmed deceased at 12 weeks.
UrgoStart. Transition probability: closed pre -> open pre	*0.005460204*		Dubsky et al, (2012), of 73 patients, 42 had a DFU recurrence within 3 years.
UrgoStart. Transition probability: closed pre -> deceased	*0.001934667*		National Diabetes Foot Care Audit Third Annual Report, 2018. 520/22653 patients confirmed deceased at 12 weeks.
UrgoStart. Transition probability: open post -> complicated post	*0.009793975*		Explorer (treatment arm). Of 84 patients with open wound with prior amputation, 15 became infected by 20 weeks.
UrgoStart. Transition probability: open post -> closed post	*0.037715221*		Explorer (treatment arm). Of 69 patients with open wound with prior amputation, 37 healed by 20 weeks.
UrgoStart. Transition probability: open post -> deceased	*0.001934667*		National Diabetes Foot Care Audit Third Annual Report, 2018. 520/22653 patients confirmed deceased at 12 weeks.
UrgoStart. Transition probability: complicated post -> closed post	*0.015398578*		Explorer (treatment arm). Of 15 patients with infected wound with prior amputation, 4 healed by 20 weeks.
UrgoStart. Transition probability: complicated post -> deceased	*0.001934667*		National Diabetes Foot Care Audit Third Annual Report, 2018. 520/22653 patients confirmed deceased at 12 weeks.
UrgoStart. Transition probability: closed post -> open post	*0.005460204*		Dubsky et al, 2012, of 73 patients, 42 had a DFU recurrence within 3 years.
UrgoStart. Transition probability: closed post -> deceased	*0.001934667*		National Diabetes Foot Care Audit Third Annual Report, 2018. 520/22653 patients confirmed deceased at 12 weeks.
Health State utility scores	*0.619 (Open pre)* *0.570 (Complicated pre)* *0.738 (Closed pre)* *0.596 (Open post* *0.583 (Complicated post)* *0.715 (Closed post)*		Explorer
Disutility	*-0.28 (Disutility associated with amputation event)*	*95% CI (–0.389 to –0.170)*	Clarke, et al 2002
Duration of amputation event disutility	*4 weeks*		Clinical experts
CI, confidence interval			

Table 7 C5b Summary of variables applied in the LU cost model (Base

Case)

Variable	Value	Range or 95% CI (distribution)	Source
Age	*72.6 years*	*SD: 13*	Challenge
Duration of infection	*3 weeks*	2-4 weeks	Expert opinion.
Neutral Dressing: Transition probability: open -> infected	*0.0081884*		Of 94 patients, 6 became infected over 8 weeks.
Neutral Dressing: Transition probability: open -> closed	*0.0474747*		Using method described in Cardinal et al, the 32% RWAR gave a weekly healing rate of 4.75%
Neutral Dressing: Transition probability: infected -> open	*0.3333333*		1/duration of infection from expert opinion.
Neutral Dressing: Transition probability: closed -> open	*0.0033382*		Clarke-Moloney et al, 2012, of 100 patients 16 had a recurrence over 1 year.
UrgoStart: Transition probability: open -> infected	*0.0097073*		Of 93 patients, 7 became infected over 8 weeks
UrgoStart: Transition probability: open -> closed	*0.1093336*		Using method described in Cardinal et al, the 58% RWAR gave a weekly healing rate of 10.93%
UrgoStart: Transition probability: infected -> open	*0.3333333*		1/duration of infection from expert opinion.
UrgoStart: Transition probability: closed -> open	*0.0033382*		Clarke-Moloney et al, 2012, of 100 patients 16 had a recurrence over 1 year.
Health State utility scores	*0.52 (Open)* *0.52 (Infected)* *0.67 (Closed)*		Palfreyman, S., 2008. Assessing the impact of venous ulceration on quality of life. Nursing times, 104(41), pp.34-37.
CI, confidence interval			

2.3 Resource identification, measurement and valuation

NHS costs

2.3.1 Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff.

DFU:

Amputation codes: chosen because they refer to an amputation undertaken with diabetes as a cause.

YQ23A	Multiple, Amputation Stump or Partial Foot Amputation Procedures, for Diabetes or Arterial Disease, with CC Score 8+
YQ23B	Multiple, Amputation Stump or Partial Foot Amputation Procedures, for Diabetes or Arterial Disease, with CC Score 0-7
YQ24A	Single, Amputation Stump or Partial Foot Amputation Procedure, for Diabetes or Arterial Disease, with Other Open Blood Vessel Procedure, with CC Score 8+
YQ24B	Single, Amputation Stump or Partial Foot Amputation Procedure, for Diabetes or Arterial Disease, with Other Open Blood Vessel Procedure, with CC Score 0-7
YQ25A	Single, Amputation Stump or Partial Foot Amputation Procedure, for Diabetes or Arterial Disease, with Imaging Intervention, with CC Score 8+
YQ25B	Single, Amputation Stump or Partial Foot Amputation Procedure, for Diabetes or Arterial Disease, with Imaging Intervention, with CC Score 0-7
YQ26A	Single, Amputation Stump or Partial Foot Amputation Procedure, for Diabetes or Arterial Disease, with CC Score 8+
YQ26B	Single, Amputation Stump or Partial Foot Amputation Procedure, for Diabetes or Arterial Disease, with CC Score 5-7
YQ26C	Single, Amputation Stump or Partial Foot Amputation Procedure, for Diabetes or Arterial Disease, with CC Score 0-4

Hospital admission codes: chosen because they refer to diabetic lower limb complications

KB03C	Diabetes with Lower Limb Complications, with CC Score 9+
KB03D	Diabetes with Lower Limb Complications, with CC Score 5-8
KB03E	Diabetes with Lower Limb Complications, with CC Score 0-4

LU: Hospital admission codes: chosen non-elective short-stay skin disorder codes.

JD07A	Skin Disorders with Interventions, with CC Score 12+
JD07B	Skin Disorders with Interventions, with CC Score 8-11
JD07C	Skin Disorders with Interventions, with CC Score 4-7
JD07D	Skin Disorders with Interventions, with CC Score 0-3
JD07E	Skin Disorders without Interventions, with CC Score 19+
JD07F	Skin Disorders without Interventions, with CC Score 14-18
JD07G	Skin Disorders without Interventions, with CC Score 10-13
JD07H	Skin Disorders without Interventions, with CC Score 6-9
JD07J	Skin Disorders without Interventions, with CC Score 2-5
JD07K	Skin Disorders without Interventions, with CC Score 0-1

2.3.2 State the Office of Population, Censuses and Surveys Classification of Surgical Operations and Procedures (OPCS) codes for the operations, procedures and interventions relevant to the use of the technology for the clinical management of the condition.

None known.

Resource identification, measurement and valuation studies

2.3.3 Provide a systematic search of relevant resource data for the NHS in England. Include a search strategy and inclusion criteria, and consider published and unpublished studies.

The search was entered into the MMU library search as follows:

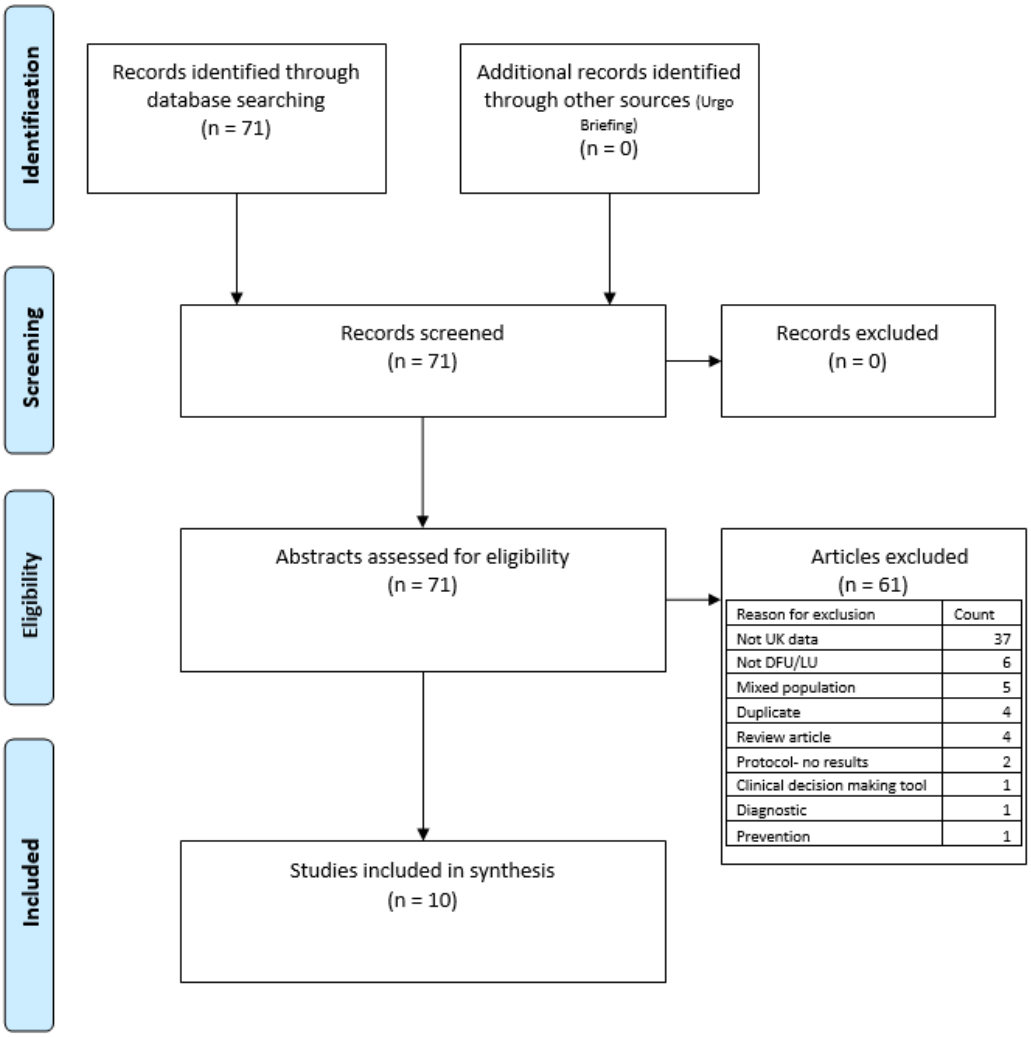
((TitleCombined:(COST)) OR (TitleCombined:(Economic*)) OR (TitleCombined:(resource))) AND ((Abstract:("diabetic foot ulcer")) OR ("venous leg ulcer"))

This tool searches multiple databases, including PubMed, Medline, Cochrane and Ovid.

71 results were returned, and the inclusion criteria were applied as follows:

Inclusion	
Population	DFU or LU only
Intervention	Management
Comparator	N/A
Outcomes	Resource use
Study	UK perspective
Date	2015 onwards
Exclusion	
Population	Acute wounds, or a mixed chronic wound population
Intervention	Prevention, diagnostic, decision making tools
Comparator	N/A
Outcomes	Not including resource use
Study	Not UK
Date	Before 1st Jan 2015.

Figure 4PRISMA Diagram for resource use studies



Reason for exclusion	Count
Not UK data	37
Not DFU/LU	6
Mixed population	5
Duplicate	4
Review article	4
Protocol- no results	2
Clinical decision making tool	1
Diagnostic	1
Prevention	1

Of the 10 included studies (7 LU and 3 DFU) 5 LU studies and 2 DFU studies contained data for resource use. Resource use was extracted and transformed to a weekly rate. Only 1 study for each DFU and LU included multiple health states.

For DFU, Guest et al (2018) *Diabetic foot ulcer management in clinical practice in the UK: costs and outcomes* was selected as this used real world data to estimate health resource use for healed, unhealed and amputated wounds and the fact that this data is the most up to date. No standard deviation of the mean values provided, +/- 30% used in sensitivity analysis.

A second source of data, NICE costing report for DFU provided information about NHS costs and assumptions.

For LU, Guest et al (2018) *Venous leg ulcer management in clinical practice in the UK: Costs and outcomes* was used. This is due to the provision of health state estimates, and the fact that this data is the most up to date. Standard deviation of the mean values provided, this was used in sensitivity analysis.

Neither of the included papers included absolute values for health resource use for infected/complicated wounds; these were aggregated with the unhealed health states for both DFU and LU. The values given were varied around the mean to determine the values for open and complicated/infected wounds, as per the Guest papers, open DFUs cost 67% less than infected DFUs and open LUs cost 69% less than infected LUs.

The tables below shows the resource use for the DFU and LU health states per week. These figures have been derived by transforming the reported annual values into weekly values (*7/365.25). For DFU these figures were adjusted for the reported difference in open and complicated/infected health states multiplying by 0.5, and 1.5 respectively, to allow the open wounds to cost 67% less. For LU the adjustment for open and infected health states was to multiply by 0.475 and 1.525 respectively, to allow the open wounds to cost 69% less.

The use of secondary dressings was informed by an Urgo Medical chart extraction study, showing that in open DFUs and infected DFUs 22% and 9% less secondary dressings were used than primary and in open LUs and infected LUs 57% and 30% less secondary dressings were used than primary

The figures have been rounded to 4 decimal places in the below tables.

DFU weekly resource use (item units)	**Open pre**	**Complicated pre**	**Closed pre**	**Open post**	**Complicated post**	**Closed post**
Hospital admission	0.0002	0.0006	0.00	0.0144	0.0433	0.00

GP	0.0239	0.0718	0.0294	0.0158	0.0473	0.0294
Hospital outpatient	0.0192	0.0577	0.0196	0.0433	0.1298	0.0196
Podiatrist	0.0032	0.0095	0.0040	0.0017	0.0052	0.0040
Practice Nurse	0.0998	0.2994	0.0937	0.0826	0.2478	0.0937
Community Nurse	0.8103	2.4309	0.3789	0.5869	1.7608	0.3788
Antibiotic prescriptions	0.0795	0.2386	0.0627	0.1204	0.3612	0.0627
Analgesia prescriptions	0.3268	0.9805	0.2410	0.1324	0.3972	0.2410
Primary dressings	2.0800	6.2400	1.0392	1.5084	4.5251	1.0392
Secondary dressings	1.6224	5.6784	0.8106	1.1765	4.1178	0.8106
Bespoke orthosis	Assumed at 1 per year. (0.0192 per week for all health states)					

LU weekly resource use (item units)	**Open**	**Infected**	**Closed**
Hospital admission	0.0002	0.0006	0.0002
GP	0.0155	0.0496	0.0134
Hospital outpatient	0.0094	0.0301	0.0025
Practice Nurse	0.1480	0.4749	0.0709
Community Nurse	1.4159	4.5424	0.6635
Antibiotic prescriptions	0.0559	0.1793	0.0324
Analgesia prescriptions	0.0876	0.2809	0.0397
Primary dressings	1.5452	4.9570	0.5065
Secondary dressings	0.6644	3.4699	0.2178
Compression	0.5586	1.7919	0.3471
Hosiery	0.2184	0.7006	0.1098

Expert opinion questioned the use of antibiotics in a non-infected/complicated health state. The sensitivity analysis for these items included testing the use of 0 antibiotics unless in the infected or complicated health states.

2.3.4 Provide details of the process used when clinical advisers assessed the applicability of the resources used in the model[1].

- (Internal) Martin Tadej- Clinical Specialist
- (Internal) Serge Bohbot- Medical Director
- Dave Russell – Consultant Vascular Surgeon
- Chris Manu – Consultant Diabetologist
- Experts were selected due to their knowledge of DFU and LU.
- 2 internal experts and 2 external experts were approached
- 2 internal experts and 2 external expert participated
- Martin Tadej and Serge Bohbot are employed by Urgo Medical.
- The two Guest 2018 papers used to derive resource use were provided as background information.
- Use of questionnaire survey, self-administered.

Technology and comparators' costs

2.3.5 Provide the list price for the technology.

£4.28 per UrgoStart dressing

2.3.6 If the list price is not used in the de novo cost model, provide the alternative price and a justification.

The list price is used

2.3.7 Summarise the annual costs associated with the technology and the comparator technology (if applicable) applied in the cost model. A suggested format is provided in tables C6 and C7. Table C7

[1] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

should only be completed when the most relevant UK comparator for the cost analysis refers to another technology.

Table 8 C6. Costs per patient associated with the technology in the cost model

Items	Value	Source
Price of the technology per treatment/patient	£4.28 per dressing used. Mean value 2.08 dressings used per week for an open wound.	UrgoStart and Guest 2018
Consumables (if applicable)	None	N/A
Maintenance cost	None	N/A
Training cost	None	N/A
Other costs	None	N/A
Total annual cost per patient	£462.92	

Table 9 C7 Costs per patient associated with the comparator technology in the cost model

Items	Value	Source
Cost of the comparator per treatment/patient	£3.13 per dressing used. Mean value 2.08 dressings used per week.	UrgoTul and Guest 2018
Consumables (if applicable)	None	N/A
Maintenance cost	None	N/A
Training cost	None	N/A
Other costs	None	N/A
Total annual cost per patient	£338.54	

Health-state costs

2.3.8 If the cost model presents health states, the costs related to each health state should be presented in table C8. The health states should refer to the states in section 9.1.7. Provide a rationale for the choice of values used in the cost model.

Table 10 Table C8a List of health states and associated costs in the DFU

economic model

DFU Health states. Weekly cost per patient.	Items	Value	Reference
Open wound pre-amputation	**Technology cost (UrgoStart/Neutral Dressing)**	£8.90/£6.51	Urgo Medical – UK Drug Tariff * Guest 2018 resource use.
	Inpatient costs	£0.45	NHS Schedule of costs * Guest 2018 resource use.
	Outpatient costs	£25.25	PSSRU Unit Costs of Health and Social Care 2017. OR NHS Schedule of costs * Guest 2018 resource use.
	Medications	£.80	BNF costs * Guest 2018 resource use.
	Devices (excluding primary dressing)	£15.18	Urgo Medical list costs * Guest 2018 resource use.
	Total (UrgoStart/Neutral Dressing)	£50.58/£48.19	
Complicated wound pre-amputation	**Technology cost (UrgoStart/Neutral Dressing)**	£26.71/£19.53	Urgo Medical – UK Drug Tariff
	Inpatient costs	£1.34	NHS Schedule of costs * Guest 2018 resource use.
	Outpatient costs	£75.77	PSSRU Unit Costs of Health and Social Care 2017 OR NHS Schedule of costs * Guest 2018 resource use.
	Medications	£2.40	BNF costs * Guest 2018 resource use.
	Devices (excluding primary dressing)	£27.87	Urgo Medical list costs OR NICE costing report * Guest 2018 resource use.
	Total (UrgoStart/Neutral Dressing)	£134.09/£126.92	
Closed wound pre-amputation	**Technology cost (UrgoStart/Neutral Dressing)**	£4.45/£3.25	Urgo Medical – UK Drug Tariff * Guest 2018 resource use.
	Inpatient costs	£0.00	NHS Schedule of costs * Guest 2018 resource use.
	Outpatient costs	£16.44	PSSRU Unit Costs of Health and Social Care 2017. OR NHS Schedule of costs * Guest 2018 resource use.
	Medications	£0.60	BNF costs * Guest 2018 resource use.
	Devices (excluding primary dressing)	£12.64	Urgo Medical list costs OR NICE costing report * Guest 2018 resource use.
	Total (UrgoStart/Neutral Dressing)	£34.13/£32.93	

Open wound post-amputation	**Technology cost (UrgoStart/Neutral Dressing)**	£6.46/£4.72	Urgo Medical – UK Drug Tariff * Guest 2018 resource use.
	Inpatient costs	£33.61	NHS Schedule of costs * Guest 2018 resource use.
	Outpatient costs	£22.77	PSSRU Unit Costs of Health and Social Care 2017. OR NHS Schedule of costs * Guest 2018 resource use.
	Medications	£0.46	BNF costs * Guest 2018 resource use.
	Devices (excluding primary dressing)	£13.78	Urgo Medical list costs * Guest 2018 resource use.
	Total (UrgoStart/Neutral Dressing)	£77.08/£75.34	
Complicated wound post-amputation	**Technology cost (UrgoStart/Neutral Dressing)**	£19.37/£14.16	Urgo Medical – UK Drug Tariff
	Inpatient costs	£100.84	NHS Schedule of costs * Guest 2018 resource use.
	Outpatient costs	£68.31	PSSRU Unit Costs of Health and Social Care 2017. OR NHS Schedule of costs * Guest 2018 resource use.
	Medications	£1.39	BNF costs * Guest 2018 resource use.
	Devices (excluding primary dressing)	£22.99	Urgo Medical list costs * Guest 2018 resource use.
	Total (UrgoStart/Neutral Dressing)	£212.90/£207.69	
Closed wound post-amputation	**Technology cost (UrgoStart/Neutral Dressing)**	£4.45/£3.25	Urgo Medical – UK Drug Tariff
	Inpatient costs	£0.00	NHS Schedule of costs * Guest 2018 resource use.
	Outpatient costs	£16.44	PSSRU Unit Costs of Health and Social Care 2017. OR NHS Schedule of costs * Guest 2018 resource use.
	Medications	£0.60	BNF costs * Guest 2018 resource use.
	Devices (excluding primary dressing)	£12.64	Urgo Medical list costs * Guest 2018 resource use.
	Total (UrgoStart/Neutral Dressing)	£34.13/£32.93	

Table 11 Table C8b List of health states and associated costs in the

LU economic model

LU Health states. Weekly cost per patient.	Items	Value	Reference
Open wound	**Technology cost (UrgoStart/Neutral Dressing)**	£6.61/£4.84	Urgo Medical – UK Drug Tariff
	Inpatient costs	£0.08	NHS Schedule of costs * Guest 2018 resource use.
	Outpatient costs	£38.22	PSSRU Unit Costs of Health and Social Care 2017 OR NHS Schedule of costs * Guest 2018 resource use.
	Medications	£0.27	BNF costs * Guest 2018 resource use.
	Devices (excluding primary dressing)	£8.53	Urgo Medical list costs * Guest 2018 resource use.
	Total (UrgoStart/Neutral Dressing)	£53.71/£51.94	
Infected wound	**Technology cost (UrgoStart/Neutral Dressing)**	£21.23/£15.53	Urgo Medical – UK Drug Tariff
	Inpatient costs	£0.26	NHS Schedule of costs * Guest 2018 resource use.
	Outpatient costs	£122.69	PSSRU Unit Costs of Health and Social Care 2017. OR NHS Schedule of costs * Guest 2018 resource use.
	Medications	£0.86	BNF costs * Guest 2018 resource use.
	Devices (excluding primary dressing)	£31.57	Urgo Medical list costs * Guest 2018 resource use.
	Total (UrgoStart/Neutral Dressing)	£176.61/£170.91	
	Total		
Closed wound	**Technology cost (UrgoStart/Neutral Dressing)**	£2.17/£1.59	Urgo Medical – UK Drug Tariff
	Inpatient costs	£0.09	NHS Schedule of costs * Guest 2018 resource use.
	Outpatient costs	£17.96	PSSRU Unit Costs of Health and Social Care 2017. OR NHS Schedule of costs * Guest 2018 resource use.
	Medications	£0.13	BNF costs * Guest 2018 resource use.
	Devices (excluding primary dressing)	£4.39	Urgo Medical list costs * Guest 2018 resource use.
	Total (UrgoStart/Neutral Dressing)	£24.74/£24.16	

Adverse-event costs

2.3.9 Complete table C9 with details of the costs associated with each adverse event referred to in 9.2.4 included in the cost model. Include all adverse events and complication costs, both during and after longer-term use of the technology.

Table 12 C9 List of adverse events and summary of costs included in the cost model

DFU Adverse events	Items	Value	Reference
Minor Amputation	**Amputation surgery**	£4440.32	NHS National Schedule of costs 2015/16. Weighted average of Amputation codes: YQ23B YQ24B YQ25B YQ26B YQ26C
	Follow up physiotherapy	£532.80	NICE. National costing report: diabetic foot care (August 2015). £15,230,000/28585 patients.
	Total	£4973.12	
Major amputation	**Amputation surgery**	£9.269.23	NHS National Schedule of costs 2015/16. Weighted average of Amputation codes: YQ23A YQ24A YQ25A YQ26A
	Follow up physiotherapy	£532.80	NICE. National costing report: diabetic foot care (August 2015). £15,230,000/28585 patients.
	Prosthesis	£2,876.00	NICE. National costing report: diabetic foot care (August 2015). £16,968,000/5900 patients.
	Total	£12,678.03	

No adverse events were included in the cost analysis for LU.

Miscellaneous costs

2.3.10 Describe any additional costs and cost savings that have not been covered anywhere else (for example, PSS costs, and patient and carer costs). If none, please state.

None considered

2.3.11 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

None considered.

2.4 Approach to sensitivity analysis

Section 9.4 requires the sponsor to carry out sensitivity analyses to explore uncertainty around the structural assumptions and parameters used in the analysis. All inputs used in the analysis will be estimated with a degree of imprecision. For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices. Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

2.4.1 Has the uncertainty around structural assumptions been investigated? State the types of sensitivity analysis that have been carried out in the cost analysis.

Uncertainty around assumptions and variables has been tested by using one-way deterministic and probabilistic sensitivity analyses. First, deterministic sensitivity analysis (DSA) was used to identify the key cost drivers. If a parameter caused more than 5% variance to the base-case cost increment, it was determined to be a cost driver. Any parameter causing less than a 5% variance to the base case cost was excluded, and probabilistic sensitivity analysis (PSA) was used to vary the remaining parameters using 1000 runs of the model.

2.4.2 Was a deterministic and/or probabilistic sensitivity analysis undertaken? If not, why not? How were variables varied and what was the rationale for this? If relevant, the distributions and their sources should be clearly stated.

Both deterministic and probabilistic sensitivity analysis were undertaken. If the variable had a confidence interval or standard deviation available from the published literature then this was used for the distribution; otherwise, a standard 30% variance was applied; unless rationally another value should be used. In order to calculate the range from the standard deviation, the 68–95–99.7 rule was used; the range of 95% of the data was assumed to be within 2 standard deviations of the mean. For DSA the range was calculated, and minimum and maximum values set; no negative values were allowed, if the range was larger than the mean value the minimum was set at 0 and the maximum at the range value. For PSA, a stochastic was calculated using the mean and SD; if this returned a negative value it was set at 0.

All ranges are listed below in 2.4.3

2.4.3 Complete table C10.1, C10.2 and/or C10.3 as appropriate to summarise the variables used in the sensitivity analysis.

Table 13 C10.1a Variables used in DFU one-way scenario-based DSA

Variable	Base-case value	Minimum value	Maximum value
If a patient has had a prior amputation from a previous wound	50%	0.35	0.65
The proportion of major amputations	0.24	0.17	0.31
The proportion having prosthesis after major amputation	86%	0.60	1.00
The duration of amputation event disutility, in weeks	4.00	2.00	6.00
The cost of one UrgoStart Dressing	4.28	3.00	5.56
The cost of one Neutral Dressing	3.13	2.19	4.07
Hospital inpatient resource use in open pre state	0.0002	0.0001	0.0003
GP resource use in open pre state	0.0239	0.0168	0.0311
Hospital outpatient resource use in open pre state	0.0192	0.0135	0.0250
Podiatrist resource use in open pre state	0.0032	0.0022	0.0041
Practice Nurse resource use in open pre state	0.0998	0.0699	0.1298
Community Nurse resource use in open pre state	0.8103	0.5672	1.0534
Antibiotic prescription resource use in open pre state	0.0795	0.0557	0.1034
Analgesic prescription resource use in open pre state	0.3268	0.2288	0.4249
Primary dressing resource use in open pre state	2.0800	1.4560	2.7040
Secondary Dressing resource use in open pre state	1.6224	1.1357	2.1091
Bespoke orthosis resource use in open pre state	0.0192	0.0135	0.0250
Hospital inpatient resource use in complicated pre state	0.0006	0.0004	0.0008
GP resource use in complicated pre state	0.0718	0.0503	0.0934
Hospital outpatient resource use in complicated pre state	0.0577	0.0404	0.0750
Podiatrist resource use in complicated pre state	0.0095	0.0067	0.0124
Practice Nurse resource use in complicated pre state	0.2994	0.2096	0.3893
Community Nurse resource use in complicated pre state	2.4309	1.7016	3.1601
Antibiotic prescription resource use in complicated pre state	0.2386	0.1670	0.3101
Analgesic prescription resource use in complicated pre state	0.9805	0.6863	1.2746
Primary dressing resource use in complicated pre state	6.2400	4.3680	8.1120
Secondary Dressing resource use in complicated pre state	5.6784	3.9749	7.3819
Bespoke orthosis resource use in complicated pre state	0.0192	0.0135	0.0250
Hospital inpatient resource use in closed pre state	0.0000	0.0000	0.0000
GP resource use in closed pre state	0.0294	0.0206	0.0383
Hospital outpatient resource use in closed pre state	0.0196	0.0137	0.0255
Podiatrist resource use in closed pre state	0.0040	0.0028	0.0053
Practice Nurse resource use in closed pre state	0.0937	0.0656	0.1218
Community Nurse resource use in closed pre state	0.3788	0.2652	0.4925
Antibiotic prescription resource use in closed pre state	0.0627	0.0439	0.0815
Analgesic prescription resource use in closed pre state	0.2410	0.1687	0.3133
Primary dressing resource use in closed pre state	1.0392	0.7275	1.3510
Secondary Dressing resource use in closed pre state	0.8106	0.5674	1.0538
Bespoke orthosis resource use in closed pre state	0.0192	0.0135	0.0250
Hospital inpatient resource use in open post state	0.0144	0.0101	0.0188
GP resource use in open post state	0.0158	0.0110	0.0205
Hospital outpatient resource use in open post state	0.0433	0.0303	0.0563
Podiatrist resource use in open post state	0.0017	0.0012	0.0023
Practice Nurse resource use in open post state	0.0826	0.0578	0.1074
Community Nurse resource use in open post state	0.5869	0.4108	0.7630
Antibiotic prescription resource use in open post state	0.1204	0.0843	0.1565
Analgesic prescription resource use in open post state	0.1324	0.0927	0.1721
Primary dressing resource use in open post state	1.5084	1.0559	1.9609
Secondary Dressing resource use in open post state	1.1765	0.8236	1.5295

Bespoke orthosis resource use in open post state	0.0192	0.0135	0.0250
Hospital inpatient resource use in complicated post state	0.0433	0.0303	0.0563
GP resource use in complicated post state	0.0473	0.0331	0.0615
Hospital outpatient resource use in complicated post state	0.1298	0.0909	0.1688
Podiatrist resource use in complicated post state	0.0052	0.0036	0.0068
Practice Nurse resource use in complicated post state	0.2478	0.1735	0.3221
Community Nurse resource use in complicated post state	1.7608	1.2325	2.2890
Antibiotic prescription resource use in complicated post state	0.3612	0.2528	0.4695
Analgesic prescription resource use in complicated post state	0.3972	0.2780	0.5164
Primary dressing resource use in complicated post state	4.5251	3.1676	5.8826
Secondary Dressing resource use in complicated post state	4.1178	2.8825	5.3532
Bespoke orthosis resource use in complicated post state	0.0192	0.0135	0.0250
Hospital inpatient resource use in closed post state	0.0000	0.0000	0.0000
GP resource use in closed post state	0.0294	0.0206	0.0383
Hospital outpatient resource use in closed post state	0.0196	0.0137	0.0255
Podiatrist resource use in closed post state	0.0040	0.0028	0.0053
Practice Nurse resource use in closed post state	0.0937	0.0656	0.1218
Community Nurse resource use in closed post state	0.3788	0.2652	0.4925
Antibiotic prescription resource use in closed post state	0.0627	0.0439	0.0815
Analgesic prescription resource use in closed post state	0.2410	0.1687	0.3133
Primary dressing resource use in closed post state	1.0392	0.7275	1.3510
Secondary Dressing resource use in closed post state	0.8106	0.5674	1.0538
Bespoke orthosis resource use in closed post state	0.0192	0.0135	0.0250
Quality of life weight for open pre-amputation state	0.6190	0.4333	0.8047
Quality of life weight for complicated pre-amputation state	0.5700	0.3990	0.7410
Quality of life weight for closed pre-amputation state	0.7380	0.5166	0.9594
Quality of life weight for open post-amputation state	0.5960	0.4172	0.7748
Quality of life weight for complicated post-amputation state	0.5830	0.4081	0.7579
Quality of life weight for closed post-amputation state	0.7150	0.5005	0.9295
Disutility associated with amputation event	-0.2800	-0.1960	-0.3640
Neutral Dressing. Transition probability: open pre -> complicated pre	0.0187	0.0131	0.0243
Neutral Dressing. Transition probability: open pre -> closed pre	0.0167	0.0117	0.0217
Neutral Dressing. Transition probability: open pre -> deceased	0.0019	0.0014	0.0025
Neutral Dressing. Transition probability: complicated pre -> closed pre	0.0032	0.0023	0.0042
Neutral Dressing. Transition probability: complicated pre -> open post	0.0034	0.0023	0.0044
Neutral Dressing. Transition probability: complicated pre -> closed post	0.0034	0.0023	0.0044
Neutral Dressing. Transition probability: complicated pre -> deceased	0.0019	0.0014	0.0025
Neutral Dressing. Transition probability: closed pre -> open pre	0.0055	0.0038	0.0071
Neutral Dressing. Transition probability: closed pre -> deceased	0.0019	0.0014	0.0025
Neutral Dressing. Transition probability: open post -> complicated post	0.0146	0.0102	0.0189
Neutral Dressing. Transition probability: open post -> closed post	0.0256	0.0179	0.0333
Neutral Dressing. Transition probability: open post -> deceased	0.0019	0.0014	0.0025
Neutral Dressing. Transition probability: complicated post -> closed post	0.0143	0.0100	0.0186
Neutral Dressing. Transition probability: complicated post -> deceased	0.0019	0.0014	0.0025
Neutral Dressing. Transition probability: closed post -> open post	0.0055	0.0038	0.0071
Neutral Dressing. Transition probability: closed post -> deceased	0.0019	0.0014	0.0025
UrgoStart Transition probability: open pre -> complicated pre	0.0135	0.0095	0.0176
UrgoStart Transition probability: open pre -> closed pre	0.0372	0.0260	0.0484
UrgoStart Transition probability: open pre -> deceased	0.0019	0.0014	0.0025
UrgoStart Transition probability: complicated pre -> closed pre	0.0111	0.0078	0.0144
UrgoStart Transition probability: complicated pre -> open post	0.0034	0.0023	0.0044
UrgoStart Transition probability: complicated pre -> closed post	0.0034	0.0023	0.0044
UrgoStart Transition probability: complicated pre -> deceased	0.0019	0.0014	0.0025
UrgoStart Transition probability: closed pre -> open pre	0.0055	0.0038	0.0071
UrgoStart Transition probability: closed pre -> deceased	0.0019	0.0014	0.0025
UrgoStart Transition probability: open post -> complicated post	0.0098	0.0069	0.0127
UrgoStart Transition probability: open post -> closed post	0.0377	0.0264	0.0490
UrgoStart Transition probability: open post -> deceased	0.0019	0.0014	0.0025
UrgoStart Transition probability: complicated post -> closed post	0.0154	0.0108	0.0200

UrgoStart Transition probability: complicated post -> deceased	0.0019	0.0014	0.0025
UrgoStart Transition probability: closed post -> open post	0.0055	0.0038	0.0071
UrgoStart Transition probability: closed post -> deceased	0.0019	0.0014	0.0025

Table 14 C10.1b Variables used in LU one-way scenario-based DSA

Variable	Base-case value	Minimum value	Maximum value
The cost of one UrgoStart Dressing	4.28	3.00	5.56
The cost of one Neutral Dressing	3.13	2.19	4.07
The duration of infection	3.00	2.10	3.90
Hospital inpatient resource use in open health state	0.02	0.00	0.92
GP resource use in open health state	1.70	0.00	10.52
Hospital outpatient resource use in open health state	1.03	0.00	24.64
Practice Nurse resource use in open health state	16.26	0.00	123.72
Community Nurse resource use in open health state	155.54	0.00	411.52
Antibiotic prescription resource use in open health state	6.14	0.00	32.68
Analgesic prescription resource use in open health state	9.62	0.00	60.60
Primary dressing resource use in open health state	169.74	0.00	1339.32
Secondary Dressing resource use in open health state	169.74	0.00	1339.32
Compression system resource use in open health state	61.36	0.00	230.96
Hosiery resource use in open health state	23.99	0.00	84.80
Hospital inpatient resource use in infected health state	0.02	0.00	0.92
GP resource use in infected health state	1.70	0.00	10.52
Hospital outpatient resource use in infected health state	1.03	0.00	24.64
Practice Nurse resource use in infected health state	16.26	0.00	123.72
Community Nurse resource use in infected health state	155.54	0.00	411.52
Antibiotic prescription resource use in infected health state	6.14	0.00	32.68
Analgesic prescription resource use in infected health state	9.62	0.00	60.60
Primary dressing resource use in infected health state	169.74	0.00	1339.32
Secondary Dressing resource use in infected health state	169.74	0.00	1339.32
Compression system resource use in infected health state	61.36	0.00	230.96
Hosiery resource use in infected health state	23.99	0.00	84.80
Hospital inpatient resource use in closed health state	0.01	0.00	0.68
GP resource use in closed health state	0.70	0.00	4.36
Hospital outpatient resource use in closed health state	0.13	0.00	3.04
Practice Nurse resource use in closed health state	3.70	0.00	26.68
Community Nurse resource use in closed health state	34.62	0.00	80.52
Antibiotic prescription resource use in closed health state	1.69	0.00	9.00
Analgesic prescription resource use in closed health state	2.07	0.00	12.12
Primary dressing resource use in closed health state	26.43	0.00	208.36
Secondary Dressing resource use in closed health state	26.43	0.00	208.36
Compression system resource use in closed health state	18.11	0.00	68.16
Hosiery resource use in closed health state	5.73	0.00	21.76
Quality of life weight for open pre-amputation state	0.52	0.36	0.68
Quality of life weight for infected pre-amputation state	0.52	0.36	0.68
Quality of life weight for closed pre-amputation state	0.67	0.47	0.87
Neutral dressing. Transition probability: open -> infected	0.0082	0.0057	0.0106
Neutral dressing. Transition probability: open -> closed	0.0475	0.0332	0.0617
Neutral dressing. Transition probability: infected -> open	0.3333	0.2333	0.4333
Neutral dressing. Transition probability: closed -> open	0.0033	0.0023	0.0043
UrgoStart. Transition probability: open -> infected	0.0097	0.0068	0.0126
UrgoStart. Transition probability: open -> closed	0.1093	0.0765	0.1421
UrgoStart. Transition probability: infected -> open	0.3333	0.2333	0.4333
UrgoStart. Transition probability: closed -> open	0.0033	0.0023	0.0043

Table 15 C10.2 Variables used in multi-way scenario-based sensitivity

analysis

Variable	*Parameter 1*	*Parameter 2*	*Parameter 3*
Base case	N/A- this was not performed		
Scenario 1			
Scenario 2			

Table 16 C10.3a Variable values used in DFU PSA

Variable	Base-case value	Minimum value	Maximum value
If a patient has had a prior amputation from a previous wound	50%	35%	65%
The cost of one UrgoStart Dressing	£4.28	£3.00	£5.56
The cost of one Neutral Dressing	£3.13	£2.19	£4.07
Community Nurse resource use in complicated pre state	2.4309	1.7016	3.1601
Bespoke orthosis resource use in closed pre state	0.0192	0.0135	0.0250
Hospital inpatient resource use in complicated post state	0.0433	0.0303	0.0563
Community Nurse resource use in complicated post state	1.7608	1.2325	2.2890
Transition probability: open pre -> complicated pre	0.0187	0.0131	0.0243
Transition probability: open pre -> closed pre	0.0109	0.0076	0.0141
Transition probability: open pre -> deceased	0.0019	0.0014	0.0025
Transition probability: complicated pre -> open post	0.0034	0.0023	0.0044
Transition probability: complicated pre -> closed post	0.0034	0.0023	0.0044
Transition probability: closed pre -> deceased	0.0019	0.0014	0.0025
Transition probability: open post -> complicated post	0.0146	0.0102	0.0189
Transition probability: open post -> closed post	0.0256	0.0179	0.0333
Transition probability: open post -> deceased	0.0019	0.0014	0.0025
Transition probability: complicated post -> closed post	0.0143	0.0100	0.0186
UrgoStart Transition probability: open pre -> complicated pre	0.0135	0.0095	0.0176
UrgoStart Transition probability: open pre -> closed pre	0.0372	0.0260	0.0484
UrgoStart Transition probability: open pre -> deceased	0.0019	0.0014	0.0025
UrgoStart Transition probability: complicated pre -> closed pre	0.0111	0.0078	0.0144
UrgoStart Transition probability: closed pre -> deceased	0.0019	0.0014	0.0025
UrgoStart Transition probability: open post -> complicated post	0.0098	0.0069	0.0127
UrgoStart Transition probability: open post -> closed post	0.0377	0.0264	0.0490
UrgoStart Transition probability: complicated post -> closed post	0.0154	0.0108	0.0200

Table 17 C10.3b Variable values used in LU PSA

Variable	Base-case value	Minimum value	Maximum value
The cost of one UrgoStart Dressing	£4.28	£3.00	£5.56
The cost of one Neutral Dressing	£3.13	£2.19	£4.07
Hospital inpatient resource use in open health state	0.02	0.00	0.92
GP resource use in open health state	1.70	0.00	10.52
Hospital outpatient resource use in open health state	1.03	0.00	24.64
Practice Nurse resource use in open health state	16.26	0.00	123.72
Community Nurse resource use in open health state	155.54	0.00	411.52
Primary dressing resource use in open health state	169.74	0.00	1339.32
Secondary Dressing resource use in open health state	169.74	0.00	1339.32
Compression system resource use in open health state	61.36	0.00	230.96
Hosiery resource use in open health state	23.99	0.00	84.80
Hospital outpatient resource use in infected health state	1.03	0.00	24.64
Practice Nurse resource use in infected health state	16.26	0.00	123.72
Community Nurse resource use in infected health state	155.54	0.00	411.52
Secondary Dressing resource use in infected health state	169.74	0.00	1339.32
Hospital inpatient resource use in closed health state	0.01	0.00	0.68
GP resource use in closed health state	0.70	0.00	4.36
Hospital outpatient resource use in closed health state	0.13	0.00	3.04
Practice Nurse resource use in closed health state	3.70	0.00	26.68
Community Nurse resource use in closed health state	34.62	0.00	80.52
Primary dressing resource use in closed health state	26.43	0.00	208.36
Secondary Dressing resource use in closed health state	26.43	0.00	208.36
Compression system resource use in closed health state	18.11	0.00	68.16
Hosiery resource use in closed health state	5.73	0.00	21.76
Neutral dressing. Transition probability: open -> infected	0.0082	0.0057	0.0106
Neutral dressing. Transition probability: open -> closed	0.0475	0.0332	0.0617
Neutral dressing. Transition probability: infected -> open	0.3333	0.2333	0.4333
Neutral dressing. Transition probability: closed -> open	0.0033	0.0023	0.0043
UrgoStart. Transition probability: open -> infected	0.0097	0.0068	0.0126
UrgoStart. Transition probability: open -> closed	0.1093	0.0765	0.1421
UrgoStart. Transition probability: infected -> open	0.3333	0.2333	0.4333
UrgoStart. Transition probability: closed -> open	0.0033	0.0023	0.0043

2.4.4 If any parameters or variables listed in section 9.2.6 were omitted from the sensitivity analysis, provide the rationale.

The below items were omitted from the all sensitivity as they were considered to be a constant; or in the case of proportion of minor amputations; this was dependent on the proportion of major amputations and was varied accordingly so the two values equal 100%.

- The cost of a hospital admission episode
- The cost of a GP appointment
- The cost of a hospital outpatient appointment
- The cost of a Podiatrist appointment
- The cost of a Practice Nurse appointment
- The cost of a Community Nurse appointment
- The cost of a prescription for antibiotics
- The cost of a prescription for analgesics
- The cost of a bespoke orthosis
- The cost of a minor amputation
- The cost of a major amputation
- The cost of a course of physiotherapy
- The cost of a prosthesis
- The cost of a compression system
- The cost of a pair of hosiery
- The proportion of minor amputations

Any parameter that failed to cause more than 5% variance to the base case cost in the DSA was omitted from the PSA. These can be seen in the model, in the sensitivity analysis sheets.

2.5 Results of de novo cost analysis

Section 9.5 requires the sponsor to report the de novo cost analysis results. These should include the following:

- costs
- disaggregated results such as costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment
- a tabulation of the mean cost results
- results of the sensitivity analysis.

Base-case analysis

2.5.1 Report the total costs associated with use of the technology and the comparator(s) in the base-case analysis. A suggested format is presented in table C11.

Table 18 C11a DFU Base-case results

	Total per patient cost (£)
UrgoStart	£3184.35
Neutral dressing	£3850.86

Table 19 C11b LU Base-case results

	Total per patient cost (£)
UrgoStart	£1582.58
Neutral dressing	£1856.83

2.5.2 Report the total difference in costs between the technology and comparator(s).

DFU

UrgoStart incurred £666.51 less cost than the neutral dressing

LU

UrgoStart incurred £274.25 less cost than the neutral dressing

2.5.3 Provide details of the costs for the technology and its comparator by category of cost. A suggested format is presented in table C12.

Table 20 C12a Summary of DFU costs by category of cost per patient

Item	Cost UrgoStart	Cost neutral dressing	Increment	Absolute increment	% absolute increment
Technology	£390.72	£359.63	£31.09	£31.09	4%
Inpatient	£597.61	£811.94	-£214.33	£214.33	29%
Outpatient	£1280.27	£1564.24	-£283.97	£283.97	39%
Medication	£37.95	£44.69	-£6.74	£6.74	1%
Devices (excluding primary dressing)	£734.94	£802.96	-£68.02	£68.02	9%
Amputation event	£142.86	£267.40	-£124.54	£124.54	17%
Total	£3184.35	£3850.86	-£666.51	728.69	100%
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee					

Table 21 C12a Summary of LU costs by category of cost per patient

Item	Cost UrgoStart	Cost neutral dressing	Increment	Absolute increment	% absolute increment
Technology	£157.77	£151.94	£5.83	5.83	2%
Inpatient	£4.60	£4.53	£0.07	0.07	0%
Outpatient	£1140.25	£1370.58	-£230.33	230.33	81%
Medication	£8.19	£9.78	-£1.59	1.59	1%
Devices (excluding primary dressing)	£271.78	£320.00	-£48.22	48.22	17%
Total	£1582.58	£1856.83	-£274.25	286.04	100%
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee					

2.5.4 If appropriate, provide details of the costs for the technology and its comparator by health state. A suggested format is presented in table C13.

Table 22 C13a Summary of DFU costs by health state per patient

Health state	Cost UrgoStart	Cost neutral dressing	Increment	Absolute increment	% absolute increment
Open pre-amputation	£464.04	£556.70	-£92.66	£92.66	7%
Complicated pre-amputation	£433.58	£771.50	-£337.92	£337.92	27%
Closed pre-amputation	£403.79	£206.09	£197.70	£197.70	16%
Open post-amputation	£758.98	£834.95	-£75.97	£75.97	6%
Complicated post-amputation	£545.13	£877.62	-£332.49	£332.49	26%
Closed post-amputation	£435.96	£336.60	£99.36	£99.36	8%
Amputation costs	£142.86	£267.40	-£124.54	£124.54	10%
Total	£3,184.35	£3,850.86	-£666.51	£1260.64	100%
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee					

Table 23 C13b Summary of LU costs by health state per patient

Health state	Cost UrgoStart	Cost neutral dressing	Increment	Absolute increment	% absolute increment
Open	£489.07	£1,009.64	-£520.57	£520.57	63%
Infected	£51.43	£84.02	-£32.59	£32.59	4%
Closed	£1,042.09	£763.17	£278.92	£278.92	34%

Total	£1,582.58	£1,856.83	-£274.25	£832.08	100%
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee					

2.5.5 If appropriate, provide details of the costs for the technology and its comparator by adverse event. A suggested format is provided in table C14.

Table 24 C14 Summary of costs by DFU adverse events per patient

Adverse event	Cost UrgoStart	Cost neutral dressing	Increment	Absolute increment	% absolute increment
Amputation costs	£142.86	£267.40	-£124.54	£124.54	100%
Total	£142.86	£267.40	-£124.54	£124.54	100%
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee					

Sensitivity analysis results

2.5.6 Present results of deterministic one-way sensitivity analysis of the variables described in table C10.1.

DFU

Table 25 Results of DFU DSA.

Variable	Min	Max	Variance
Transition probability: open post -> closed post	*-£ 804.39*	*-£ 551.85*	*-£ 252.53*
The cost of one UrgoStart Dressing	*-£ 784.06*	*-£ 549.68*	*-£ 234.38*
UrgoStart Transition probability: open pre -> complicated pre	*-£ 782.52*	*-£ 562.40*	*-£ 220.12*
UrgoStart Transition probability: open post -> complicated post	*-£ 771.01*	*-£ 570.28*	*-£ 200.72*
Transition probability: open pre -> closed pre	*-£ 737.89*	*-£ 603.56*	*-£ 134.33*
Transition probability: complicated post -> closed post	*-£ 722.97*	*-£ 616.90*	*-£ 106.06*
UrgoStart Transition probability: closed pre -> deceased	*-£ 707.59*	*-£ 627.42*	*-£ 80.16*
If a patient has had a prior amputation from a previous wound	*-£ 694.78*	*-£ 639.33*	*-£ 55.45*
UrgoStart Transition probability: open pre -> deceased	*-£ 691.58*	*-£ 643.07*	*-£ 48.50*
Transition probability: open post -> deceased	*-£ 684.87*	*-£ 649.50*	*-£ 35.37*
Bespoke orthosis resource use in closed pre state	*-£ 683.94*	*-£ 650.17*	*-£ 33.77*
UrgoStart Transition probability: complicated pre -> open post	-£ 683.42	-£ 651.27	-£ 32.15
UrgoStart Transition probability: closed post -> open post	-£ 682.11	-£ 652.47	-£ 29.64
Transition probability: complicated pre -> closed pre	-£ 681.43	-£ 653.03	-£ 28.40
UrgoStart Transition probability: complicated pre -> closed post	-£ 680.88	-£ 653.76	-£ 27.12
Community Nurse resource use in closed pre state	-£ 679.99	-£ 654.13	-£ 25.86
Primary dressing resource use in closed pre state	-£ 676.66	-£ 657.27	-£ 19.38
Transition probability: complicated post -> deceased	-£ 676.13	-£ 658.12	-£ 18.01
UrgoStart Transition probability: closed pre -> open pre	-£ 675.74	-£ 658.64	-£ 17.10
Practice Nurse resource use in closed pre state	-£ 674.80	-£ 659.14	-£ 15.66
Bespoke orthosis resource use in closed post state	-£ 674.79	-£ 659.32	-£ 15.46
Primary dressing resource use in closed post state	-£ 674.03	-£ 659.86	-£ 14.17
UrgoStart Transition probability: complicated pre -> deceased	-£ 673.44	-£ 660.83	-£ 12.62
Community Nurse resource use in closed post state	-£ 672.98	-£ 661.14	-£ 11.84
Hospital outpatient resource use in closed pre state	-£ 671.57	-£ 662.54	-£ 9.03
Secondary Dressing resource use in closed pre state	-£ 671.29	-£ 662.82	-£ 8.47
Transition probability: closed post -> deceased	-£ 671.15	-£ 663.03	-£ 8.12
Practice Nurse resource use in closed post state	-£ 670.53	-£ 663.36	-£ 7.17
Primary dressing resource use in open post state	-£ 670.32	-£ 663.69	-£ 6.63
Hospital outpatient resource use in closed post state	-£ 669.12	-£ 664.99	-£ 4.13
Primary dressing resource use in open pre state	-£ 669.03	-£ 665.09	-£ 3.94
Secondary Dressing resource use in closed post state	-£ 669.00	-£ 665.12	-£ 3.88
GP resource use in closed pre state	-£ 668.83	-£ 665.10	-£ 3.73
GP resource use in closed post state	-£ 667.80	-£ 666.09	-£ 1.71
Analgesic prescription resource use in closed pre state	-£ 667.89	-£ 666.22	-£ 1.67
Analgesic prescription resource use in closed post state	-£ 667.44	-£ 666.67	-£ 0.77
Podiatrist resource use in closed pre state	-£ 667.27	-£ 666.66	-£ 0.61
Antibiotic prescription resource use in closed pre state	-£ 667.22	-£ 666.89	-£ 0.33
Podiatrist resource use in closed post state	-£ 667.08	-£ 666.80	-£ 0.28

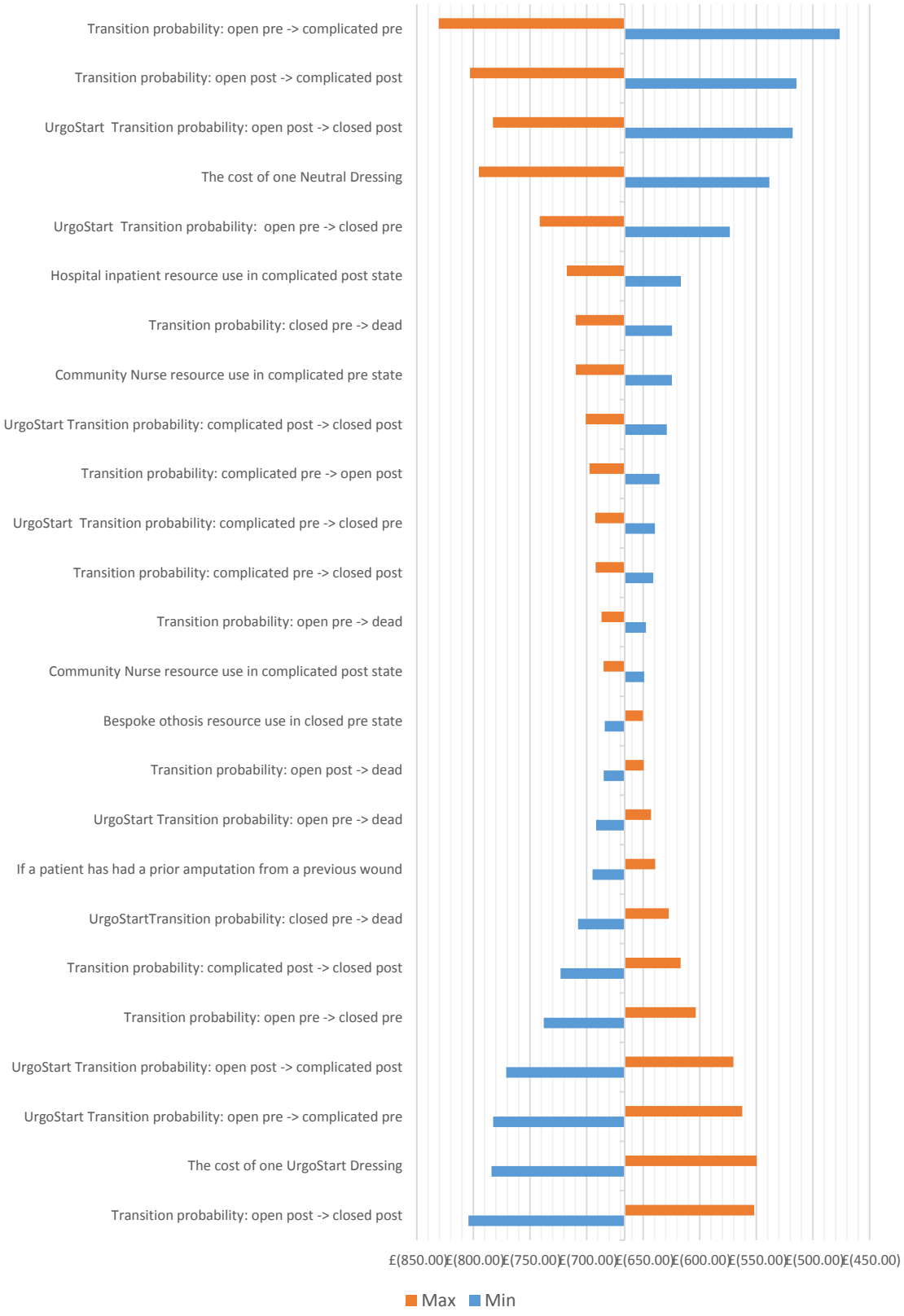
Antibiotic prescription resource use in closed post state	-£ 667.13	-£ 666.98	-£ 0.15
Podiatrist resource use in open post state	-£ 667.03	-£ 666.98	-£ 0.05
The duration of amputation event disutility, in weeks	-£ 667.06	-£ 667.06	£ -
Hospital inpatient resource use in closed pre state	-£ 667.06	-£ 667.06	£ -
Hospital inpatient resource use in closed post state	-£ 667.06	-£ 667.06	£ -
Quality of life weight for open pre-amputation state	-£ 667.06	-£ 667.06	£ -
Quality of life weight for complicated pre-amputation state	-£ 667.06	-£ 667.06	£ -
Quality of life weight for closed pre-amputation state	-£ 667.06	-£ 667.06	£ -
Quality of life weight for open post-amputation state	-£ 667.06	-£ 667.06	£ -
Quality of life weight for complicated post-amputation state	-£ 667.06	-£ 667.06	£ -
Quality of life weight for closed post-amputation state	-£ 667.06	-£ 667.06	£ -
Disutility associated with amputation event	-£ 667.06	-£ 667.06	£ -
Podiatrist resource use in open pre state	-£ 666.96	-£ 667.06	£ 0.10
Analgesic prescription resource use in open post state	-£ 666.96	-£ 667.06	£ 0.10
Antibiotic prescription resource use in open pre state	-£ 666.96	-£ 667.15	£ 0.19
Podiatrist resource use in complicated post state	-£ 666.94	-£ 667.17	£ 0.23
Antibiotic prescription resource use in open post state	-£ 666.88	-£ 667.13	£ 0.25
GP resource use in open post state	-£ 666.83	-£ 667.28	£ 0.44
Hospital inpatient resource use in open pre state	-£ 666.75	-£ 667.27	£ 0.53
Antibiotic prescription resource use in complicated post state	-£ 666.77	-£ 667.34	£ 0.57
Antibiotic prescription resource use in complicated pre state	-£ 666.74	-£ 667.34	£ 0.59
Podiatrist resource use in complicated pre state	-£ 666.69	-£ 667.43	£ 0.74
Analgesic prescription resource use in complicated post state	-£ 666.64	-£ 667.43	£ 0.79
Analgesic prescription resource use in open pre state	-£ 666.58	-£ 667.44	£ 0.86
GP resource use in open pre state	-£ 666.41	-£ 667.61	£ 1.19
GP resource use in complicated post state	-£ 666.16	-£ 667.96	£ 1.80
Hospital inpatient resource use in complicated pre state	-£ 665.86	-£ 668.16	£ 2.30
Transition probability: complicated pre -> deceased	-£ 665.79	-£ 668.49	£ 2.70
Secondary Dressing resource use in open post state	-£ 665.59	-£ 668.32	£ 2.73
Practice Nurse resource use in open post state	-£ 665.52	-£ 668.59	£ 3.06
Analgesic prescription resource use in complicated pre state	-£ 665.32	-£ 668.79	£ 3.47
Hospital outpatient resource use in open pre state	-£ 665.06	-£ 668.96	£ 3.90
Hospital outpatient resource use in open post state	-£ 664.84	-£ 669.17	£ 4.33
GP resource use in complicated pre state	-£ 664.72	-£ 669.39	£ 4.67
The proportion having prosthesis after major amputation	-£ 663.76	-£ 668.85	£ 5.09
Primary dressing resource use in complicated post state	-£ 663.97	-£ 670.14	£ 6.16
Practice Nurse resource use in open pre state	-£ 663.49	-£ 670.62	£ 7.13
Secondary Dressing resource use in open pre state	-£ 663.44	-£ 670.58	£ 7.14
Bespoke orthosis resource use in open post state	-£ 663.21	-£ 67.80	£ 7.59
Community Nurse resource use in open post state	-£ 662.51	-£ 671.51	£ 9.00
Bespoke orthosis resource use in complicated post state	-£ 662.01	-£ 672.10	£ 10.09
UrgoStart Transition probability: closed post -> deceased	-£ 661.63	-£ 672.40	£ 10.77
UrgoStart Transition probability: complicated post -> deceased	-£ 661.36	-£ 672.67	£ 11.31
Transition probability: closed pre -> open pre	-£ 660.85	-£ 673.05	£ 12.20
Practice Nurse resource use in complicated post state	-£ 660.86	-£ 673.25	£ 12.39
Secondary Dressing resource use in complicated post state	-£ 660.61	-£ 673.46	£ 12.85
Hospital outpatient resource use in complicated pre state	-£ 660.26	-£ 673.86	£ 13.60
Bespoke orthosis resource use in open pre state	-£ 659.85	-£ 674.26	£ 14.41
Bespoke orthosis resource use in complicated pre state	-£ 658.43	-£ 675.68	£ 17.24
Hospital outpatient resource use in complicated post state	-£ 658.07	-£ 676.00	£ 17.93

Primary dressing resource use in complicated pre state	-£ 657.33	-£ 676.75	£ 19.41
The proportion of major amputations	-£ 657.32	-£ 676.79	£ 19.47
Community Nurse resource use in open pre state	-£ 655.15	-£ 678.88	£ 23.73
Hospital inpatient resource use in open post state	-£ 654.60	-£ 679.42	£ 24.81
Practice Nurse resource use in complicated pre state	-£ 654.22	-£ 679.80	£ 25.58
Transition probability: closed post -> open post	-£ 652.77	-£ 680.88	£ 28.10
UrgoStart Transition probability: open post -> deceased	-£ 652.63	-£ 681.29	£ 28.67
Secondary Dressing resource use in complicated pre state	-£ 651.89	-£ 682.19	£ 30.30
Community Nurse resource use in complicated post state	*-£ 649.05*	*-£ 685.02*	*£ 35.98*
Transition probability: open pre -> deceased	*-£ 647.53*	*-£ 686.80*	*£ 39.27*
Transition probability: complicated pre -> closed post	*-£ 641.05*	*-£ 692.04*	*£ 50.99*
UrgoStart Transition probability: complicated pre -> closed pre	*-£ 639.56*	*-£ 692.34*	*£ 52.78*
Transition probability: complicated pre -> open post	*-£ 635.53*	*-£ 697.43*	*£ 61.90*
UrgoStart Transition probability: complicated post -> closed post	*-£ 629.10*	*-£ 700.79*	*£ 71.69*
Community Nurse resource use in complicated pre state	*-£ 624.66*	*-£ 709.46*	*£ 84.80*
Transition probability: closed pre -> deceased	*-£ 624.55*	*-£ 709.60*	*£ 85.05*
Hospital inpatient resource use in complicated post state	*-£ 616.64*	*-£ 717.43*	*£ 100.78*
UrgoStart Transition probability: open pre -> closed pre	*-£ 573.43*	*-£ 741.38*	*£ 167.95*
The cost of one Neutral Dressing	*-£ 538.53*	*-£ 795.15*	*£ 256.62*
UrgoStart Transition probability: open post -> closed post	*-£ 517.91*	*-£ 782.74*	*£ 264.83*
Transition probability: open post -> complicated post	*-£ 514.54*	*-£ 803.07*	*£ 288.53*
Transition probability: open pre -> complicated pre	*-£ 476.30*	*-£ 830.60*	*£ 354.30*

Tornado diagram of results of DFU DSA, for items reaching a variance of at least 5%

Figure 5. Results of DFU DSA

DFU Deterministic Sensitivity Analysis Results



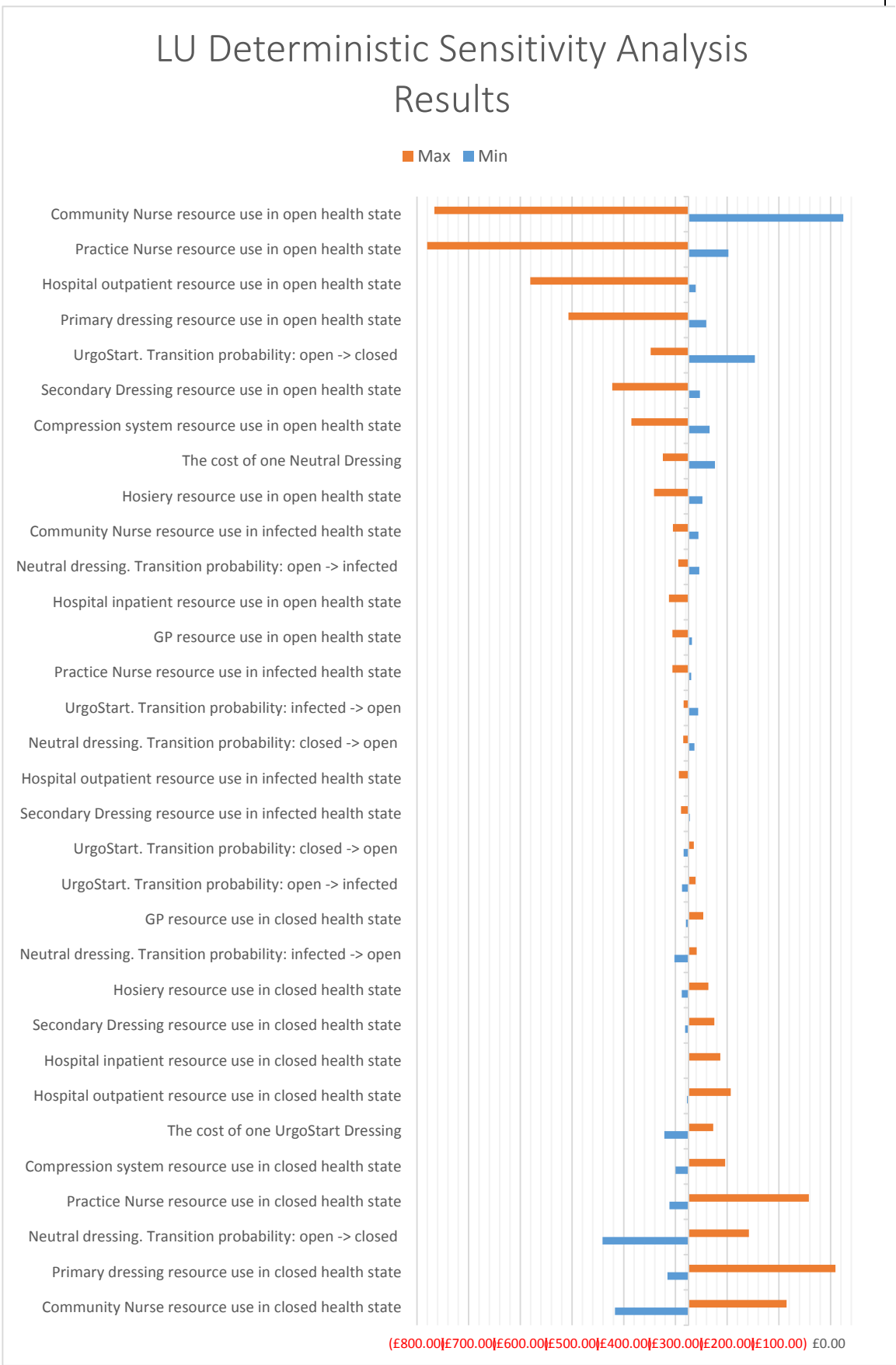
LU DSA results

Table 26 Results of LU DSA

Variable	Min	Max	Variance
The cost of one UrgoStart Dressing	-£321.52	-£226.90	-£94.62
The cost of one Neutral Dressing	-£223.66	-£324.42	£100.76
The duration of infection	-£274.25	-£274.25	£0.00
Hospital inpatient resource use in open health state	-£273.43	-£312.59	£39.16
GP resource use in open health state	-£268.16	-£305.77	£37.61
Hospital outpatient resource use in open health state	-£260.92	-£580.73	£319.80
Practice Nurse resource use in open health state	-£197.69	-£780.15	£582.46
Community Nurse resource use in open health state	£24.68	-£766.20	£790.88
Antibiotic prescription resource use in open health state	-£273.32	-£278.18	£4.86
Analgesic prescription resource use in open health state	-£272.39	-£284.17	£11.78
Primary dressing resource use in open health state	-£240.36	-£507.00	£266.64
Secondary Dressing resource use in open health state	-£252.76	-£422.32	£169.56
Compression system resource use in open health state	-£234.06	-£385.23	£151.17
Hosiery resource use in open health state	-£247.80	-£341.42	£93.62
Hospital inpatient resource use in infected health state	-£274.20	-£276.64	£2.44
GP resource use in infected health state	-£273.88	-£276.22	£2.34
Hospital outpatient resource use in infected health state	-£273.42	-£293.34	£19.92
Practice Nurse resource use in infected health state	-£269.49	-£305.76	£36.27
Community Nurse resource use in infected health state	-£255.64	-£304.89	£49.25
Antibiotic prescription resource use in infected health state	-£274.20	-£274.50	£0.30
Analgesic prescription resource use in infected health state	-£274.14	-£274.87	£0.74
Primary dressing resource use in infected health state	-£272.80	-£284.25	£11.45
Secondary Dressing resource use in infected health state	-£272.08	-£289.26	£17.19
Compression system resource use in infected health state	-£271.75	-£281.17	£9.42
Hosiery resource use in infected health state	-£272.61	-£278.43	£5.83
Hospital inpatient resource use in closed health state	-£275.20	-£213.16	-£62.04
GP resource use in closed health state	-£279.63	-£246.13	-£33.50
Hospital outpatient resource use in closed health state	-£277.84	-£193.15	-£84.69
Practice Nurse resource use in closed health state	-£311.65	-£42.10	-£269.55
Community Nurse resource use in closed health state	-£417.09	-£84.97	-£332.12
Antibiotic prescription resource use in closed health state	-£274.78	-£271.94	-£2.84
Analgesic prescription resource use in closed health state	-£275.10	-£270.04	-£5.06
Primary dressing resource use in closed health state	-£315.43	£9.57	-£325.00
Secondary Dressing resource use in closed health state	-£281.42	-£224.85	-£56.56
Compression system resource use in closed health state	-£299.74	-£204.00	-£95.75
Hosiery resource use in closed health state	-£287.84	-£236.33	-£51.51
Quality of life weight for open pre-amputation state	-£274.25	-£274.25	£0.00
Quality of life weight for infected pre-amputation state	-£274.25	-£274.25	£0.00
Quality of life weight for closed pre-amputation state	-£274.25	-£274.25	£0.00
Neutral dressing. Transition probability: open -> infected	-£253.92	-£294.49	£40.57
Neutral dressing. Transition probability: open -> closed	-£441.15	-£157.98	-£283.17
Neutral dressing. Transition probability: infected -> open	-£301.94	-£258.95	-£42.99
Neutral dressing. Transition probability: closed -> open	-£263.35	-£284.95	£21.60
UrgoStart. Transition probability: open -> infected	-£287.32	-£261.21	-£26.10
UrgoStart. Transition probability: open -> closed	-£146.51	-£348.01	£201.50
UrgoStart. Transition probability: infected -> open	-£255.98	-£284.21	£28.22
UrgoStart. Transition probability: closed -> open	-£284.14	-£264.50	-£19.64

Tornado diagram of results of LU DSA, for items reaching a variance of at least 5%

Figure 6 Results of LU DSA



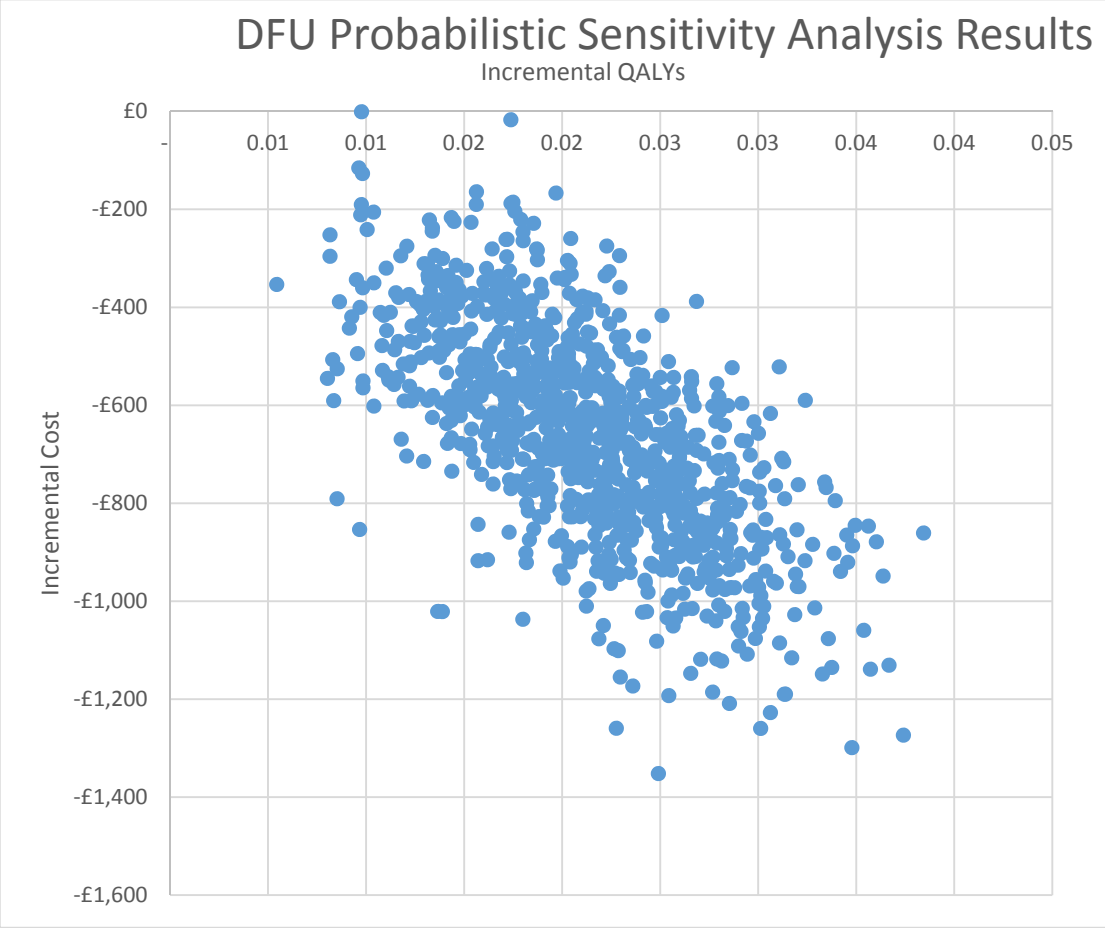
2.5.7 Present results of deterministic multi-way scenario sensitivity analysis described in table C10.2.

N/A

2.5.8 Present results of the probabilistic sensitivity analysis described in table C10.3.

DFU: The PSA showed that in all cases UrgoStart resulted in a cost saving and a QALY gain.

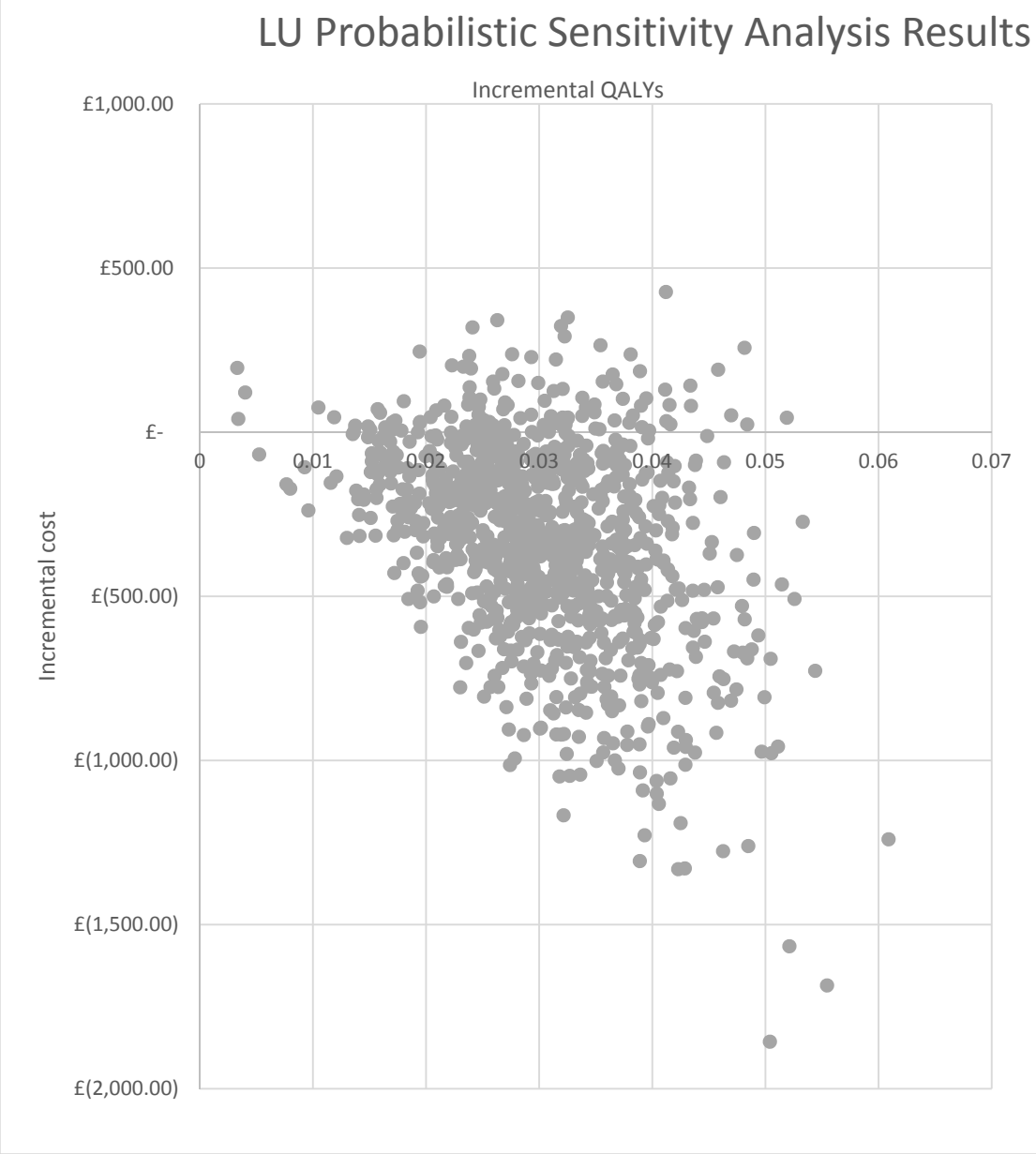
Figure 7 Results of DFU PSA



	Cost increment	ICER
min	-£1,352	-£92,789
median	-£661	-£31,193
max	-£1	-£99
mean	-£664	-£31,713
stdev	£212	£9,085
2.50%	-£1,092	-£49,704
97.50%	-£262	-£15,209

LU: The PSA showed that in approximately 90% of cases UrgoStart resulted in a cost saving and a QALY gain.

Figure 8 Results of LU PSA



	Cost increment	ICER
min	-£1,857	-£36,964
median	-£305	-£10,577
max	£427	£58,872
mean	-£335	-£10,632
stdev	£302	£9,184
2.50%	-£1,000	-£29,202
97.50%	£150	£5,225

2.5.9 What were the main findings of each of the sensitivity analyses?

DFU

The DSA showed that when varying parameters individually the cost of the dressings were important, as were transitions for UrgoStart and Neutral dressing. However, these could be varied and UrgoStart would still be cost saving in any scenario. Scenario analysis also showed that if the competitor product were free (£0) UrgoStart would remain cost saving (-£239.05) due to the increased efficacy and shorter healing time.

The PSA varied all parameters shown to cause more than 5% variance on the cost increment in the DSA. For DFU the mean cost saving was £664 (range: -£1352 - -£1). When looking at the ICER, UrgoStart is dominant, saving cost and gains QALYs.

LU

The DSA showed that when varying parameters individually then resource use during the open health state cause the largest variance in costs. In only two scenarios does UrgoStart incur costs- with community nurse visits at 0; UrgoStart incurs £24.59 per patient and with primary dressing use at maximum in the closed health state, UrgoStart incurs £9.68 per patient cost. UrgoStart remains cost saving in all other scenarios tested. Scenario analysis also showed that if the competitor product were free (£0) UrgoStart would remain cost saving (-£105.80) due to the increased efficacy and shorter healing time.

The PSA varied all parameters shown to cause more than 5% variance on the cost increment in the DSA. For LU the mean cost saving was £340 (range: -£1723- £423). There was a broader range in the LU figures due to the large standard deviations of the mean resource use figures. When looking at the mean ICER produced, UrgoStart is dominant, saving cost and gains QALYs.

2.5.10 What are the key drivers of the cost results?

Key drivers of the cost results are the cost of the dressings, the transitions for healing and infection/complication and the resource use with regards to community nursing and hospital visits. The increased likelihood of healing drives the cost savings for UrgoStart.

Miscellaneous results

2.5.11 Describe any additional results that have not been specifically requested in this template. If none, please state.

The incremental cost effectiveness ratio was calculated for DFU and LU. For the base case, UrgoStart was the dominant strategy. UrgoStart remained dominant in the DSA and PSA.

2.6 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. Sponsors are required to complete section 9.6 in accordance with the subgroups identified in the scope and for any additional subgroups considered relevant. Types of subgroups that are not considered relevant are those based solely on the following factors. • Subgroups based solely on differential treatment costs for individuals according to their social characteristics. • Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, if the costs of facilities available for providing the technology vary according to location).

2.6.1 Specify whether analysis of subgroups was undertaken and how these subgroups were identified. Cross-reference the response to the decision problem in table A1 and sections 3.2 and 7.4.4.

A1 in Section A of this document referred to the following wound types:

- Patients with venous leg ulcers
- Patients with arterial leg ulcers
- Patients with leg ulcers of mixed aetiology
- Patients with diabetic foot ulcers
- Patients with chronic ulcers
- Patients with non-healing ulcers
- Pressure ulcers

Venous/arterial and mixed aetiology wounds were included in the Challenge trial and are thus included in the economic model for Leg Ulcers. Diabetic foot ulcers and Leg ulcers are examples of chronic ulcers, or non-healing ulcers. Pressure ulcers were excluded from the economic analysis due to the lack of data available when using UrgoStart.

2.6.2 Define the characteristics of patients in the subgroup(s).

The patients included in the Challenge trial had to have the following characteristics:

- Wound area between 5 and 50 cm2,
- Wound between 6- and 36-month duration,
- Ankle Brachial Pressure Index (ABPI) between 0.8 and 1.3
- At least 50% of wound bed covered with granulation tissue without any black
- necrotic/devitalized tissue (colorimetric scale).

Patients were excluded on the following basis:

- Suspected clinical infection,
- Known contact dermatitis to carboxymethylcellulose (CMC),
- a history of venous surgery within the previous 2 months,
- the occurrence of deep vein thrombosis in the previous 3 months
- A concomitant severe comorbid disease or poor health status that could impair the expected 8-week follow-up,
- any known malignant wound degeneration,

- concomitant treatment with immunosuppressive agents or high dose of oral corticosteroids.

For DFU, the patients included in the Explorer trial had to have the following characteristics:

- Adults with diabetes and a non-infected neuro-ischaemic DFU of grade IC (ischaemic, non-infected superficial wound) or IIC (ischaemic, non-infected wound penetrating to tendon or capsule), as defined by the University of Texas Diabetic Wound Classification system.
- Glycaemic control was confirmed by an HbA1c of 10% (85·8 mmol/mol) or lower in the 3 months before enrolment or during screening.
- Neuropathy verified by insensitivity to 5·07 Semmes-Weinstein 10 g monofilament.
- Peripheral artery disease without critical limb ischaemia confirmed by vascular assessment of the affected foot.
- The ulcer located on the toe or lateral/dorsal/plantar aspect of the foot;
- wound surface area between 1 and 30 cm² after clinical debridement;
- wound duration of between 1 and 24 months at inclusion;
- no local infection of any wound on the lower limbs,

Patients were excluded on the following basis:

- Severe illness that might lead to premature discontinuation of the trial
- Surgery or surgical revascularisation (vascular reconstruction or angioplasty) in the month before trial entry.

2.6.3 Describe how the subgroups were included in the cost analysis.

Two models presented, one for DFU and one for LU.

2.6.4 What were the results of the subgroup analysis/analyses, if conducted? The results should be presented in a table similar to that in section 9.5.1 (base-case analysis).

N/A see base-case analysis.

2.6.5 Were any subgroups not included in the submission? If so, which ones, and why were they not considered?

Pressure ulcers were excluded for lack of data.

2.7 Validation

2.7.1 Describe the methods used to validate and cross-validate (for example with external evidence sources) and quality-assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical and resources sections.

The models have been created using peer reviewed and published data. The double-blind randomised controlled trials, Challenge and Explorer, provided data for the efficacy of UrgoStart on the wound aetiologies. Both Challenge and Explorer show the improved outcomes for patients when using UrgoStart, which the model demonstrates. It is this efficacy, leading to shorter healing times, that drives the cost saving. Wounds treated with UrgoStart are more likely to heal, and thus less likely to spend time in the complicated/infected health states, where more resources are used. Particularly, for DFU patients, the avoidance of amputation is a driver of cost savings. The literature used specifies that wounds are more expensive to the healthcare system post-amputation (with a much higher likelihood of hospital admission) and by healing patients faster, some of these consequences are avoided. In addition to the use of literature, the model was validated by clinical experts, technical experts, and by academics at Manchester Metropolitan University.

2.8 Interpretation of economic evidence

2.8.1 Are the results from this cost analysis consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

In terms of resource use, this has been taken from the two papers published in March 2018 by Julian Guest et al in the Journal of Wound Care. These papers estimated the annual levels of healthcare resource use by wounds in different health states. For DFU this was a cohort of 130 patients and for (V)LU a cohort of 505 patients. Data was collected from The Health Improvement Network (THIN) database, which is kept up to date by GPs. The DFU paper highlights a cost range of £2140 - £16,900 dependent on the wound status. Our model shows an average per patient cost of £3627.76/£4172.54 (UrgoStart/Neutral Dressing) which falls within these bounds. In the Markov model, patients move between the health states, incurring the relevant weekly cost. In the Guest (2008) paper DFU patients were shown to receive compression, this was excluded from our model as it is not recommended for the treatment of DFUs. In the paper, 13% of costs come from amputations, which is higher than the 3-5% shown in our model. It is possible that the likelihood of amputation in the general population is higher than the sample population in the Explorer clinical trial.

The LU paper from Guest et al (2018), estimated the costs of treating a LU as between £3000-£13,500 dependent on wound status. Our model shows a more modest cost of £1579.23/£1856.56 (UrgoStart/Competitor) despite using the values published in this paper This is likely driven by the large standard deviations of the resource use mean values, which were used in the base-case. When performing sensitivity analysis the standard deviation was used to estimate the range of values, and the highest cost for neutral dressing was £3737. The healing rate applied from the RCT (Challenge) was higher to the healing rate in Guest et al; and this perhaps reflects the

benefits of a highly protocolised treatment regimen as used in randomised clinical trials.

2.8.2 Is the cost analysis relevant to all groups of patients and NHS settings in England that could potentially use the technology as identified in the scope?

Yes.

2.8.3 What are the main strengths and weaknesses of the analysis? How might these affect the interpretation of the results?

The DFU analysis used the same weekly cost for patients with closed wounds both pre and post amputation. After discussion with clinical experts, closed wounds post amputation are likely to cost more; however without the data available, this was left at the same level. This is a conservative assumption, and will have affected both groups in the analysis and as such does not serve to undermine the cost-saving effectiveness of UrgoStart.

The LU analysis relies on the mean values from the Guest paper, which mostly have a large standard deviation. These values were tested using the sensitivity analysis, where UrgoStart remained cost saving in all but two scenarios.

Both analyses rely on RCT results to model the rate of healing, it is possible that real world treatment practices deviate from these and as such, wound healing may take longer, but still be expedited with use of UrgoStart.

2.8.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

Further real world data collection regarding use of the technology could provide data to show the effectiveness of UrgoStart in patients receiving wound care outside of randomised clinical trials.

References

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Clarke-Moloney, M. et al., 2012. Randomised controlled trial comparing European standard class 1 to class 2 compression stockings for ulcer recurrence and patient compliance. *International Wound Journal,* 11(4), pp. 404-8.

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Guest, J., Fuller, G. & Vowden, P., 2018. Diabetic foot ulcer management in clinical practice in the UK: cost and outcomes. *International Wound Journal,* Volume 15, pp. 43-52.

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Meaume, S. et al., 2012. A randomized, controlled, double-blind prospective trial with a Lipido-Colloid Technology-Nano-OligoSaccharide Factor wound dressing in the local management of venous leg ulcers. *Wound Repair and Regeneration ,* 20(4), pp. 500-11.

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Palfreyman, S., 2008. Assessing the impact of venous ulceration on quality of life. *Nursing Times,* 104(41), pp. 34-37.

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Appendices

2.9 Appendix 3: Search strategy for economic evidence (section 8.1.1)

The following information should be provided.

2.9.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- EconLIT
- NHS EED.

MMU Library search, which accesses Medline, Medline R in process, Embase, Science Direct, Cochrane library

2.9.2 The date on which the search was conducted.

10/04/18

2.9.3 The date span of the search.

None specified

2.9.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

(UrgoStart or TLC-NOSF or KSOS) AND ((Resource AND (Use OR Utilisation)) OR Cost)

2.9.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Urgo internal search.

2.9.6 The inclusion and exclusion criteria.

Inclusion criteria	
Population	Leg Ulcer or Diabetic Foot Ulcer
Interventions	UrgoStart
Outcomes	Economic outcomes, resource use, cost, ICER, cost per patient
Study design	Modelling, economic studies
Language restrictions	English
Search dates	No restrictions
Exclusion criteria	
Population	Paediatrics (<18), Acute wounds (including Burns, Trauma, Surgery)
Interventions	Surgical Novel non-surgical (including electrical stimulation, hyperbaric treatment, vacuum therapy) Infection control measures (including silver, iodine or honey) Debridement (including, surgical, maggot) Bioengineered skin substitutes Offloading
Outcomes	No economic outcomes reported
Study design	In vitro studies, review or discussion articles
Language restrictions	Non-English Language
Search dates	N/A

2.9.7 The data abstraction strategy.

One reviewer undertook the search, which was checked by a second reviewer.

2.10 Appendix 4: Resource identification, measurement and valuation (section 9.3.2)

The following information should be provided.

2.10.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- NHS EED
- EconLIT.

MMU Library search, which accesses Medline, Medline R in process, Embase, Science Direct, Cochrane library

2.10.2 The date on which the search was conducted.

18/04/18

2.10.3 The date span of the search.

From 1st Jan 2015 – date of search. This was to ensure data was extracted with up to date costing and resource use.

2.10.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

((TitleCombined:(COST)) OR (TitleCombined:(Economic*)) OR (TitleCombined:(resource))) AND ((Abstract:("diabetic foot ulcer")) OR ("venous leg ulcer"))

2.10.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Urgo internal search.

2.10.6 The inclusion and exclusion criteria.

Inclusion	
Population	DFU or LU only
Intervention	Management
Comparator	N/A
Outcomes	Resource use
Study	UK perspective
Date	2015 onwards
Exclusion	
Population	Acute wounds, or a mixed chronic wound population
Intervention	Prevention, diagnostic, decision making tools
Comparator	N/A
Outcomes	Not including resource use
Study	Not UK
Date	Before 1st Jan 2015.

2.10.7 The data abstraction strategy.

One reviewer undertook the search, which was checked by a second reviewer.

3 Related procedures for evidence submission

3.1 Cost models

An electronic executable version of the cost model should be submitted to NICE with the full submission.

NICE accepts executable cost models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the External Assessment Centre, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the External Assessment Centre with temporary licences for the non-standard software for the duration of the assessment. NICE reserves the right to reject cost models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model programme and the written content of the evidence submission match.

NICE may distribute the executable version of the cost model to a consultee if they request it. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The consultee will be advised that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing comments on the medical technology consultation document.

Sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. NICE may request additional information not submitted in the original submission of evidence. Any other information will be accepted at NICE's discretion.

When making a full submission, sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- a copy of the instructions for use, regulatory documentation and quality systems certificate have been submitted
- an executable electronic copy of the cost model has been submitted
- the checklist of confidential information provided by NICE has been completed and submitted.

- A PDF version of all studies (or other appropriate format for unpublished data, for example, a structured abstract) included in the submission have been submitted

3.2 Disclosure of information

To ensure that the assessment process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Medical Technologies Advisory Committee's decisions should be publicly available at the point of issuing the medical technology consultation document and medical technology guidance.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence').

When data are 'commercial in confidence' or 'academic in confidence', it is the sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

It is the responsibility of the sponsor to ensure that any confidential information in their evidence submission is clearly underlined and highlighted

correctly. NICE is assured that information marked ‘academic in confidence’ can be presented and discussed during the public part of the Medical Technologies Advisory Committee meeting. NICE is confident that such public presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as ‘academic in confidence’.

Please therefore underline all confidential information, and highlight information that is submitted under ‘commercial in confidence’ in blue and information submitted under ‘academic in confidence’ in yellow.

NICE will ask sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the External Assessment Centre and the Medical Technologies Advisory Committee. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as ‘commercial in confidence’ may be exempt under the Act. On receipt of a request for information, the NICE secretariat will make every effort to contact the designated company representative to confirm the status of any information previously deemed ‘commercial in confidence’ before making any decision on disclosure.

3.3 Equality

NICE is committed to promoting equality and eliminating unlawful discrimination, including paying particular attention to groups protected by equalities legislation. The scoping process is designed to identify groups who are relevant to the evaluation of the technology, and to reflect the diversity of the population. NICE consults on whether there are any issues relevant to equalities within the scope of the evaluation, or if there is information that could be included in the evidence presented to the Medical Technologies Advisory Committee to enable them to take account of equalities issues when developing guidance.

Evidence submitters are asked to consider whether the chosen decision problem could be impacted by NICE's responsibility in this respect, including when considering subgroups and access to recommendations that use a clinical or biological criterion.

For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).

NICE National Institute for Health and Care Excellence

Expert adviser collated comments table

MT380 UrgoStart for the treatment of leg ulcers and diabetic foot ulcers

Expert #1	Ms Gail Powell, Clinical Nurse Specialist, Wound Care Service, Bristol Community Health CIC
Expert #2	Dr Leanne Atkin, Vascular Nurse Consultant, University of Huddersfield / Mid Yorks NHS Trust
Expert #3	Mr David Russell, Consultant Vascular Surgeon and Honorary Clinical Associate Professor, Leeds Vascular Institute, Leeds General Infirmary
Expert #4	Ms Louise Mitchell, Clinical Lead Podiatrist, Birmingham Community HealthCare NHS FT
Expert #5	Dr Chris Manu, Consultant Diabetologist and Diabetes Foot Medicine, King's College Hospital NHS Foundation Trust
Expert #6	Ms Jo-anne Beresford, Wounds Clinical Nurse Specialist, Leeds Community Healthcare, Wounds Prevention and Management Service
Expert #7	Ms Sarah Gardner, Clinical Lead, Tissue Viability Service, Oxford Health NHS Foundation Trust
Expert #8	Mrs Nicci Aylward-Wotton, Tissue Viability Lead Community, Peninsula Community Health Community Interest Company

#	Question	Expert responses	
1	*Please describe your level of experience with the technology, for example:*	Expert #1:	I am familiar with the technology. I have used urgo start on a lot of patients over the last 5 years. I have managed to heal one lady who had leg ulceration for 10 years and never improved despite compression. She did take two years to completely heal. Other patients have progressed after many other treatments tried. Then Urgo start was used and progress started and many healed. Mainly venous leg ulcers in my experience. Urgostart is now called urgostart contact on our formulary.

	- *Are you familiar with the technology?* - *Have you used it?* - *Are you currently using it?* - *Have you been involved in any research or development on this technology?* - *Do you know how widely used this technology is in the NHS?*		The product was on our specials formulary but has now been moved to the generalised formulary to help the nurses access the product as it is part of our complex venous leg ulcer pathway I have written an article many years ago on urgo start which was published. Podiatry have started using Urgostart plus for the diabetic foot as an evaluation over the last 3 months.
		Expert #2:	This technology is relevant to my area of practice of expertise. I have had direct involvement with its use and I have treated patients with this technology and this dressing is currently available to patients attending my clinics. It is likely to be used in non healing ulceration - especially venous leg ulcerations which are 'stuck' in the inflammatory stage of healing. I was involved in a Delphi study exploring the role of NOSF in chronic wounds but I have not been part of any of the clinical research or development of the dressing. The technology is used in pockets throughout the UK with Urgo start being on a number of wound care formularies – it is not though used in every NHS organisation
		Expert #3:	I am familiar with the technology and our unit currently uses UrgoStart products as part of the clinical management pathway for hard-to-heal venous leg ulcers, and to a lesser extent in diabetic foot ulcers. We performed an evaluation in 24 patients with hard-to-heal diabetic foot ulcers, of which 78.5% with a SINBAD score <3, indicating a lower severity of ulceration, achieved healing within 12 weeks and 50% with a SINBAD score of ≥3 achieved healing at 12 weeks (previous mean ulcer duration 27 weeks). I am aware of the product being integrated into leg ulcer pathways, in particular hard-to-heal community venous leg ulcer pathways, across the UK.
		Expert #4:	As a Clinical lead podiatrist specialising in Diabetic Foot Disease, I work across both primary & secondary care settings. My work involves providing podiatry input for active foot problems such as diabetic foot ulceration, acute & chronic in presentation. I am familiar with the Urgostart dressings and have been using the products within clinic since 2015. The product is currently a wound formulary item. I have been involved with the evaluation of this product. I am not aware how widely used this technology is in the NHS.

		Expert #5:	I have been involved as a sub-investigator in the use of the product in a double blinded RCT with regards to the use of the technology in diabetic foot ulceration. I am aware of its use in leg ulceration.
		Expert #6:	Yes I am familiar with the technology. I have used it on a few occasions. It is not being currently used on the patients I am treating. It is not currently on our dressing choice list (local formulary). But as a specialist I would be able to apply to prescribe when required following an assessment. No I have not been involved in any research or development on this technology. I know that it is used in the NHS. It is not currently widely used in Leeds Community Healthcare
		Expert #7:	This is a technology which is relevant to my area or practice or expertise. I have had direct involvement with its use. I have referred patients for its use. I have been involved in clinical case studies of this technology. When a wound fails to progress in a timely way it can be associated with elevated matrix metalloproteinases (MMPs) that keep the wound in an inflammatory status. For example - A leg ulcer (Chronic wound) that is not healing as expected or has become static. This technology/ dressing inhibits the production of these proteases thus allowing progression in to the proliferation stage of healing. For the same reasons, this technology can be used as part of a treatment pathway (for example a complex venous leg ulcer pathway) for ulcers that remain unhealed after 6 months. The technology/ dressing can be used on other Inflammatory/ static chronic wounds not associated with infection - for example non healing pressure ulcers, surgical wounds and diabetic foot ulcers.
		Expert #8:	Yes familiar with technology The team are in the process of evaluating but haven't done so myself We haven't been involved in any of the research and development It is currently being used in our acute unit
2	*Has the technology been superseded or replaced?*	Expert #1:	Only that the name has changed to urgotul contact and there is now urgostart plus border and urgostart plus which is without the border available. These are now on our specialist formulary. With these plus products they can be applied to sloughy wounds as before with urgotul contact the wound had to be at least 70% granulation.

		Expert #2:	No Urgo start has superseded Promogram
		Expert #3:	No.
		Expert #4:	Not to my knowledge
		Expert #5:	No
		Expert #6:	No
		Expert #7:	No.
		Expert #8:	no
3	*How innovative is this technology, compared to the current standard of care? Is it a minor variation or a novel concept/design?*	Expert #1:	With venous leg ulcers I feel it does progress wound healing when compression alone hasn't worked.
		Expert #2:	The technology is a minor variation on existing technologies, however it does target an area of growing academic reasons for non healing – that being raised MMP – so the technology may have the potential to impact wound outcomes.
		Expert #3:	The active TLC-NOSF component of the product is novel, with the target (MMP modulation) being a variation on other products on the market (Promogran).
		Expert #4:	The product is very innovative.
		Expert #5:	It is an innovative technology compared with current standard wound care and the design of the technology is a novel concept.
		Expert #6:	Current practice is Atrauman (7.5 x 10cm = 0.35p) as a contact dressing with compression therapy for a venous leg ulcer. Compared to Urgostart contact (5 x 7cm = £3.03 FP10 price). It would not be a minor variation in practice relating to the product cost. It is an innovative product compared to current practice.

		Expert #7:	This technology is thoroughly novel- different in concept and/or design to any existing technology.
		Expert #8:	Similar to other products
4	*Are you aware of any other competing or alternative technologies available to the NHS which have a similar function/mode of action to the notified technology?* *If so, how do these products differ from the technology described in the briefing?*	Expert #1:	Promogran – the local rep is trying to get this product evaluated but we have to stick to what our formulary group wants to evaluate. Promogran has been around for many years and I used this product about 15 years ago with limited success at the time. It however may have been changed since.
		Expert #2:	Promogran. Urgo start is on a different 'vehicle' compared to the above – so promogran dissolves into the wound and always requires a secondary dressing which does increase the cost, whereas, Urgo start comes in a form where no secondary dressing is required therefore could reduce cost, number of prescriptions needed and reduce storage space.
		Expert #3:	Other dressings design to modulate protease activity include: By absorbance - Cadesorb (Smith & Nephew), Helisorb (Medira), Kerramax Cure (Crawford Healthcare), Suprasorb (Activa Healthcare), Xtrasorb (Derma Sciences); by MMP modulation - Promogran (Systagenix).
		Expert #4:	Yes Promogran It inhibits proteases and protects growth factors. It is absorbed by the wound.
		Expert #5:	No
		Expert #6:	Yes. Promogran Promgran can be used in higher exuding wounds. UrgoStart is suitable for low to moderate exudate levels. Promogran, is intended to be used only after the wound has been tested to identify raised protease activity (as seen in Briefing 82, 2017). This is at an additional cost and unsure whether this product is still available to purchase. The Systagenix website currently does not state this is required to use Promogran.
		Expert #7:	Promogran - although this is a protease modulator not a protease inhibitor.
		Expert #8:	Promogram. Im not sure it does differ

5	*What do you consider to be the potential benefits to patients from using this technology?*	Expert #1:	Cost. It would encourage nurses not to change the bandages too often. Weekly is usually all that most patients need. It can be used under compression Hosiery as a stand-alone foam dressing.
		Expert #2:	Potential for increased healing in hard to heal wounds. This benefit might be measured by improved time to healing - less patient suffering - less impact on QoL. The evidence for this is poor low level evidence. There are many others factors that influence wound healing - MMPs are only a small obstacle in the whole picture.
		Expert #3:	Improved healing rates and quicker time to healing in hard to heal wounds; reduced frequency of dressings changes compared to standard dressings; possibly reduced pain; reduced incidence of infective episodes (including risk of hospitalisation and amputation) should healing occur more quickly.
		Expert #4:	I have experienced faster healing when using this product compared to other dressings. For my patient population (high risk) this reduces the risk of infection and potential amputation. Quality of Life is improved with faster wound healing.
		Expert #5:	Expect patients to have a quicker ulcer healing if this technology is added to optimum standard of care. The shorter duration of ulceration period would also mean a decrease in the risk of infection, decrease in risk of hospital admissions and a decrease in the risk of minor and major amputations associated with diabetic foot ulcerations
		Expert #6:	According to evidence improved healing times.
		Expert #7:	Patients will have improved healing rates and therefore will experience a reduction in the symptoms or consequences that are associated with having a chronic wound. These include pain, odour, immobility, a poor quality of life, low mood etc. There is a reasonable amount of evidence out there relating to chronic wounds and quality of life, wound pain and quality of life and using wound measurement as an indicator of healing progression. Many of the patients that i choose to use this technology on have had their wounds (often leg ulcers) for many years and have often lost hope of ever healing. This dressing offers a chance to progress to healing.
		Expert #8:	Reduction in healing time. Reduction in DN/TVN visits
6	*Are there any groups of people who would particularly benefit from this technology?*	Expert #1:	Patients with chronic wounds.
		Expert #2:	Yes those with known ‘chronic’ wounds such as pressure ulcers, diabetic foot ulcers and venous leg ulcers.

		Expert #3:	Evidence suggests that this technology may particularly help those with non-healing venous and diabetic foot ulcers.
		Expert #4:	My experience is only with patients with diabetes suffering with diabetic foot ulceration – chronic wound.
		Expert #5:	People at risk of chronic wounds, such as those with diabetic foot ulceration or leg ulcers. Especially patient with diabetes as most of these patients have neuroischaemic ulcers and are more likely to have prolonged duration of ulceration despite
		Expert #6:	Venous leg ulcers Mixed aetiology and arterial leg ulcers Chronic surgical wounds Diabetic foot ulcers Patients who have comorbidities.
		Expert #7:	I don't think there are specific groups of people as it should be considered for those whose wounds are failing to demonstrate progress at re assessment (e.g. at 4-6 weeks. Maybe those groups who are more vulnerable in terms of healing risk such as diabetics?
		Expert #8:	All chronic wounds
7	*Does this technology have the potential to change the current pathway or clinical outcomes? Could it lead, for example, to improved outcomes, fewer hospital visits or less invasive treatment?*	Expert #1:	Reduced dressing changes, Less nurse contact. Reduced healing times. More cost effective.
		Expert #2:	If the technology is shown to improve healing then it may influence the number of referrals, changing pathways and reducing patients suffering. However, must referrals are due to unclear diagnosis or the need to treat the underlying cause not solely related to wound bed preparation to it is unlikely to influence the number of referrals into secondary centres.

		Expert #3:	This is a technology which is simple to use, and does not carry any additional burden to the patient, meaning it is likely to be accepted into clinical practice. The provisional Explorer trial results, in addition to the earlier published results of UrgoStart evaluations, suggest that use of the technology in ulcers that are failing to otherwise achieve a healing trajectory at 4 weeks with optimal standard care, may lead to improved healing rates, reduced nursing visits, and if reduced healing rates are realised then reduction in associated hospitalisation for infection (and potential for reduction in minor amputations).
		Expert #4:	Definitely improved outcomes for my patient group; reduced risk of infection, reduced risk of amputation and decrease risk of mortality. With the wound healed faster, less appointments will be needed.
		Expert #5:	Yes this technology has the potential to improve clinical outcome of patients with chronic ulcerations. The potential to heal ulcers quicker should confer better outcomes such as decrease in minor and major amputations as well as fewer hospital visits.
		Expert #6:	Yes. Improved healing rates = reduced community specialist leg ulcer clinic, practice nurse and district nurse appointments/visits. Improved healing also reduces patient's risk of infection.
		Expert #7:	Yes, but there needs to be the measures in place to prove this. Time to undertake wound measurement may be an obstacle in some clinical areas, although this shouldn't be time consuming. Quality of life measures are not routinely used in clinical areas therefore may be seen as additional 'paperwork'.
		Expert #8:	Yes it could lead to improved outcomes if it works. However there needs to be a screening tool to ensure it is used on the right paitents otherwise it will be used on everyone.
8	*What do you consider to be the potential benefits to the health or care system from using this technology?*	Expert #1:	As above
		Expert #2:	Same benefits as above.

		Expert #3:	If improvements in reduction in wound area, and rate of wound healing translate into improved numbers of wounds healing, then there would be both an economic and HRQoL benefit to the use of UrgoStart.
		Expert #4:	Cost savings – if wounds heal faster less appointments are needed, therefore less clinician time, fewer dressings required. Recuperation of appointments. Cost saving in relation to wound healing (faster healing times), amputation avoidance.
		Expert #5:	The care system stands to benefit from the use of this technology. As the ability to heal ulcers quicker would mean cost savings on treatment of chronic wounds, reduction in hospital admissions, antibiotic cost etc…
		Expert #6:	Improved healing rates.
		Expert #7:	Non healing/ chronic wounds impact significantly on the healthcare system in terms of clinical time (clinic time, nursing resources), dressings costs, drugs (antibiotics analgesia etc) and hospital admissions. Improving the healing rates of wounds will reduce the demand on clinical time (patients discharged more quickly) and reduce costs in terms of dressings and hospital admissions. Baseline measurement in terms of wound duration followed by an ongoing measurement of healing rates (time to heal) on a 4 - 6 weekly basis after the technology/ dressing is commenced. This would demonstrate the effectiveness of the dressing on healing rates. Clinical audit of wounds - comparing numbers of patients/ wounds month by month. A reduction in numbers would indicate improvements in healing rates. Audit of clinical time spent on wound management - comparison month on month. A reduction in time spent on wound care would indicate Improvements in healing outcomes. Spend on dressings month on month (prescribing data). A reduction in spend would indicate improvements in wound healing. Although not directly aimed at measuring the impact on nursing/ clinical time or dressings spend, the RCTs undertaken on this technology would certainly help argue the benefits for including it within local formularies. The evidence that indicates improvements in healing rates would have a direct effect on both clinical/ nursing resources and formulary spend. This research should be considered seriously. Evidence from Guest et al, 2015 re burden of non healing wounds in the UK
		Expert #8:	Reduction in nurse visits, reduction in hospital visits, reduction in prescribing costs

9	*Considering the care pathway as a whole, including initial capital and possible future costs avoided, is the technology likely to cost more or less than current standard care, or about the same?*	Expert #1:	Nurses worry about using the product as it costs more in some instances depending on size of the dressing. However if it reduces the time to healing then this can only lead to better use of resources. I wish more nurses would access the product. (We have now put this on the generalist formulary to encourage use).
		Expert #2:	Similar price to other dressings which claim to reduce MMP levels - much more expensive that simple dressings. This technology has the potential to cost more per unit BUT the majority of costs of wound care are not related to the product but the staff/visits needed – therefore if this can reduce time to healing it could be cost effective.
		Expert #3:	If improved wound reduction at 8-12 weeks translates into earlier healing rates (and the Explorer results suggest this does), then overall costs for use of the technology are likely to be less than for persisting with standard care in ulcers that are not achieving a wound healing trajectory. The obstacle would be persuading health care providers to accept an increase in cost of treatment up front, for a longer term cost saving.
		Expert #4:	Less.
		Expert #5:	Overall, I would expect the technology cost less than the current standard of care. If the technology is used correctly and promptly in addition to optimum standard of care then it should cost less for the clinical pathway.
		Expert #6:	There would be an increase in cost: Current practice is Atrauman (7.5 x 10cm = 0.35p) as a contact dressing with compression therapy for a venous leg ulcer. Compared to Urgostart contact (5 x 7cm = £3.03 FP10 price). Example: simple venous leg ulcer healed at 18 weeks with twice weekly dressing change with Arauman = £12.60 (compression therapy would be additional). UrgoStart = £109.08 (compression therapy would be additional). However this cost could be reduced if the healing time is proven to be reduced.
		Expert #7:	The cost of the technology (dressing) is not significantly more than a standard wound dressing and needs to be weighed up against the cost of having a non healing wound being treated with products that are not assisting healing. Although marginally more expensive i would suggest that it is cost effective as more patients heal more quickly negating the need for lengthy treatment.

		Expert #8:	The initial outlay will be more. The cost savings predicted have not been broken down, the savings will impact all budgets if works. The initial increase in costs will be on the prescribing budget however if it works this could be reduced in the long term.
10	*What do you consider to be the resource impact from adopting this technology?* *Could it, for example, change the number or type of staff needed, the need for other equipment, or effect a shift in the care setting such as from inpatient to outpatient, or secondary to primary care?*	Expert #1:	I haven't really noticed an increase in dressing costs. Each PN and DN team have their own budget and are managing to do that most of the time. Anybody can apply once shown, even patients themselves.
		Expert #2:	If this technology was adopted it would not impact on the current resources, as it is just another type of dressing – it has the potential to positively impact resources if proven to heal patient quicker. If this technology is adopted there would need to be education of where it should be used and how it should be involved in clinical pathways.
		Expert #3:	Targeted adoption of this technology may allow shift of care from secondary to primary care, and a reduction in inpatient care episodes. If earlier healing was achieved then this may also lead to a reduction in the community care wound management case load.
		Expert #4:	N/a as this is a dressing that would be part of the current standard of wound care given. Wounds need to be covered by a dressing.
		Expert #5:	If adopted and used correctly it has the potential to shift patients from the inpatient to outpatient. As the longer chronic wounds remain open then the higher the risk of them getting infected and needing inpatient antibiotic treatment or debridement. The ability to get ulcers healed quicker would also imply that more ulcerations will heal within primary care hence decreasing the number that need secondary care for non-healing.
		Expert #6:	I don't consider there to be a resource impact on adopting this technology.
		Expert #7:	If anything, the resource impact in terms of nursing time should reduce as wounds improve. There would not be a need for additional resource to use the technology, technology can be used in any clinical setting.
		Expert #8:	The main impact will be a reduction in DN visits and a reduction in prescribing costs, possible bed days.
11	*Are any changes to facilities or infrastructure, or any specific*	Expert #1:	No it's really easy to use.
		Expert #2:	No changes in infrastructure. The only training needed would be in its appropriate use.

	training needed in order to use the technology?	Expert #3:	No.
		Expert #4:	No
		Expert #5:	No
		Expert #6:	There would need to be a change in local wound care policy/guidelines and wound care formularies across organisation. Community nurses would require education on when to apply the product and the length of time for the product to be used to prevent misuse.
		Expert #7:	I would say that to ensure effective use of this technology it is best used as part of a locally agreed evidence based treatment pathway with a clear criteria for inclusion. There needs to be local education relating to the use of this technology in order for it to be used correctly. Clinicians or prescribers need to understand the indications for use and the mode of action of the product. It is not a panacea for healing and there are wounds where it is not indicated. This should be clearly set out in locally agreed guidelines.
		Expert #8:	Yes to ensure it is used on appropriate patient
12	*Are you aware of any safety concerns or regulatory issues surrounding this technology?*	Expert #1:	No
		Expert #2:	None
		Expert #3:	No.
		Expert #4:	No.
		Expert #5:	No
		Expert #6:	No
		Expert #7:	No
		Expert #8:	no
13	*Please add any further comments on your particular experiences or knowledge of the technology, or experiences within your organisation.*	Expert #1:	Blank
		Expert #2:	There is some controversy about the whole MMP debate - do certain dressings reduce this - is a reduction linked to improved clinical outcomes. There are also issues with the current technology for detection of MMP as the test costs more than the initial 2 weeks treatment, so why not treat and revaluation rather than test? – there is also clinical concern that the technology for testing is not sensitive or specific enough.

		Expert #3:	Given the cost of the technology, and the active TLC-NOSF component, UrgoStart should not be included with standard foam dressings in wound management pathways. It has been established that wounds that fail to reduce in area by >50% in the first 4 weeks of specialist management are less likely to heal at 12,16 and 24 weeks. These wounds need to be identified, and if standard care (off-loading, compression) is thought to be optimal then adjuvant therapies should be considered at that time point. The provisional results of the Explorer study, mirrored by our clinical experience, would support UrgoStart being considered as an adjuvant therapy at 4 weeks, rather than being included as a foam dressing on formulary which may also be used on ulcers which would heal with simple dressings. Trials in wound healing are recognised to be of low quality, with reduction in wound healing at a 12 week endpoint being standard in most studies of diabetic foot ulcers.
		Expert #4:	From experience the impact of the dressing (technology) is often seen the greatest within the first 2-3 weeks of application.
		Expert #5:	It is important that patients on whom the technology is used continue to receive optimum standard of wound care, be it adequate off-loading, treatment of infection, regular sharp debridement o wound when applicable etc…. The full benefit of this technology would be better appreciated if it is added onto adequate standard of care and not seen as a treatment in isolation.
		Expert #6:	No comment
		Expert #7:	In my clinical area it is used as part of a complex leg ulcer pathway so within very clear inclusion criteria. Previous to the pathway being developed, the cost of the product was questioned by some GPs and in some cases would not be prescribed, having the pathway in place has resolved this problem.
		Expert #8:	I do have concerns that it could be over used without the proper screening to ensure it is used on the right patient who are predicted to have a positive result, this needs to be investigated further and not a blanket approach
14	*Approximately how many people each year would be eligible for intervention with this technology, either as an estimated number, or a proportion of the target population ?*	Expert #1:	Unsure
		Expert #2:	Well that depends on where the evidence states it should sit on the clinical pathway – is this for all wounds or just stalled wounds? It is impossible to estimate how many patients per year – there are currently 730,000 with an active leg ulcer in the UK – so the numbers could be massive.

		Expert #3:	Approximately 25% of patients have diabetic foot ulcers which become hard-to-heal and therefore eligible for this technology.
		Expert #4:	Estimated numbers would be in the region of 150-200 patients as a collective across both primary & secondary care within my field of work.
		Expert #5:	2 to 2.5% of patient with diabetes do have an active foot ulceration, and about 30 to 40% of then remain active or non-healing at 12weeks of follow-up (as per data from National Diabetes Foot Care Audit – NDFA).
		Expert #6:	Sorry I have not got this information but according to Guest el al (2017) 2012/13 the NHS was managing 2.2 million people with a wound. Not all these wounds would be complex or have delayed healing.
		Expert #7:	Unsure
		Expert #8:	Potentially 1-3% of the population
15	*Would this technology replace or be an addition to the current standard of care?*	Expert #1:	An addition
		Expert #2:	In my service this has replaced the use of promogran
		Expert #3:	This technology would be an addition to current standard of care, although it is already being used in this capacity for hard-to-heal ulcers in some healthcare pathways.
		Expert #4:	Addition as it would not necessarily be suitable for all patients.
		Expert #5:	It would be expected to be an addition to current standard of care, but it would also be expected to decrease the duration of that standard of care.
		Expert #6:	It would be additional with specific instructions when to use and how long to prevent misuse. More likely to be under specialist instruction at present.
		Expert #7:	Addition
		Expert #8:	Not sure yet
16		Expert #1:	No
		Expert #2:	No easy to use – highly patient acceptance – no reports of pain

	Are there any issues with the usability or practical aspects of the technology?	Expert #3:	No.
		Expert #4:	No
		Expert #5:	No
		Expert #6:	No
		Expert #7:	NO
		Expert #8:	no
17	*Are you aware of any issues which would prevent (or have prevented) this technology being adopted in your organisation or across the wider NHS?*	Expert #1:	No
		Expert #2:	No – this has recently been added to local formulary, on the basis that it does cost more but could aid healing of chronic wounds therefore being cost effective.
		Expert #3:	No.
		Expert #4:	Dressing costs when compared to other advanced/non-advanced dressings
		Expert #5:	The luck of support form NICE recommendation, and the availability of possible cost savings and RCT results which may now become available for review
		Expert #6:	Ensuring that the clinical evidence is robust and valid as the cost is greater for the product then current practice.
		Expert #7:	There needs to be a good understanding of the technology in order for it to be used correctly. Poor knowledge and skills re indications for use, mode of action etc may be an obstacle.
		Expert #8:	The initial cost and the quality of the research available and cost analysis and whose budget it effects.
18	*Are you aware of any further evidence for the technology that is not included in this briefing?*	Expert #1:	No
		Expert #2:	The explorer trail is now published in the Lancet.

		Expert #3:	Full details from the Explorer trial are awaited.
		Expert #4:	Yes
		Expert #5:	The full analysis of the “Explorer RCT Study” on the diabetic foot ulceration are in progress
		Expert #6:	Sucrose octasulfate dressing versus control dressing in patients with neuroischaemic diabetic foot ulcers (Explorer): an international, multicentre, double-blind, randomised, controlled trial. The Lancet; 2018 Mar;6(3):186-196. doi: 10.1016/S2213-8587(17)30438-2. Epub 2017 Dec 20. Edmonds M1 et al
		Expert #7:	No
		Expert #8:	The best patients and wounds to use it on to ensure there is not a blanket approach or a last chance approach
19	*Are you aware of any further ongoing research or locally collected data (e.g. audit) on this technology?* *Please indicate if you would be able/willing to share this data with NICE. Any information you provide will be considered in confidence within the NICE process and will not be shared or published.*	Expert #1:	No
		Expert #2:	Only the challenger study which you referred to.
		Expert #3:	No.
		Expert #4:	Yes – The Explorer study
		Expert #5:	No
		Expert #6:	No
		Expert #7:	No
		Expert #8:	We are trying to develop a screen tool and evaluate
20	*Is there any research that you feel would be needed to address uncertainties in the evidence base?*	Expert #1:	No
		Expert #2:	It would be beneficial if we had a point of contact test for MMP levels which was reliable in clinical practice.
		Expert #3:	Randomised trials to wound healing in venous (and pressure) ulcers would be beneficial. Associated health related quality of life and economic data alongside clinical outcomes from these trials (including the Explorer study) would also be useful.
		Expert #4:	Not that I am aware of.

		Expert #5:	No
		Expert #6:	Yes. Independent studies that have not been supported or funded by Urgo. Use of UrgoStart with compression therapy for venous leg ulceration compared to using a non-adherent dressing (Atruaman). Also evidence to support using in arterial and mixed aetiology leg ulcers. Interesting to know the past medical history of the patients included in the current research, as patients are complex with multiple long term conditions.
		Expert #7:	No
		Expert #8:	A sound health economic cost analysis
21	*How useful would NICE guidance on this particular technology be to you or other NHS colleagues?*	Expert #1:	Clarification and all the evidence in one document which is really helpful when making informed decisions around care.
		Expert #2:	It would help practitioners make appropriate decisions whether the dressing is of value and worth the cost. It would impact the wider formulary group decisions.
		Expert #3:	Guidance would be useful in supporting (or otherwise) use in clinical practice.
		Expert #4:	Yes definitely
		Expert #5:	Current data shows very promising outcomes and results and it would be beneficial to incorporate the technology into wound care pathways across the NHS for patients benefit and cost savings to be made.
		Expert #6:	Yes guidance would be useful.
		Expert #7:	It would be very useful. In some clinical areas, treatment modalities can be questioned due to it not having a NICE recommendation against it. NICE is seen as 'Gold Standard'. The guidance would complement the education delivered locally and support compliance with the treatment pathway in place.
		Expert #8:	It helps when discussing with prescribing provided there is enough evidence and its not biased

National Institute for Health and Care Excellence

External Assessment Centre correspondence

MT380 UrgoStart for treating leg ulcers and diabetic foot ulcers

The purpose of this table is to show where the External Assessment Centre relied in their assessment of the topic on information or evidence not included in the sponsors' original submission. This is normally where the External Assessment Centre:

a) become aware of additional relevant evidence not submitted by the sponsor
b) need to check "real world" assumptions with NICE's expert advisers, or
c) need to ask the sponsor for additional information or data not included in the original submission, or
d) need to correspond with an organisation or individual outside of NICE

These events are recorded in the table to ensure that all information relevant to the assessment of the topic is made available to MTAC. The table is presented to MTAC in the Assessment Report Overview, and is made available at public consultation.

Submission Document Section/Sub-section number	Question / Request *Please indicate who was contacted. If an Expert Adviser, only include significant correspondence and include clinical area of expertise.*	Response *Attach additional documents provided in response as Appendices and reference in relevant cells below.*
Clinical section	**Initial questions sent to manufacturer 12.04.18** **1.** Can you explain the origin of the included studies i.e. in which database were they found? For example, Edmonds et al 2018 was published after the search date so presumably it came from Urgo's internal database – is this the case for other included studies? **2.** Can you provide a rationale for the date limits used (1997 to 7th Oct 2017)? **3.** Can you explain how the Science Direct database was searched i.e. which limits were applied? The search string returns a very high number of records (~2,400), more than reported in the PRISMA flow diagram.	**Responses received from manufacturer during the TC 16.04.18 and afterwards on 24.04.18 (see appendix 1a, 1b)** **1.** During the search Urgo was aware of the draft Edmonds copy therefore this was included. **2.** In wound care there were very few studies of good quality on advanced dressing before the year 1997. The 20-year range was considered in an attempt to capture evidence related to the field of wound care management rather than the intervention itself. SD asked why the end point was October 2017. IO answered that this was the original strategy for submission in September but it ended up delayed. **3/4.** *Minutes*: BD noted that NICE is interested only in the publications related to UrgoStart. Urgo agreed to provide KiTEC with search strategy details. *Afterwards (as amendment to minutes):* This search was completed in October 2017; using the advanced search option in Science direct, restricting to titles and abstracts. No error message was received from NICE evidence search and results were returned. For maximum transparency, please see the .ris export files, and the xls export sheet used to select the studies.

	4. Can you explain how the NICE Evidence Search was searched? The search string given is too long for the platform.	
	5. Was the CRD database (PROSPERO) searched in order to find ongoing systematic reviews and were any found?	**5.** *Minutes*: Urgo did search CRD database. *Afterwards (as amendment to minutes):* No results directly pertaining to UrgoStart on CRD were included.
	6. Were any other sources of adverse events consulted e.g. FDA MAUDE or MHRA?	**6.** *Minutes*: No, Urgo assumed they were out of scope. Only Cochrane reports were searched. *Afterwards (as amendment to minutes):* The cases reported have all come from the field - it is the information that is transmitted by the users (health care professionals, patients, hospitals etc.) to the company = materiovigilance reports (real life data)
	7. Can you please explain why you included in the submitted evidence 2 studies that used Promogran as the intervention? Is Promogram and Urgostart the same device using different names?	**7.** *Minutes:* IO updated that Promogran was mentioned only for the purposes of transparency that this particular product exists. GA updated that Promogran is a product made by different manufacturer having different mode of actions and different clinical outcomes, however it is very often included in the same group that UrgoStart - protease modulating dressing. Urgo run a comparative study against them that was included for completeness. AC added that the study on Promogran as an intervention by Vin et al. and Verves et al. did not include UrgoStart. *Afterwards (as amendment to minutes):* Please discard these studies.
	8. Can you please provide more details for the PRO study abstract? Did the authors use UrgoStart to treat these	**8.** IO said that utilities were being sourced for the cost utility Markov model (for the economic submission). MK raised the issue that cost consequences methodology was the preferred method for Medical Technologies programme. BD confirmed that this was discussed with Urgo at the

	patients? Is there a protocol for this study?	scoping meeting, cost-utility analysis is fine however for a positive recommendation for MTG the technology must be shown to be cost-saving. Urgo is confident that the technology is cost saving. The wound heals much sooner and the cost of the product is not much different than other technologies. KiTEC agreed that cost-utility analysis is fine for the submission as long as KiTEC could disaggregate the costs and outcomes, to estimate cost-savings. Urgo agreed to provide KiTEC with Utility Scores from the clinical trials (full results)
	9. Have all the submitted studies used the same version of UrgoStart? If not can you provide more details about the different versions?	**9.** GA confirmed that there are 5 different versions of the product available on market, all contain *TLC-NOSF* technology. Clinicians choose to use them depending on the type of wound. (See answers in Q11).
	10. In table B1 where you list your inclusion criteria you have listed as the intervention 'Protease Matrix Modulating Dressings'. Can you please explain why you used this general term rather than the one listed in the final scope 'UrgoStart dressing formats which contain the TLC-NOSF technology'?	**10.** GA updated that this was a broader category that UrgoStart falls into, however not all protease dressings are the same as they are different in their mode of action and outcomes. The reason for referring to this search term is that even though UrgoStart classifies under this category, it is very different from others.
	11. Can you please provide more information for the following technologies that you listed in your submission? a. UrgoStart contact layer 08/2006, b. UrgoStart Non Adhesive Foam 02/2009, c. UrgoStart Foam Border 04/2014, UrgoStart Plus pad 05/2014,	**11.** a. *UrgoStart contact layer 08/2006* – very conformable, used for cavity wounds, in any difficult-to-dress locations, you can cut it to fit the size of the wound; b. *UrgoStart Non Adhesive Foam 02/2009* – there is the same TLC NOSF matrix but with a foam backing, you can use it in wounds with more moisture where the foam backing will absorb it; c. *UrgoStart Foam Border 04/2014* – it has an adhesive border and the foam is able to absorb more exudate than the non-adhesive version; d. *UrgoStart Plus pad 05/2014* - polyabsorbant fibres cleaning wounds (pad version) in addition to TLC NOSF;

	d. UrgoStart Plus border 08/2016 Are they all currently available for purchase? Is there any of them currently obsolete? What are their main differences?	e. *UrgoStart Plus border 08/2016* – bordered version of the above;

	Minutes of TC sent to manufacturer 23.04.18 (see appendix 1a)	**Response from manufacturer 24.04.18 (see below and appendix 1b and appendix 2a)** Please see the comments from Urgo in the attached document. These are in bold text highlighted yellow. The search string was used in Science direct's advanced search which used to allow restriction by title and abstract for the terms- however I've just looked and this page has been updated since last October. Perhaps this is causing the discrepancy? In order to ensure transparency, I have attached here a zip file containing the .ris files that were exported from the databases into EndNote, and then the xls file that was created in order to allow inclusion/exclusion. You may notice that the .ris files were originally exported on the 09/10/17- this is when I first ran the search and exported the titles to EndNote; this was repeated on the 17/10/18 just before I exported the endnote file to Excel (checking for new titles; but none added, and thus the original .ris files are used). Please also find attached the health state utility scores that have been derived from the Explorer study.

<table>
<tr>
<td>Clinical evidence section</td>
<td>E-mail sent to manufacturer 27.04.18

We were wondering if you could provide us with a protocol for the PRO study as this is the only thing we seem to be missing?

Response sent to manufacturer 30.04.18:

Regarding your query, we presume that the increment refers to the difference in costs between X and Y. The absolute increment appears to ask for absolute value, which is simply the number as a positive value whether it is positive or negative. The absolute difference in technology cost is divided by the absolute difference in total cost to generate a percentage. The value of such a percentage in terms of decision making is limited.</td>
<td>Response from manufacturer 29.04.18 (see below and appendix 2b)

Please find attached the study synopsis/protocol and the questionnaire pack that was used in data collection.

Additionally, I was hoping you could clarify an element of the Section C submission for us; specifically Table C12. Can you please explain what is required in the ‘Increment’ and ‘Absolute Increment’ columns; is one to be presented as a percentage and the other in £? Table shown below:

<table>
<tr><th>Item</th><th>Cost intervention (X)</th><th>Cost comparator (Y)</th><th>Increment</th><th>Absolute increment</th><th>% absolute increment</th></tr>
<tr><td>Technology cost</td><td>Xtech</td><td>Ytech</td><td>Xtech – Ytech</td><td>|Xtech – Ytech|</td><td>|Xtech – Ytech|/ (Total absolute increment)</td></tr>
<tr><td>Total</td><td>XTotal</td><td>YTotal</td><td>XTotal – YTotal</td><td>Total absolute increment</td><td>100%</td></tr>
</table>
</td>
</tr>
</table>

Economic and clinical section	**Additional questions to manufacturer – 16.05.18** Following economic evidence submission, your input on the below points would be much appreciated: 1. There are a number of unpublished studies cited as evidence in the submission in table 2 C2. Summary list of all evaluations involving costs. Would you be able to forward these studies to us? 2. Can you please provide a clear description of the derivation of the dressing costs for UrgoStart and the comparator neutral dressing for both leg ulcers and diabetic foot ulcers? Can you also advise on what size dressing was assumed and what product you costed as the comparator neutral dressing? 3. We have noticed some typos in table 6 C5a Summary of variables applied in the DFU cost model (Base Case) - errors in the source column. Could you send us a revised table? 4. Finally, can you confirm that the resource use stated in the table	**Response from manufacturer – 17.05.18 (see appendix 2c)** 1. Unpublished studies; these are not yet written into manuscripts, however this work is underway and we can forward drafts as soon as they are available. I've attached the Excel files for the two budget impact models, the presentation summary for the two French cost utility models and the report from the commercial-in-confidence study that is not intended for publication. Please let me know if there is a problem with the attachments and I can forward them using WeTransfer. 2. The prices are for UrgoStart Contact 10x10, and (UrgoTul Contact Layer) 10x10. Prices are Drug Tariff prices. UrgoTul Contact Layer was used as comparator as this was the comparator in the Explorer 2018 study. 3. I have corrected these typos, updated in the attached Section C, v6.2 4. Yes, resource use is per week. Also updated in the v6.2

straddling P48-49 for leg ulcers is per week and not annual as stated?

And on clinical evidence:

5. Can we check if the studies submitted for the clinical evidence were conducted in a secondary setting? If that isn't the case, can you provide this information for each study included?

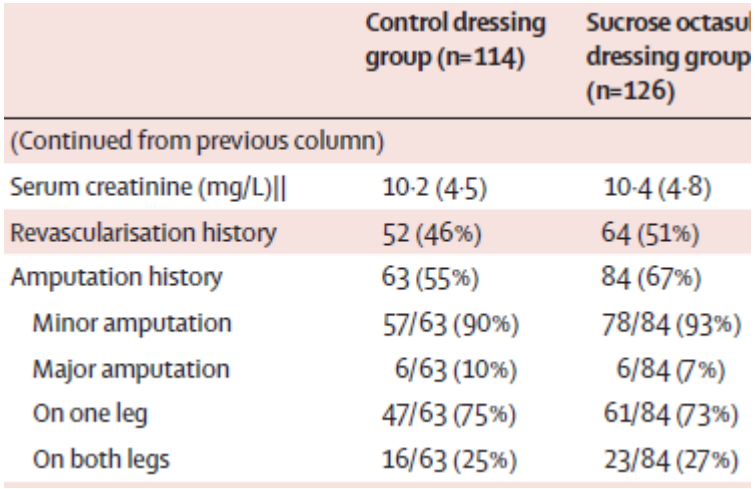
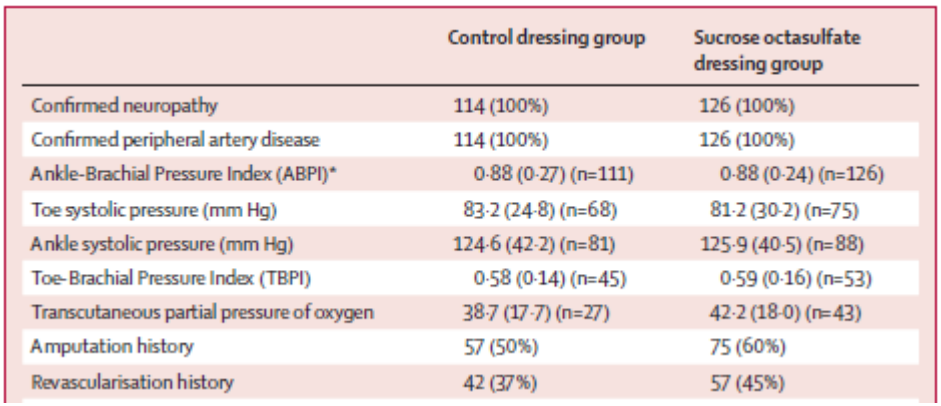
5. The studies included in the analysis were carried out in the following settings. I've not listed the Promogran studies, as per a previous TC these are not within scope.

Study		Setting
Meaume et al, 2012	A randomized, controlled, double-blind prospective trial with a Lipido-Colloid Technology-Nano-OligoSaccharide Factor wound dressing in the local management of venous leg ulcers	Secondary, majority hospital very few community setting.
Schmutz et al, 2008	Evaluation of the nano-oligosaccharide factor lipido-colloid matrix in the local management of venous leg ulcers: results of a randomised, controlled trial	Secondary, hospitals
Edmonds et al, 2018	Sucrose octasulfate dressing versus control dressing in patients with neuroischaemic diabetic foot ulcers (Explorer): an international, multicentre, double blind, randomised, controlled trial.	Secondary, majority hospital very few community setting.
Meaume et al, 2017	Quality of life in patients with leg ulcers: results from CHALLENGE, a double-blind randomised controlled trial	Secondary (same as Meaume 2012)
Richard et al, 2012	Management of diabetic foot ulcers with a TLC-NOSF wound dressing	Secondary, only in hospitals
Münter et al, 2017	The reality of routine practice: a pooled data analysis on chronic wounds treated with TLC-NOSF wound dressings	Secondary, mostly in community with some hospitals.

6. Can you please also let us know why your exclusion criteria from the

6. This was used as an exclusion criteria as we were focusing solely on an adult population. To my knowledge there have been no trials of UrgoStart on children, and all studies included have an inclusion criteria of over 18 years. Perhaps, considering this, the exclusion criteria was redundant.

	original clinical evidence submission lists 'paediatrics' (page 20)?	Two records were excluded using this criteria, but they also didn't have the correct intervention. The titles were: - Rentea et al, 2013.Negative pressure wound therapy in infants and children: A single-institution experience. Journal of Surgical Research, 184 (1) - Hua et al, 2015. The Effect of Virtual Reality Distraction on Pain Relief During Dressing Changes in Children with Chronic Wounds on Lower Limbs. Pain Management Nursing, 16 (5)
Economic section	**E-mail sent to manufacturer 22.05.18** We were wondering if you could share with us the price when buying in bulk for both UrgoStart and UrgoTul?	**Response from manufacturer 24.05.18** We provide a discount structure to our wholesalers for buying in bulk, on a simple basis of greater volume = greater discount. NHS Supply Chain (who supply most Hospitals) buy in reasonable quantities at the moment, and therefore pay: UrgoStart Contact 10x10 = £4.09 UrgoTul 10x10 = £3.03 We also have some community wholesalers (supplying prescriptions through pharmacies) who buy in even bigger quantities, and they pay: UrgoStart Contact 10x10 = £3.76 UrgoTul 10x10 = £2.75 I think these should be treated commercial in confidence if possible please, as I don't want to share our volume pricing strategy widely.
Economic section	**E-mail sent to manufacturer 23.05.18** We have unearthed an inconsistency in the parameterisation of the DFU model	**Response from manufacturer 04.06.18 (see appendix 2d)** 1.

	and the data source reported (Explorer – Edmonds paper). In the paper Edmonds reports the proportion of patients in the control and intervention arm who entered the trial with an amputation as 50% and 60%, respectively. This is inconsistent with the data used to parameterize the model and reported in table 6 C5a of the report where, for instance, it is assumed that 51 patients had no previous amputation in the control arm and 63 patients had a previous amputation. It also seems that the unpublished data from the Explorer trial were used to aid estimation of the relevant transition parameters. 1. Can you please explain the discrepancy between the Edmond's publication on Explorer and the data used? 2. Can you provide us with the additional data from Explorer you used for the estimation of the relevant transition parameters?	a. The Edmond's publication reported in Table 1 and Table 2 the history of amputation in general, and also the amputation history of the target leg, as follows: i. Amputation History of the patients included in the RCT: 67% (84 patients) in the NOSF Group and 55% (63 patients) in the Control Group. Table 1. ii. Amputation History of Target Foot (the treated one): 60% (75 patients) in the NOSF Group and 50% (57 patients) in the Control Group. Table 2 b. We have used the overall amputation history figure for the economic modelling. Table 1  Table 2 :  [redacted]

	Control dressing group (n=114)	Sucrose octasu dressing group (n=126)
(Continued from previous column)		
Serum creatinine (mg/L)‖	10·2 (4·5)	10·4 (4·8)
Revascularisation history	52 (46%)	64 (51%)
Amputation history	63 (55%)	84 (67%)
Minor amputation	57/63 (90%)	78/84 (93%)
Major amputation	6/63 (10%)	6/84 (7%)
On one leg	47/63 (75%)	61/84 (73%)
On both legs	16/63 (25%)	23/84 (27%)

	Control dressing group	Sucrose octasulfate dressing group
Confirmed neuropathy	114 (100%)	126 (100%)
Confirmed peripheral artery disease	114 (100%)	126 (100%)
Ankle-Brachial Pressure Index (ABPI)*	0·88 (0·27) (n=111)	0·88 (0·24) (n=126)
Toe systolic pressure (mm Hg)	83·2 (24·8) (n=68)	81·2 (30·2) (n=75)
Ankle systolic pressure (mm Hg)	124·6 (42·2) (n=81)	125·9 (40·5) (n=88)
Toe-Brachial Pressure Index (TBPI)	0·58 (0·14) (n=45)	0·59 (0·16) (n=53)
Transcutaneous partial pressure of oxygen	38·7 (17·7) (n=27)	42·2 (18·0) (n=43)
Amputation history	57 (50%)	75 (60%)
Revascularisation history	42 (37%)	57 (45%)

Appendix 1

a) Minutes of teleconference with sponsor 16.04.18:

MT380 UrgoStart_sponsor

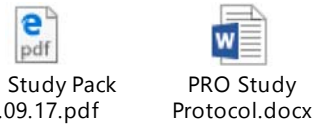
b) Amendments/clarification added to minutes by sponsor sent on 24.04.18 (marked in yellow):

MT380 UrgoStart_sponsor

Appendix 2

a) Attachments received in e-mail from sponsor dated 24.04.18:

b) Attachments received in e-mail from sponsor dated 29.04.18:



1.

c) Attachments received in e-mail from sponsor dated 17.05.18:

[redacted]

NICE National Institute for Health and Care Excellence

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

External Assessment Centre Report factual check

UrgoStart for treating leg ulcers and diabetic foot ulcers

Please find enclosed the assessment report prepared for this assessment by the External Assessment Centre (EAC).

You are asked to check the assessment report from KiTEC to ensure there are no factual inaccuracies contained within it. If you do identify any factual inaccuracies you must inform NICE by 12pm, **11th June 2018** using the below proforma comments table. All your comments on factual inaccuracies will receive a response from the EAC and when appropriate, will be amended in the EAC report. This table, including EAC responses will be presented to the Medical Technologies Advisory Committee and will subsequently be published on the NICE website with the Assessment report.

06/06/2018

NICE National Institute for Health and Care Excellence

Issue 1

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 9 “the study was not adequately powered to detect differences in quality of life (secondary outcome).”	2 of the 5 parameters introduced in the EuroQuol Questionnaire were documented as significant (anxiety-depression and Pain-discomfort)	Accuracy	The statistical significance achieved for these 2 parameters and the study being adequately powered to detect an effect in terms of QoL are two separate issues. High false discovery rates are a well-documented issue of underpowered studies involving multiple comparisons. No further changes were made to the report based on this comment.

Issue 2

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 13 “clinicians choose to use them depending on usually the shape of the wound.”	Each dressing is used for different wound types (not shapes) – so a wound with more exudate would need UrgoStart Foam whereas a low exudate or more cavity wound would need UrgoStart Contact Layer	Accuracy	Thank you for the clarification we have amended the section to mention type of wound rather than shape.

Issue 3

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 14 “RCT by Schmutz 2008 also included 2 UK sites.”	9 UK sites were involved in the RCT (5 active and 4 inactive (no inclusion)	Accuracy	Thank you for the additional information. We have amended this section accordingly.

Issue 4

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 14 “Munter 2017: secondary mostly.	No, very probable most of the 2792 investigators were GPs, private physicians and nurses.	Accuracy	Thank you for clarifying this aspect. Our entry was based from previous correspondence from your team. We have updated according to the new information you provided.

Issue 5

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 15. “UrgoTul is considered as a simple non-adherent dressing”	UrgoTul Absorb was used in Challenge; a neutral hydrocelluar dressing	Accuracy	We have added the term UrgoTul Absorb as well to the description of the dressings.

Issue 6

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 16 “Meaumne	Meaume	Spelling typo	We amended accordingly this section.

Issue 7

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 37 “UrgoTul = 2.5 ± 11.9 UrgoTul = 21.4 ± 81 UrgoTul = -0.56 ± 1.19	UrgoTul = 2.5 ± 11.9 cm2 UrgoTul = 21.4 ± 81 % UrgoTul = -0.56 ± 1.19 mm	Spelling typo	We amended accordingly this section.

Issue 8

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 38 “Pain” and “Anxiety”	“Pain-discomfort” and “anxiety-depression”	Spelling typo	We amended accordingly this section.

Issue 9

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 40. “Three of the comparative studies compared UrgoStart with UrgoTul”	And UrgoTul Absorb	Accuracy	We amended accordingly this section.

Issue 10

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 41 “The RCT by Edmonds 2018 analysing people with DFUs, included 2 UK sites”	5 UK sites	Accuracy	We amended accordingly this section.

Issue 11

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 41 “to a maximum of 24 weeks	20 weeks	Accuracy	We amended accordingly this section.

NICE National Institute for Health and Care Excellence

Issue 12

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 42 “Schmutz 2018”	2008	Spelling typo	We amended accordingly this section.