Title: UrgoStart for the treatment of leg ulcers and diabetic foot ulcers

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Declared interests of the authors

Description of any pecuniary relationship with the company, both personal and of the EAC. Please refer to NICE's Code of Practice for declaring and dealing with conflicts of interests.
http://www.nice.org.uk/niceMedia/pdf/Guidanceondeclarationsofinterest.pdf

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Rider on responsibility for report

The views expressed in this report are those of the authors and not those of NICE. Any errors are the responsibility of the authors.

Contents

ABBREVIATIONS

Term	Definition
ABPI	Ankle-brachial pressure index
BMI	Body mass index
CRD	Centre of Review and Dissemination
CDSR	Cochrane Database of Systematic Reviews
CWC	Complete wound closure
CWU	Chronic wound ulcer
DFU	Diabetic foot ulcer
VLU	Venous leg ulcer
HR	Healing rate
EAC	External Assessment Centre
EQ-5D	5-Dimension Health-Related Quality of Life Questionnaire
HTA	Health Technology Assessment
ITT	Intention to treat
IQR	Interquartile range
MAE	Major Adverse Events
MAUDE	Manufacturer and User Facility Device Experience
MHRA	Medicines & Healthcare products Regulatory Agency
MTEP	Medical Technologies Evaluation Programme
MIB	Medtech Innovation Briefing
NR	Not reported
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NICE CG	NICE clinical guideline
NICE MTG	NICE medical technology guidance
NOSF	Nano-Oligosaccharide Factor
NICE QS	NICE quality standard
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PU	Pressure ulcer
QOL	Quality of Life
QUORUM	Quality of Reporting of Meta-analyses
RCT	Randomised Clinical Trial
SD	Standard Deviation
TBPI	Toe brachial pressure index
TLC	Technology Lipido-Colloid
VAS	Visual Analogue Score
Vs.	Versus
WAR	Wound Area Reduction

1 Executive Summary

The sponsor identified 8 clinical studies (7 were published and 1 was unpublished) reported in 8 peer-reviewed papers and 1 conference abstract. Three of the studies included an intervention that did not fit the scope so only evidence from 6 peer-reviewed publications were included. The EAC did not identify any further relevant evidence.

The pivotal study for people with neuro-ischaemic DFUs was the multi-centre double-blind international EXPLORER (n = 240) RCT, which compared UrgoStart with UrgoTul with a 20 week follow up (Edmonds 2018). The results reported a statistically significant increase in wound closure, in favour of UrgoStart (p=0.002). The two groups performed equally in terms of safety and quality of life. The EAC considered that this RCT, which was fully funded by the sponsor and included UK sites, was subject to low risk of bias and the comparative benefit was mainly attributable to UrgoStart. The level of benefit in terms of complete wound closure was also broadly supported by evidence from a pooled data analysis of non-comparative observational data (Munter 2017).

The pivotal study for people with venous leg ulcers was the multi-centre double-blind international CHALLENGE (n = 187) RCT, which compared UrgoStart with UrgoTul Absorb with an 8 weeks follow up (Meaume 2012, Meaume 2017). The results reported a statistically significant increase in relative wound area reduction, in favour of UrgoStart (p=0.002). Use of UrgoStart also resulted in improved quality of life (p=0.022). The two groups performed equally in terms of safety and tolerance. The EAC considered that this RCT, which was fully funded by the sponsor and conducted in France, was subject to low risk of bias and the comparative benefit was mainly attributable to UrgoStart. It should be noted however that the study was not adequately powered to detect differences in quality of life (secondary outcome).

As a part of the economic submission, the sponsor performed a systematic review of economic evidence. After confirmation with its own systematic

review, the EAC included only two studies on leg ulcers, which reported that UrgoStart was cost savings compared to neutral dressing. Following this, two Markov model; for diabetic foot ulcers and leg ulcers were submitted. The EAC reviewed the models and found the model structure to be appropriate. The diabetic foot ulcer model used clinical data to estimate transition probabilities from the Explorer study and the leg ulcer model used the CHALLENGE study. The EAC decided that some of the unit cost parameters (practice nurse visit, leg ulcer hospitalization and neutral dressing (UrgoTul)) needed to be revised. After updating the parameters, the EAC analysis showed that UrgoStart was cost saving for both diabetic foot ulcers (£342) and leg ulcers (£541). The sponsor also reported cost savings for the technology which were higher than the EAC estimates for DFUs and lower than the EAC estimates for leg ulcers.

2 Background

2.1 Overview and critique of company's description of clinical context

The sponsor provided an overview of the prevalence, pathophysiology and management of diabetic foot ulcers and leg ulcers. A brief description of the main national guidelines for the treatment of chronic wounds was also given, without however providing more details on the treatment pathway. The sponsor also did not use as a source the National Diabetes Foot Care Audit. The clinical context provided by the sponsor is considered appropriate. However, it doesn't distinguish between care provided in a primary vs. a secondary setting. The sponsor only states that the care pathway would not need to change in order to adopt UrgoStart. According to the clinical experts the pathway depends on how services are commissioned locally and varies nationally. Based on the feedback the EAC received, leg ulcers are mainly treated in primary care and DFUs mainly in secondary care as they require multidisciplinary team input.

Relevant guidance

NICE has published a guideline on the prevention and management of foot problems in people with diabetes. The guideline does not provide recommendations on the use of specific wound dressings. NICE has also published a Clinical Knowledge Summary on venous leg ulcers. It recommends that low-adherent dressings are applied and replaced weekly. Alternative dressings to consider are hydrocolloid for pain, alginate for heavy exudate and hydrogels for slough.

The NICE advice on wound care products and advanced and antimicrobial dressings for chronic wounds recommends that the selection of an appropriate dressing should be based on careful clinical assessment of the person's wound, their underlying clinical condition, and their personal preferences. The NICE advice also states that the least costly dressings that meet the required clinical performance characteristics should be used, as there is insufficient evidence to determine whether modern or advanced

dressings (such as hydrocolloids, alginates and hydrofibre dressings) are more clinically effective than conventional dressings for treating wounds.

The use of antimicrobial dressings (such as silver, iodine or honey) over non-medicated dressings for treating chronic wounds is currently not supported by robust evidence according with the NICE advice. The Scottish Intercollegiate Guideline Network (SIGN) guideline on the management of venous leg ulcers recommends simple non-adherent dressings and compression therapy. As no evidence was identified to support superiority of any dressing type over another when applied under appropriate multilayer bandaging.

NICE has also published advice for Woundchek Protease Status for assessing elevated protease status in chronic wounds (MIB83), a point-of-care diagnostic test to assess protease activity in chronic wounds.

2.2 Critique of company's definition of the decision problem

Table 1 below outlines the main issues with the company's definition of the decision problem based on the original scope.

Table 1: Critique of decision problem

Decision problem	Company submission	Matches decision problem? (Y/N/partially)	EAC comment
Population	Scope: "Patients with leg ulcers in any setting and patients with diabetic foot ulcers in any setting." Submission: Two of the submitted studies (RCTs) involved people with VLUs (Meaume 2012, Schmutz 2008) and 2 involved people with DFUs (1 RCT by Edmonds 2018 and 1 non-comparative study by Richard 2012). The pooled data-analysis by Munter 2017 included patients with VLUs, DFUs and pressure ulcers. The sponsor only considered for inclusion studies with an adult population. The RCT by Edmonds 2018 analysing people with DFUs included	Partially	Some of the evidence submitted meets the final scope for the population. All populations in the submitted evidence were adults with either VLUs or DFUs as children were excluded according to the sponsor's selection criteria. The pooled analysis of primary data by Munter 2017 provided separately the results for DFUs, VLUs and pressure ulcers. The study did not clarify if in these patients the pressure ulcers were leg ulcers as specified in the final scope. All sponsor submitted studies were mostly conducted in a secondary setting: • Meaume 2012 and 2017: secondary setting mostly • Schmutz 2008: secondary setting only • Edmonds 2018: secondary setting mostly • Richard 2012: secondary only

	5 UK sites and it is considered the most relevant to a UK setting. Also the RCT by Schmutz 2008 also included 9 UK sites (5 active and 4 inactive).		• Munter 2017: primary mostly
Intervention	Scope: 'UrgoStart dressing formats which contain the TLC-NOSF technology'' Submission: 6 studies (Edmonds 2018, Meaume 2012, Meaume 2017, Munter 2017, Richard 2012, Schmutz 2008) included the UrgoStart dressing. Two of the submitted studies (Vin 2002, Veves 2002) included the Promogran dressing. One study (PRO) did not include any intervention.	Partially	Although the majority of the submitted evidence referred to the intervention as UrgoStart, the sponsor claimed that the 5 different formats of UrgoStart have identical mode of action (all contain TLC-NOSF technology) and clinical effectiveness and clinicians choose to use them depending on the wound type (for example a wound with more exudate would need UrgoStart Foam whereas a low exudate or more cavity wound would need UrgoStart Contact Layer). The sponsor submitted further details on the UrgoStart format used for each study: • Meaume 2012 and 2017: UrgoStart Non Adhesive Foam • Schmutz 2008: UrgoStart Contact layer • Edmonds 2018: UrgoStart Contact layer • Richard 2012: UrgoStart Contact layer • Munter 2017: UrgoStart Non Adhesive Foam and UrgoStart Contact layer

			The sponsor clarified that the studies including Promogran were mentioned in the submission only for the purposes of transparency that this particular product exists. Although Promogran is a product made by a different manufacturer and has a different mode of action and different clinical outcomes, it is often included in the same group with UrgoStart - protease modulating dressings. CE marking regulatory requirements are complied with.
Comparator(s)	Scope: 'Other wound dressing including conventional wound dressings and advanced wound dressings. Standard care is likely to vary with the different types of wounds and stage of healing.'' Submission: The sponsor submitted both comparative and non-comparative evidence. Three of the comparative studies submitted by the sponsor compared the intervention with UrgoTul or UrgoTul Absorb (Edmonds 2018, Meaume 2012,	Partially	Comparative evidence from 3 RCTs were included in the final report. The other 2 RCTs (Veves 2002, Vin 2002) were excluded because the intervention used was not UrgoStart. Despite the availably of multiple comparators, only 3 (UrgoTul, Promogran) were used to produce all the comparative data. Based on feedback received from the clinical experts UrgoTul and UrgoTul Absorb are considered as simple non-adherent dressings. Promogran is considered an advanced dressing.

	Meaume 2017) and 1 used Promogran (Schmutz 2008). All studies providing comparative data were RCTs.		
Outcomes	Scope: "The outcome measures to consider include: – time to complete wound healing – time to wound closure – wound area reduction (WAR) – wound area progression – wound healing rate – health related quality of life (HRQoL) – patient tolerance – patient acceptability – device-related adverse events	Yes	In the sponsor submission outcomes are tabulated by study (table B9 and B10). Outcomes from 3 RCTs and 2 non-comparative studies are presented in 6 references (6 full texts). Two of the references (Meaume 2012, Meaume 2017) provided outcomes from overlapping populations (CHALLENGE trial). All primary outcomes in the evidence submitted relates to wound healing with slightly different definitions in the included studies. The most common definition adopted by 3 studies was the relative wound area reduction. According to the experts, key outcomes are complete wound closure or time to reach CWC. Quality of life outcomes were studied as a secondary outcome in two of the included studies (Edmonds 2018, Meaume 2017).

	– nurse, GP and outpatient visits – amputation rates – wound-related complications – total dressings used'' Details on outcomes are given by study submitted in tables B9 (published) and B10 (unpublished).		Three studies (Meaume 2017, Richard 2012, Schmutz 2008) presented evidence with regards to patient tolerance and acceptability. No evidence was found on the rate of hospitalisation. One study (Edmonds 2018) reported amputation rates.
Cost analysis	Scope: Comparator(s): Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be sufficiently long to reflect any differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different	Yes	The cost analysis submitted by the sponsor matches the cost analysis specified in the final scope. The time horizon is appropriate to capture the costs and consequences of the technology compared to the specified comparator.

	numbers and combinations of devices are needed.		
Subgroups	• 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 The sponsor submitted 2 RCTs (Meaume 2012, Meaume 2017, Schmutz 2008) and 1 non-comparative study (Munter 2017) with VLUs. They also included 1 RCT (Edmonds 2018) and 2 non-comparative studies (Munter 2017, Richard 2012) with DFUs.	Partially	Four studies provided subgroup analyses (Edmonds 2018, Meaume 2012, Richard 20012, Schmutz 2008). All subgroup analyses reported were post-hoc. The pooled data analysis by Munter 2017 also presented results based on population subgroups (VLUs, DFUs and PUs). Wound duration and size seemed to be the most relevant subgroup analyses. Due to the inherent heterogeneity of the population as defined by the scope, the limited data provided for analyses based on patient characteristics are not sufficient to contribute to the decision problem. Only 1 non-comparative study (Munter 2017) provided evidence on pressure ulcers, however, no information on the location of the ulcers was provided.

	The sponsor also proposed additional subgroup analyses outside the scope, based on the following patient characteristics: age, sex, BMI, ABPI/TBPI, history of amputation or revascularisation.		

Special considerations, including issues related to equality

No equality issues were identified in the sponsor submission (see section 6).

The EAC notes that a number of population groups are identified by the scope as having potential special considerations for equality. The scope identifies the following groups: "Leg ulcers are more common in older people. Women are 2 times more likely to have a leg ulcer than men. 1 in 10 people with diabetic foot ulcers will have an amputation. Leg ulcers, and diabetic foot ulcers may be associated with other disabilities. People with leg ulcers or diabetic foot ulcers may meet the criteria for being disabled under the Equality Act 2010. Age, sex and disability are all protected characteristics under the 2010 Equality Act."

The EAC has not identified equality issues other than those highlighted in the scope.

Two of the studies investigated the effectiveness of the intervention in a purely diabetic population (Edmonds 2018, Richard 2012).

3 Clinical evidence

3.1 Critique of and revisions to the company's search strategy

The sponsor provided details of their search strategy in the original submission and further details were sent subsequently following a request for information from the EAC. The sponsor stated they searched PubMed, Science Direct, NICE Evidence Search, Cochrane Database of Systematic Reviews (CDSR), and Centre of Review and Dissemination (CRD) University of York. The sponsor did not provide details on their search strategy for finding unpublished material.

The EAC considered the sponsor's search strategy to be inadequate for a variety of reasons. The sponsor's search did not include 'urgostart' (or variations) as free-text terms and did not include any keywords (e.g. MeSH

terms). The search string was highly restrictive in its use of Boolean commands and the elements did not conform to a recognised structure (such as PICO). When it was tested by the EAC the search string was too long for the Science Direct, NICE Evidence Search, and CRD platforms, although the search platforms may have changed between the sponsor's search and when the EAC received the submission. When tested in PubMed and the CDSR the search did not return a number of the studies which were included in the sponsor's submission and which are available in those databases. The sponsor provided the .ris files for the citations found by their searches, but these did not contain a number of the studies included in the submission.

The sponsor's search was neither clear nor reproducible and therefore the EAC conducted their own search run in the databases listed in Appendix A. A search of Clinicaltrials.gov, WHO ICTRP, ISRCTN and PROSPERO was performed using a modified search strategy. The EAC also searched a variety of sources for grey literature using a simpler set of search terms.

The EAC's search found 7390 records of which 4257 were unique. (See Appendix A for details of all search strategies and PRISMA flow diagram.)

3.2 Critique of the company's study selection

The sponsor's inclusion/exclusion criteria are listed in *Table 2* below.

Table 2: Sponsor's inclusion/exclusion criteria for study selection

Inclusion criteria	
Population	Diabetic Foot Ulcers, Leg Ulcers, Pressure Ulcers, or a study of chronic wounds that included the aforementioned.
Interventions	Protease Matrix Modulating Dressings
Outcomes	• Wound Area Reduction, • Wound Closure Rate, • Quality of Life Outcomes,

	• Economic outcomes
Study design	• Randomised Controlled Trials • Patient Reported Outcomes • Observational studies • Epidemiology Studies • Modelling • Case Studies • Economic studies • Database Studies • Systematic/ Literature Reviews • Treatment pathway/guidelines
Language restrictions	English Language
Search dates	Search was carried out for the period from 1997 to 7th October 2017, a 20 year period.
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	Not meeting inclusion criteria
Study design	In vitro studies, review or discussion articles
Language restrictions	Non-English language (if the abstract was available in English and enough data was available, this was included in the data extraction, otherwise these articles were excluded).
Search dates	Before 1997

The EAC requested further clarification on 2 of the sponsor's selection criteria:

- The limits for the search dates
- The exclusion of a paediatric studies

According to the sponsor the upper limit was October 2017 as this was the original deadline for submitting their evidence to MTEP, however, it ended up being delayed. The Edmonds 2018 publication was included as an exception because the sponsor was aware of its upcoming publication by the study authors. The sponsor clarified that with regards to the lower limit for the search dates, in wound care there were very few studies of good quality on advanced dressings before the year 1997. The 20-year range for the search dates was considered appropriate to capture evidence related to the field of wound care management rather than just the intervention itself.

The original NICE scope does not exclude children. In addition, as advised by the clinical experts the care pathway for CWUs of similar etiology treated in the community would be the same for children and adults. The pathways would be different in secondary care. The sponsor provided the following explanation for the exclusion of a paediatric population from their clinical evidence search '*"this was used as an exclusion criteria* (sic) *as we were focusing solely on an adult population. To our knowledge there have been no trials of UrgoStart on children"*. The EAC's search strategies did not restrict for the age of the participants, although no relevant evidence relating to children was identified.

The EAC considered the rest of the inclusion/exclusion criteria to be appropriate.

3.3 Included and excluded studies

Table 3: List of included studies identified by the sponsor and the EAC

Primary study number	Primary study reference	Study name	Sponsor inclusion	EAC inclusion	Reason for disagreement
1.	EXPLORER	Edmonds 2018	Yes	Yes	N/A
2.	CHALLENGE	Meaume 2012	Yes	Yes	N/A
3.	CHALLENGE	Meaume 2017	Yes	Yes	N/A
4.	N/A	Munter 2017	Yes	Yes	N/A
5.	N/A	Richard 2012	Yes	Yes	N/A
6.	N/A	Schmutz 2008	Yes	Yes	N/A
7.	N/A	Veves 2002	Yes	No	Intervention outside the scope
8.	N/A	Vin 2002	Yes	No	Intervention outside the scope
9.	PRO study	n/a	Yes	No	Intervention outside the scope

Included studies

The EAC included the following studies (see Appendix C for excluded studies):

RCTs

Full text publications

Edmonds (2018) – EXPLORER – ClinicalTrials.gov number NCT01717183

This double-blind RCT compared UrgoStart Contact, containing sucrose octasulfate potassium salt (referred to as NOSF elsewhere), with UrgoTul in 240 adult patients with neuroischaemic diabetic foot ulcers (grade IC or IIC[1]). Patients, randomised 1:1, were followed for 20 weeks (or until complete wound closure) in 43 hospitals located in France, Spain, Italy, Germany, and the UK. The primary endpoint was binary: occurrence of wound closure. There were no significant differences between the groups at baseline. A total of 126 patients were treated with UrgoStart and 114 with UrgoTul. The odds ratio for wound closure was 2·60 (1·43–4·73; p=0·002), significantly in favour of UrgoStart. The Kaplan-Meier estimated time to wound closure was also significantly in favour of UrgoStart (120 days (110–129) vs. 180 (163–198); p=0·029), as were median Gilman parameter at week 20 (0.4 mm per week vs. 0.2; p=0.021) and absolute (1.8cm^2 vs. 1.2cm^2; p=0.022) and relative (98% vs. 90%; p=0.024) wound area reduction from baseline to week 20. Adverse events were not significantly different between the groups (overall 64 vs. 66, death 3 vs. 4, admission to hospital >24-hrs 22 vs. 19, local infection 33 vs. 36, amputation 1 vs. 2).

Critical appraisal

The concealment and blinding of the study was effective (the 2 dressings were identical in appearance) resulting in no significant issues around selection bias or performance bias. There were no significant issues around

[1] According to the University of Texas Diabetic Wound Classification system link.

attrition bias or detection bias, although the follow-up period was only just long enough for the primary endpoint. There is a potential question mark around generalisability because the median number of patients per centre was 3. In addition, the 2016 report of the National Diabetes Footcare Audit of England and Wales, reports that 20% of ulcers were located on the heel, 43% were infected, and 52% were less than 1 cm^2 all of which were exclusion criteria in the trial. Finally, the study included only neuro-ischaemic ulcers which may limit the generalisability of the reported results. According to the National Diabetes Foot Audit of England and Wales, an average of 35% of ulcer were thought to have ischaemia, but this proportion increased to 50% for those in secondary care. Other aspects of the study are methodologically strong and an independent organisation was in charge of the randomisation procedure and data analysis. The study recruited participants from UK centres. The sample size was adequate to detect the estimated effect. Sensitivity analyses on the wound closure outcome confirmed the findings of the primary analysis. The study was funded by the sponsor (Laboratories Urgo Medical).

Meaume (2012) – CHALLENGE

This study is a double-blind RCT comparing UrgoStart non-adhesive foam (TLC-NOSF) with UrgoTul Absorb (TLC alone) in 187 patients suffering from non-infected leg ulcers (venous and mixed). The patients were randomised 1:1 and followed for 8 weeks (median 56 days) in 45 hospitals in France. The primary endpoint was relative wound area reduction (WAR). There were no significant differences between the groups at baseline. Median relative WAR was significantly higher in the UrgoStart group compared to the UrgoTul group (-58.3% vs. -31.6%, a difference of -26.7% (95% CI -38.3 to -15.1%; p=0.002). Absolute WAR was also significantly higher in the UrgoStart group (-6.1cm^2 vs. -3.2cm^2; p=0.003) as well as healing rate (-10.81mm^2/day vs. -5.15mm^2/day; p=0.005) and Gilmans wound area progression (–1.15±1.20mm vs. -0.56±1.19mm). The odds ratio of patients in the UrgoStart group achieving WAR ≥40% was 2.9 (95% CI 1.6-5.3; p=0.0003), and for achieving WAR ≥60% it was 2.2 (95% CI 1.2-4.0; p=0.013). A blind review of 168 patients considered 81.4% of UrgoStart ulcers and 65.9% of UrgoTul ulcers to

be ‘improved’ (p=0.022). By week 8 in the UrgoStart and UrgoTul groups there were 6 and 7 completely healed wounds, respectively. There were no significant differences between the groups in acceptability or adverse events.

Critical appraisal

As with other studies comparing UrgoStart to UrgoTul there were no issues surrounding blinding and concealment as the two dressings are indistinguishable, so there are likely to be no issues surrounding performance or selection biases. There was a very low dropout rate, reducing the likelihood of attrition bias. However, the follow-up of 8 weeks is potentially too short to assess healing in complex wounds and only 13 wounds in total were completely healed by the end of the study. Compression therapy was used in both the intervention and control groups. The study was powered to detect its primary outcome, taking into account the dropouts. As with the EXPLORER study there was a small number of patients treated per centre (mean of 4.155) which could call into question the generalisability of the study. Also no UK sites were included. The study was funded by the sponsor.

Meaume (2017) – CHALLENGE

This double-blind RCT compared UrgoStart non-adhesive foam, containing TLC-NOSF, with UrgoTul Absorb (TLC alone). There were 187 people with non-infected leg ulcers (venous and mixed), randomised 1:1, followed for a maximum of 8 weeks (or until complete wound closure if this happened during the 8 week period). The patients were recruited as a part of an earlier RCT (Meaume 2012) from 45 hospitals in France. This study’s endpoint was health related quality of life (HRQoL) as measured by the EQ-5D-3L. There were no significant differences between the groups at baseline. Of the five dimensions evaluated by the EQ-5D, there were no significant differences between the groups in mobility, self-care and usual activities. However, UrgoStart scored significantly better than UrgoTul in pain/discomfort (1.53±0.52 vs. 1.74±0.65; p=0.02) and anxiety/depression (1.35±0.53 vs. 1.54±0.59; p=0.03). Patients reported ‘significant pain’ significantly less often in the UrgoStart group (1 vs. 9 for UrgoTul; p=0.009). VAS outcomes were not significantly different

between the groups (baseline 65.8±17.7 and 65.6±17.4; end of trial 72.1±17.5 vs.67.3±18.7; p=0.072).

Critical appraisal

This study is a re-analysis of Meaume (2012) and as such was not powered to detect differences in the primary endpoint of HRQoL, although there were statistically significant differences in some of the dimensions. Other aspects of the CHALLENGE study's methodology are as discussed above.

Schmutz (2008)

This study is an open-label RCT comparing UrgoStart Contact (TLC-NOSF) to Promogran (collagen-ORC [oxidised regenerated cellulose] matrix) in 117 patients suffering from venous leg ulcers (ankle brachial pressure index ≥0.80), treated in 22 French hospitals and 5 UK wound specialist centres. Patients were randomised 1:1 and followed for 12-weeks. The primary endpoint was relative WAR. There were no significant differences between the groups at baseline. On the per protocol population (n=99) the UrgoStart group saw significantly larger relative WAR compared to the Promogran group (61.1% vs. 7.7%, a difference of 33.6±15.0%; p=0.0059). On the intention-to-treat analysis the result was similar (54.4% vs. 12.9%; p=0.0286). Relative WAR was greater in the UrgoStart group throughout the study period. Absolute WAR was also significantly larger in the UrgoStart group (2.3±10.2cm^2 vs. 0.2±10.4cm^2; p=0.01), as was mean wound healing rate (-0.016±0.285cm^2/day vs. +0.075±0.475cm^2/day; p=0.029). 56% of the UrgoStart group and 35% of the Promogran group reached WAR40% (p=0.022) and following multivariate analyses for ulcer aetiology, ulcer duration, extent of baseline granulation tissue and perilesional skin aspect in the model, the odds ratio was 2.4 (95% CI: 1.1–5.3; p=0.026) in favour of UrgoStart. Ulcer duration of <6 months was also a significant factor in achieving WAR40% (odds ratio 2.2 [95% CI: 1.0-4.9; p=0.043]). In sub-group analyses there were no significant differences between the groups in ulcers with <6months duration (relative and absolute WAR, healing rate, and ulcers reaching WAR40%). By week 12 in the UrgoStart and Promogran groups

there were 10 and 8 completely healed ulcers, respectively. There were no significant differences between the groups in adverse events.

Critical appraisal

This study was open label so there are potential selection and performance biases, although the groups were well matched and care was similar between the groups (both received compression therapy as well as the intervention or control dressing). In sub-group analyses there were no significant differences when ulcer duration was <6 months; overall there were significant differences between the groups which was accounted for entirely by ulcers ≥6 months duration. The dropout rate was substantial (17 in the study group and 24 in the control group) but intention-to-treat analysis was used for all analyses, mitigating risk of attrition bias. However, the study required 69 patients in each group in order to detect differences in relative WAR and this was achieved in neither group (50 patients completed in the study group, 49 in the control group) so the study was not powered for its primary endpoint, though statistically significant differences were detected anyway. The EAC considered the 12 week follow-up period was potentially too short, increasingly the likelihood of detection bias. The study recruited participants from UK centres. The study was funded by the sponsor.

Non-comparative studies

Full-text publications

Richard (2012)

This study was a non-randomised prospective observational study conducted as a pilot to evaluate the UrgoStart Contact in 34 patients with uninfected, Texas grade IA diabetic neuropathic foot ulcers. The study was an open-label design conducted in 14 French hospitals where patients were followed for 12 weeks. The primary endpoint was relative WAR. At final follow-up the median WAR was 82.7% (mean 62.7±49.9%). In 10 patients (30%) the wound was completely healed (median healing time of 58 days). There were 7 local adverse events, of which 2 were considered to be potentially related to the

dressing. Of 13 general adverse events, none were considered related to the dressing. Nurses reported application and removal of the dressing was ‘easy’ or ‘very easy’ in 95.6% and 99.1% of cases, respectively.

Critical appraisal

The study was a non-randomised trial reported on the before-after relative WAR in a small cohort of 34 patients, all of whom received the same treatment. Nine patients did not complete the study (1 missing data, 5 serious adverse events, and 3 switched to alternative dressing), resulting in a substantial drop out rate of 26.4%. As a non-comparative study there were no power calculations, therefore, the effect of the substantial drop-out rate is unknown.95% confidence intervals were not reported. All patients but one were treated with offloading boots and wounds were debrided if deemed necessary by the hospital nurse; therefore, it is not clear that the results will be generalisable in a wider context. The study did not include any UK sites.

Munter (2017)

This study is a pooled analysis of data collected in 6 French and 2 German healthcare settings, comprising 10,220 patients suffering from leg ulcers (7903 patients), diabetic foot ulcers (1306), and pressure ulcers (1011), treated with UrgoStart. A total of 25.3% of the included leg ulcers were of mixed aetiology or arterial. Median follow-up was 4.5 weeks (varied from 4 weeks to 20 weeks). The primary endpoint was binary: wound closure as defined by a PUSH (Pressure Ulcer Scale for Healing) score of 0. The authors also considered: time to 50% reduction in PUSH score. Total wound closure was seen in 3124 patients (30.8% [95% CI: 29.9-31.7]) and varied according to ulcer-type (LU 29.8%, DFU 37.4% and PU 29.5%). Binary logistic regression revealed that patients were significantly more likely to achieve wound closure in Germany compared to France (odds ratio 1.64, 95% CI 1.42-1.88; p<0.001). Similarly, age significantly influences wound closure (51–70 years vs. <50 years odds ratio 0.65, 95% CI 0.51-0.84; p=0.001. >70 years vs. <50 years odds ratio 0.77 95% CI 0.68-0.87; p<0.001), as did patients having one or more risk factor (odds ratio 0.38; p<0.001). Gender, BMI and

diabetes mellitus status were not significant factors. Mean estimate of time to wound closure was 111.3 days (95% CI 105.5–117.2 days), which again varied by ulcer-type (LU 112.5 days, DFU 98.1 and PU 119.5). PUSH scores were available in 7047 patients (69% of the total) and times to 50% reduction in PUSH score for LUs, DFUs and PUs were 66.2 days (95% CI:64.5 to 68.0), 59.9 days (95% CI: 56.4–63.3) and 62.0 days (95% CI: 56.3–67.7), respectively. Sub-group analysis in the French cohort showed that UrgoStart as first line therapy delivered significantly faster healing than if it was second line therapy (mean estimated time to closure 70.2 days vs. 103.7 days; $p<0.001$).

Critical appraisal

The study is a pooled analysis of data gathered in 8 different settings in France and Germany, identified by a literature search and directly from the sponsor. The data is purely observational and there is no comparator included. The included studies are not identified as published studies and it is not clear whether or not any correspond to the other studies identified in the manufacturer's submission. There is substantial heterogeneity in the follow-up, outcome measure, and distribution of ulcer-type. The study included a large patient population and represent the largest cohort of patients treated with UrgoStart. The study did not include any UK sites.

Table 4 and Table 5 below provide detailed information on the patient and wound characteristics and methodology for each of the included studies.

Table 4: Patient and wound characteristics of included studies

Characteristic	Schmutz 2008 (VLU)	Edmonds 2018 (DFU)	Meaume 2012/2017 (VLU)	Richard 2012 (DFU)	Munter 2017 (VLU)	Munter 2017 (DFU)
Mean age (years)	71.3	64.5	72.6	60.5	NR	NR
Men	41%	84%	33.3%	79%	38%	63.6%
Mean BMI	29.3	30.1	30.5	32.6	NR	NR
Diabetic	15.4%	100%	14%	100%	30.2%	96.8%
Smoking	NR	17%	10.8%	NR	NR	NR
Outpatients	82.1%	93.3%	80.6%	100%	NR	NR
Mean ulcer duration (months)	11.2	7.2	15.6	NR	NR	NR
Duration >6 months	56%	42%	*58.1%	NR	33.1%	20%
Mean wound area baseline	10.9 cm^2	5.3 cm^2	17.0 cm^2	2.7 cm^2	NR	NR
Recurrent	61%	NR	54.8%	NR	NR	NR
Patients with healthy periwound skin (PWS)	12%	18%	37.6%	NR	21.9%	18.9%
Ankle Brachial Pressure Index (ABPI)	1.02	0.88	1.05	NR	NR	NR
* Duration >1 year						

Table 5: Methodological characteristics of included studies

Included reference	Design and intervention(s)	Participants and setting	Outcomes	Results	Withdrawals	EAC Comments
Schmutz 2008	Prospective, open, two-arm, multicentre randomised control trial with 12 week follow up. France and UK. UrgoStart or Promogran (control) in addition to receiving compression bandage therapy	117 adult patients (hospitalised or outpatients) with venous leg ulcers (VLUs) UrgoStart = 57 and Promogran = 60 Patients were selected if the area of their VLU [ankle brachial pressure index >0.80] ranged from 5 to 25 cm² with a duration >3 months. Ulcers free from necrotic tissue. BMI >30 kg/m² = 39.3% Ulcer > 10cm² = 41% Stagnating/worsening despite appropriate care = 68.4%	Mean difference between groups for wound relative reduction (%RR) Median relative WAR Median wound area reduction (WAR) Medial healing rate (HR) % of patients with more than 40% WAR UrgoStart versus Promogran odds ratio to reach 40% reduction	<u>Mean difference in %RR</u> in per-protocol (PP) cohort: 33.6 ± 15.0% in favour of UrgoStart (unilateral 95% CI lower limit of 8.6% not including the null value.) <u>Median %RR</u> PP cohort: UrgoStart: 61.1% Promogran: 7.7%, Intent to treat (ITT) cohort (all patients): UrgoStart: 54.4% Promogran: 12.9%	41 (35%) withdrew before the end of the 12 week period. 24 patients in the Promogran group and 17 in the UrgoStart group were withdrawn, mainly due to a local adverse event (n=19) or ulcer aggravation (n=12).	Overall, good methodological quality, however this study was not blinded. High withdrawal rate, as local adverse events often led to drop outs, where in other studies, such events only led to a change in wound dressing and patients would be allowed to continue. This also led to a higher drop-out rate in the control group, leaving 36 patients in the Promogran group and 40 in the Urgostart group. Superiority of UrgoStart effect

				(p= 0.0286). <u>Median WAR</u> UrgoStart: 4.2 cm² Promogran: 1.0cm² (P= 0.01). <u>Median HR</u> UrgoStart: 0.056 cm²/day Promogran: 0.015 cm²/day (P= 0.029). <u>>40% WAR</u> UrgoStart: 56% Promogran: 35% (P= 0.022) <u>UrgoStart versus Promogran odds ratio to reach 40% area reduction</u> 2.4 (95%CI: 1.1–5.3; P = 0.026).		compared with Promogran was concluded (P=0.0059) based on the median relative WAR in the PP cohort. More adverse events were reported for Promogran (n=27) than UrgoStart (n=16). Perilesional skin irritation was the most common for UrgoStart (n=7) and pain was the most commonly reported event for Promogran (n=12).
Edmonds 2018	Explorer study (NCT01717183)	240 adult patients (hospitalised or outpatients) with diabetes and a non-infected neuroischaemic	Proportion of patients with wound closure at week 20	<u>Proportion of patients with wound closure at</u>	37 (15%) withdrew before the 20 week period was finished, 19 in the	Good methodological quality.

	Prospective, two-arm, multicentre, double-blind, randomised controlled trial with 20 week follow-up. France, Spain, Italy, Germany, and the UK. UrgoStart and UrgoTul	diabetic foot ulcers (DFUs) were randomized to treatment with UrgoStart or UrgoTul (control group), 126 and 114 respectively. Patients were included if DFU was greater than 1 cm² and of grade IC or IIC (University of Texas Diabetic Wound Classification system). BMI >30 kg/m² = 44.6% Ulcer > 5cm² = 18%	Estimated mean time to reach wound closure Median WAR Median %RR UrgoStart versus UrgoTul adjusted odds ratio to wound closure Wound area reduction of at least 50% at week 4 Adverse events HR-QoL - mean EuroQol-5D-5L index	<u>20 weeks (ITT cohort)</u> UrgoStart: 60 patients (48%) UrgoTul: 34 patients (30%) 18% difference is significant (p=0·002). <u>Estimated mean time to reach wound closure</u> UrgoStart: 120 days UrgoTul: 180 days <u>Median absolute WAR (IQR)</u> UrgoStart: 1.8 cm² ((0.9–3.8) UrgoTul: 1.2cm² (0.6–2.4) <u>% relative WAR (IQR)</u> UrgoStart: 98% (58–100%) UrgoTul: 90% (29–100%)	control group and 18 from the treatment group. This is a lower drop-out rate than in the other study focusing on DFUs (Richard 2012). Allocation of another dressing due to local adverse events was not always grounds for withdrawal.	Powered to detect a statistically significant endpoint at 20 weeks. This study showed significantly more patients with DFUs achieved wound closure when treated by UrgoStart. Small number of patients treated per centre, median 3 patients. Long follow-up period (relative to other included studies). Study funded by Urgo.

				<u>UrgoStart versus UrgoTul adjusted odds ratio to wound closure</u> 2.60 (95%CI: 1.43–4.73; P = 0.002). <u>Adverse events</u> Wound infection: UrgoStart: 33 in 25 patients (20%) UrgoTul: 36 in 32 patients (24%) Minor amputations not affecting the wound site: UrgoStart: 1 patient (1%) UrgoTul: 2 patients (2%) Mortality: UrgoStart: 3 (2%) patients UrgoTul: 4 (4%)		

				None of the deaths were related to treatment, procedure, wound progression, or subsequent to amputation. <u>Mean EuroQol-5D-5L index</u> UrgoStart: 0.63 ± 0.32 UrgoTul: 0.69 ± 0.30 (P=0.245)		
Munter 2017	Pooled data analysis of 8 non-comparative, observational studies. France and Germany. Study durations ranged from 4 to 20 weeks. UrgoStart	Data obtained from 10,220 patients, with 7903 leg ulcers (LUs), 1306 DFUs and 1011 pressure ulcers (PUs). <u>Total population</u> Mean age = 72.9 ± 12.4 Mean BMI = 27.9 ± 5.9 Mean PUSH score = 11.1 ± 3.2 <u>LUs</u> BMI >35 kg/m² = 10.6%	Overall closure rate Time to wound closure Time to 50% PUSH score reduction Subgroup analysis on 1st or 2nd line treatment with UrgoStart– days to closure	<u>Overall closure rate</u> Total: 30.8 % [95 % confidence interval (CI): 29.9–31.7 %]. LU: 29.8% DFU: 37.4% PU: 29.5% <u>Time to complete closure</u> LU: 112.5 days	NA	Non-comparative study. The included studies varied in methodology and study outcomes. The follow-up periods of the studies varied greatly from 4 weeks to 20 weeks. The subgroup analysis was conducted with a

	 No comparator 	Duration >6 months and/or wound area > 8cm² = 48.6% PUSH score = 11 ± 3 DFUs BMI >35 kg/m² = 13.4% Duration >6 months and/or wound area > 8cm² = 35.2% PUSH score = 9 ± 3 PUs Men = 46.9% BMI >35 kg/m² = 6.2% Diabetic = 34.9% Duration >6 months = 15.6% Duration >6 months and/or wound area > 8cm² = 45.0% PUSH score = 11 ± 3 Patients with healthy PWS = 19.3% 		DFU: 98.1 days PUs:119.5 days Time to 50% PUSH score reduction LU: 66.2 days DFU: 59.9 days PUs: 62.0 days Subgroup analysis – days to closure for UrgoStart First line: 70.2 Second line: 103.7		considerably large sample size (n=4215) All included studies were funded by Urgo
Meaume 2012	8-week, French, prospective, multicentre, double-blind, randomised, controlled trial. 	187 adult patients, TLC-NOSF = 93 and TLC=94, being managed for a VLU, either as an inpatient or an outpatient from 45 centres. Selection was based on a VLU area of between 5 and	Wound area reduction (WAR) (absolute and percentage) Wound edge progression	Mean Absolute WAR UrgoStart = 6.9 ± 11.4 cm^2 UrgoTul = 2.5 ± 11.9 cm^2	5.4% of patients withdrew, including 2 deaths (1 from each group) and 3 withdrawals of consent.	Good methodological quality. Powered to detect a statistically significant endpoint at 8 weeks.

	Urgostart (TLC-NOSF wound dressing). Comparator: UrgoTul (TLC wound dressing) 	50 cm^2 and duration of 6 to 36 months. ABPI had to be between 0.8 and 1.3 and at least 50% of the ulcer covered by granulation tissue without any black necrotic tissue. BMI > 30kg/m^2 = 43.0% Ulcer area > 10cm^2 = 58.1% 	Wound healing rate Median time to reach WAR ≥ 40% Perilesional skin Acceptability Adverse events 	<u>Mean relative WAR</u> UrgoStart = 45.2 ± 47.9% UrgoTul = 21.4 ± 81 % <u>Mean Wound Edge Progression</u> UrgoStart = -1.15 ± 1.20 mm UrgoTul = -0.56 ± 1.19 mm <u>Mean HR</u> UrgoStart = -13.32 ± 24.56 mm^2/day UrgoTul = -4.54 ± 23.20 mm^2/day <u>Median time to reach WAR ≥ 40%</u> UrgoStart = 43 days UrgoTul = 63 days		Small number of patients treated per centre (mean = 4.155). The follow-up of 8 weeks is potentially too short to assess healing in complex wounds Study funded by Urgo.

				Local adverse events UrgoStart = 34 UrgoTul = 32		
Meaume 2017	8-week, French, prospective, multi-centre, double-blind, randomised, controlled trial. Urgostart (TLC-NOSF wound dressing). Comparator: UrgoTul (TLC wound dressing)	Same patients as in study above.	EQ-5D measures: Pain/discomfort Anxiety/depression Mobility Self-care Usual Activities Visual Analogue Scale (VAS) Local adverse events (same as above)	Pain - discomfort UrgoStart = 1.53 ± 0.52 UrgoTul = 1.74 ± 0.65 Anxiety – depression UrgoStart = 1.35 ± 0.53 UrgoTul = 1.54 ± 0.59 Mobility UrgoStart = 1.55 ± 0.52 UrgoTul = 1.5 ± 0.52 Self-care UrgoStart = 1.23 ± 0.44 UrgoTul = 1.27 ± 0.55 Usual activities	Same as above	Same as in Meaume 2012 QoL was a secondary outcome therefore the study was not adequately powered to detect a difference

				UrgoStart = 1.54 ± 0.61 UrgoTul = 1.51 ± 0.59 <u>VAS</u> UrgoStart = 72.1 ± 17.5 UrgoTul = 67.3 ± 18.7 <u>Local adverse events</u> UrgoStart = 34 UrgoTul = 32		
Richard 2012	French, multi-centre, open-label, non-controlled, pilot study UrgoStart No comparator	33 adult patients with type 1 or 2 diabetes mellitus presenting with neuropathic foot ulceration with Michigan Neuropathy Screening Instrument score >3 at 14 hospital departments. The diabetic foot ulcer (DFU) had to be 1-15cm^2 in size, located on the forefoot or midfoot and classified as grade 1A by the Texas University system. Granulation tissue had to cover >50% of wound surface.	Percentage DFUs healed at study end Median and Mean Healing times Percentage of patients with improving wounds at study end Median and Mean Wound Surface Area at study end	Percentage DFUs healed at study end = 30% Median healing time = 58 days Mean Healing time = 58.9 ± 25.7 days Percentage of patients with improving wounds at study end = 73%	1 not analysed due to missing data, 5 withdrew due to serious adverse events (not considered to be related to the wound management dressing) and 3 withdrew as dressing was deemed inappropriate by the investigator	Non comparative study Substantial drop-out rate (26.4%). This was mainly due to a larger percentage of serious adverse events when compared with Edmonds 2018, however, the withdrawal rate is similar to preceding studies. This shouldn't have any large effect on results as this is a

		Those with ABPI ≥ 0.8, a toe systolic pressure > 40mmHg or a transcutaneous oxygen value >40mmHg were excluded. BMI > 30kg/m2 = 43.0% Mean Duration of DFU (months) = 6.7 ± 5.2 Mean duration of diabetes = 17.5 ± 11.6 	Median reduction in wound surface area Mean reduction in wound surface area Local Adverse Events Local Adverse Events deemed to be due to dressing 	Median Wound Surface Area at study end = 0.74cm^2 Mean Wound Surface Area = 0.92 ± 1.47cm^2 Median reduction in wound surface area = 82.7% Mean reduction in wound surface area = 62.7 ± 49.9%. Local Adverse Events = 7 Local Adverse Events deemed to be due to dressing = 2		non-comparative study. 12 week follow up, adequate for DFUs.

(Green, amber or red colour coding indicates whether the study matches the scope fully, partially, or not at all: ●●●)

3.4 Overview of methodologies of all included studies

- Four of the included studies were RCTs (Edmonds 2018, Meaume 2012, Meaume 2017, Schmutz 2008) and 2 were non-comparative studies (Richard 2012, Munter 2017). All studies evaluated the intervention specified in the scope. Three of the comparative studies compared UrgoStart with UrgoTul or UrgoTul Absorb and 1 with Promogran (Schmutz 2008).

- All six of the included studies were full text publications.

- Three of the included studies (all RCTs) involved people with VLUs (Meaume 2012, Meaume 2017, Schmutz 2008) and 2 involved people with DFUs (1 RCT by Edmonds 2018 and 1 non-comparative study by Richard 2012). The pooled analysis of non-comparative data by Munter 2017 included patients with VLUs, DFUs and pressure ulcers presented separately. The RCT by Edmonds 2018 analysing people with DFUs, included 5 UK sites and it is considered the most relevant to a UK setting.

- Baseline characteristics were provided in all of the included studies. The mean age varied from 60.5 (Richard 2012) to 72.6 (Meaume 2012) and the proportion of males varied from 33% (Meaume 2012) to 84% (Edmonds 2018).

- The mean follow up durations varied from 8 weeks (Meaume 2012, Meaume 2017, Munter 2017) to 12 weeks (Richard 2012, Schmutz 2008) to a maximum of 20 weeks (Edmonds 2018). A high range of follow-up was noted from 1 week to more than 1 year.

- All of the included studies were multicentre. With the exception of Richard 2012 and Munter 2017 all other studies included a sample size calculation for the primary outcome.

- Two studies reported that adjudication of the outcomes was performed by an independent investigator (Schmutz 2008, Meaume 2012). Three studies used a double-blind design (Meaume 2012, Meaume 2017, Edmonds 2018). None of the comparative studies reported statistically significant imbalances in the baseline characteristic between the 2 groups.

- Outcomes from 3 RCTs and 2 non-comparative studies presented in 6 full text publications were included in the assessment report. Two of the references (Meaume 2012, Meaume 2017) provided outcomes

from the same population (CHALLENGE trial). All studies evaluated the intervention specified in the scope.

- All primary outcomes in the evidence submitted relates to wound healing with slightly different definitions in the included studies. The most common definition adopted by 3 studies (Meaume 2012, Richard 2012, Schmutz 2008) was the relative wound area reduction.

- Quality of life outcomes was studied as a secondary outcome in two the included RCTs (Edmonds 2018, Meaume 2012). The full results of the QoL analysis from Meaume 2012 were presented in a follow-up publication by Meaume 2017. Three studies (Meaume 2017, Richard 2012, Schmutz 2008) presented evidence with regards to patient tolerance and acceptability. No evidence was found on the rate of hospitalisation. One study (Edmonds 2018) reported amputation rates.

- With regards to adverse events, 4 studies (Edmonds 2018, Meaume 2012, Richard 2012, Schmutz 2008) reported local adverse events.

- Four studies provided subgroup analyses (Edmonds 2018, Meaume 2012, Richard 2012, Schmutz 2008). All subgroup analysis reported was post-hoc. The pooled data analysis by Munter 2017 also presented results based on population subgroups (VLUs, DFUs and PUs). Wound duration and size seemed to be the most relevant subgroup analyses.

3.5 Overview and critique of the company's critical appraisal

The sponsor used the checklist proposed by NICE for the critical appraisal included into their submission. For RCTs, they followed the "CRD's guidance for undertaking reviews in health care" from the Centre for Reviews and Dissemination, University of York, 2008 (Chapter 1, section 1.3.4.). For the observational studies they used the CASP guidelines.

The EAC carried out a separate quality appraisal of the 6 full text publications included in the assessment report. The checklist proposed by NICE's guidelines manual (Appendix C) was adapted in accordance with feedback received by the clinical experts. The EAC requested advice on a) the appropriateness of the primary outcome, b) methods for measuring WAR and c) the definition of an adequate follow-up time. For the non-comparative studies the CASP guidelines were used. A copy of the EACs methodological quality appraisal checklist is included in appendix B.

According to the experts, standard planimetry using a grid tracing method has been extensively used in most studies for measuring WAR, however, the

estimations it provides are potentially subject to a large margin of error and this needs to be taken into consideration in the interpretation of the results. Because of this fact and the implications for costing, the best primary outcome would ideally be complete wound closure or time to reach CWC, because that is the key objective. Complete wound closure at 20 weeks follow-up was reported by Edmonds 2018 while Munter 2017 reported time to reach CWC. The other studies included in the report used WAR as the primary outcome which can denote that the ulcer is smaller but still remains a chronic wound with all the implications this will have for patients' quality of life and associated healthcare costing. With regards to the follow-up time the experts noted that healing rates vary depending on patient and wound characteristics. The National Diabetic Foot Care Audit reported a 48% healing rate at 12 weeks, however, this percentage will be lower for more severe case such as the presence of an ischaemic component (approximately 30% at 12 weeks follow-up). As a guide they suggested a 12 weeks follow-up for DFUs and 16-24 weeks for VLUs.

The EACs checklist assess the risk of bias in 4 domains categorised as selection bias, performance bias, attrition bias and detection bias. The detection bias domain was adapted to include a question asking whether or not an independent events committee was involved with outcomes assessment. Finally, 1 extra general category was added to assess issues related to conflict of interest, sample size calculations and whether the study used either time to wound healing or CWC as the primary endpoint. All domains are categorised as low (risk of bias or applicability), high, or unclear. The results of the assessment are illustrated in Table 6 and Table 7 below.

Table 6: Results of methodological assessment for RCTs

Study	Schmutz 2008 VLU	Meaume 2012* VLU	Edmonds 2018 DFU
Selection Bias	Unclear/ unknown risk	Low risk of bias	Low risk of bias
Performance Bias	Unclear/ unknown risk	Low risk of bias	Low risk of bias
Attrition Bias	Low risk of bias	Low risk of bias	Low risk of bias
Detection Bias	Low risk of bias	Low risk of bias	Low risk of bias
Other (conflicts of interest, power, endpoint)	Unclear/ unknown risk	Low risk of bias	Low risk of bias
*Meaume 2017 is a re-analysis of the same cohort used in Meaume 2012. The EAC assessed the risk of biases as the same with the exception of the 'Other' category where it was judge 'unclear/unknown risk' because the 2017 study was not powered for its primary endpoint.			

Table 7: Results of methodological assessment for observational studies

Study	Richard 2012 DFU	Munter 2017 DFU/VLU
Is the study based on a representative sample selected from a relevant population?	Yes	Yes
Are criteria for inclusion explicit?	Yes	No
Did all individuals enter the study at a similar point in their disease progression?	Yes	No
Was follow up long enough for important events to occur?	No	No/unclear*
Were outcomes assessed using objective criteria or was blinding used?	Yes (no blinding)	Yes (no blinding)
If comparisons of sub-series are being made, was there sufficient description of the series and the distribution of prognostic factors?	N/A	Yes
* Follow-up varied between 4-20 weeks		

3.6 Results

The sponsor presented results from 8 studies published as full text and 1 as a conference abstract. After excluding the studies by Vin 2002, Veves 2002 and the PRO study, the EAC accepted 6 full text publications for inclusion in the assessment report. The results from these studies are included in Table 8 and **Error! Reference source not found.** below.

Table 8: Included studies outcomes associated with wound healing

References, trial name & patient group.	Mean relative WAR (%)	Wound closure (%)	Mean time to CWC (days)	Mean absolute WAR (cm^2)
Schmutz 2008 **VLUs**	NR	NR	NR	TLC-NOSF: 2.3 ± 10.2 Promogran: 0.2 ± 10.4 (p=0.01)
Meaume 2012 **CHALLENGE RCT** **VLUs**	TLC-NOSF: 45.2 ± 47.9 TLC: 21.4 ± 81.0	NR	NR	TLC-NOSF: 6.9 ± 11.4 TLC: 2.5 ± 11.9
Edmonds 2018 **EXPLORER RCT** **DFUs**	TLC-NOSF: 72 ± 47 TLC: 42 ± 115	TLC-NOSF: 48% TLC: 30%	TLC-NOSF: 120 TLC: 180 (p=0.029)	TLC-NOSF: 3.2 ± 5.2 TLC: 2.3 ± 5.5
Richard 2012 **DFUs**	TLC-NOSF: 62.7 ± 49.9	TLC-NOSF: 30%	TLC-NOSF: 58	NR
Munter 2017 **VLUs**	NR	TLC-NOSF: 29.8% [95 % CI: 28.8–30.9 %]	TLC-NOSF: 112.5 days [95%CI: 105.8–119.3]	NR
Munter 2017 **DFUs**	NR	TLC-NOSF: 37.4% [95 % CI: 34.8–40.1 %]	TLC-NOSF: 98.1 days [95 %CI: 88.8–107.5]	NR

Table 9: Included studies secondary outcomes

References, trial name & patient group.	Tolerance and acceptability	Patient compliance	Adverse events	Infection (%)	Amputation (%)	EQ5D	VAS
Schmutz 2008 VLUs	Difficult dressing removal TLC-NOSF: 0.4% Promogran: 11.2% Dressing adhered to wound bed TLC-NOSF: 3.4% Promogran: 17.1% Bleeding TLC-NOSF: 0.4% Promogran: 3.5% Pain at removal TLC-NOSF: 3.2% Promogran: 15.4%	NR	TLC-NOSF: 14 (24.5%) Promogran: 23 (38.3%)	TLC-NOSF: 7.0 Promogran: 10.0	NR	NR	Difficult dressing removal TLC-NOSF: 0.4% Promogran: 11.2% Dressing adhered to wound bed TLC-NOSF: 3.4% Promogran: 17.1% Bleeding TLC-NOSF: 0.4% Promogran: 3.5% Pain at removal TLC-NOSF: 3.2% Promogran: 15.4%
Meaume 2012 CHALLENGE RCT VLUs	Easy or very easy TLC-NOSF: 97.1% TLC: 98% Totally painless TLC-NOSF: 84.7% TLC: 86.8% Periwound maceration TLC-NOSF: 15.3% TLC: 16.9%	Week 2: 98.9% Week 4: 96.6% Week 6: 96.4%	TLC-NOSF: 29 (10 dressing-related) TLC: 27 (13 dressing-related)	TLC-NOSF: 7.53 TLC: 6.38	NR	Pain–discomfort: (1.53 ± 0.53 vs. 1.74 ± 0.65; p = 0.022) Anxiety–depression: (1.35 ± 0.53 vs. 1.54 ± 0.60; p = 0.037)	TLC-NOSF: 72.1 ± 17.5 TLC: 67.3 ± 18.7 (p = 0.072)

Edmonds 2018 EXPLORER RCT DFUs	NR	NR	TLC-NOSF: 40 (2 dressing-related) TLC: 47 (6 dressing-related)	TLC-NOSF: 20 TLC: 28	TLC-NOSF: 1 TLC: 2	TLC-NOSF: 0.63 ± 0.30 TLC: 0.69 ± 0.32; p=0.245	NR
Richard 2012 DFUs	TLC-NOSF: Ease to apply easy or very easy: 95.6% Ease to remove easy or very easy difficult: 99.1% Absence of bleeding at removal: 95% Absence of bleeding at removal: 96% Absence of pain at removal: 95% Absence of maceration: 73% Absence of adherence to wound: 96% Absence of exudation: 58% Absence of unpleasant odour: 94%	NR	TLC-NOSF: 7 (2 dressing related)	NR	NR	NR	NR
NR= not reported **EQ5D not fully reported; these were the only reported scales**							

3.7 Description of the adverse events

The sponsor reported that they ran a search for adverse events in the following databases: Cochrane, Science Direct, Scopus and Urgo Internal Search. The sponsor identified 3 studies, which are also included in the clinical evidence (Edmonds 2018 (EXPLORER), Richard 2012, and Meaume 2012 (CHALLENGE)). The sponsor also included a synthesis of vigilance data from Urgo's internal database which reported the 'global incidence of vigilance complaints representing merely cutaneous reactions' as 0.00036% (95 events); the sponsor concluded UrgoStart has a good benefit/risk ratio.

Edmonds (2018) reported 42 local adverse events (local infection, new wound, wound worsening, wound bleeding, overgranulation, local infection swab, erythema/inflammation, and blister opening) in the UrgoStart group (2 dressing-related) and 46 in the UrgoTul control group (6 dressing-related). Richard (2012) reported 7 adverse events of which 2 were dressing-related (maceration). Meaume (2012) reported 29 adverse events (contact dermatitis, pain, periwound eczema, increase of ulcer size, overgranulation, infection, inflammation/irritation, macerated periwound skin, and apparition of dark tissue on wound bed) in the UrgoStart group (10 dressing-related) and 27 in the UrgoTul control group (13 dressing-related). Schmutz (2008) reported 16 local adverse events (perilesional skin irritation, pain between dressing changes, overgranulation, and infection) in the UrgoStart group and 27 in the Promogran control group.

The EAC ran additional searches in the MHRA and FDA MAUDE databases (searching "urgostart" or "urgo") and found 0 records of adverse events.

3.8 Description and critique of evidence synthesis and meta-analysis

The sponsor did not include in their submission any evidence synthesis labelled as 'meta-analysis'. The reason for not performing a meta-analysis according to the submission is that the included studies were too heterogeneous. The EAC agrees with this conclusion. Although 4 of the reported studies reported the relative WAR (Edmonds 2018, Meaume 2012, Richard 2012, and Schmutz 2008), 3 assessed the absolute WAR (Edmonds 2018, Meaume 2012, and Schmutz 2008) and 3 wound closure (Edmonds 2018, Munter 2017, and Schmutz 2008) these studies had

different follow-up times, adjuvant treatments, population and wound characteristics, and outcomes definitions. For example Edmonds 2018 reported wound closure at 20 weeks while Schmutz 2008 reported the 12-week wound closure rate. Munter 2017 reported this outcome as time to reach complete wound closure.

The sponsor did include in the submitted evidence a pooled data analysis from observational studies conducted in France and Germany, evaluating UrgoStart in people suffering from CWUs. The study by Munter 2017 calculated time to wound closure, and time to 50% PUSH score, a measure of healing progress and closure rate. The study pooled primary data from 10 studies involving a total of 10,220 cases and reported outcomes for DFUs, LVUs and PUs separately. For their analysis they categorised the cohorts according to the presence of 1 or more risk factors consisting of the duration of a wound ≥6 months or presence of a PUSH wound size measuring ≥8 cm^2.

Although the primary studies included in the submission were not synthesized quantitatively, we describe below a qualitative comparison of the reported outcomes describing efficacy outcomes (healing and wound closure outcomes) when more than 2 studies reported the same outcome for VLUs or DFUs. One RCT (Edmonds 2018) and 2 non-comparative studies (Munter 2017, Richard 2012) reported mean time to CWC for DFUs. The time reported varied between 58 and 120 days. The RCT and the pooled data synthesis by Munter 2017 reported similar mean times, 120 and 98 days respectively. The large difference between these results and the mean time reported by Richard 2012 (58 days) is most likely attributed to the different wound characteristics between these studies. In Richard 2012 specifically the wounds were classified as grade 1A (vs. 1C/2C in Edmonds 2018), more 50% of the wound surface had to be covered by granulation tissue, and the presence of ischemia was an exclusion criterion (rather than inclusion as in Edmonds 2018).

The same studies (Edmonds 2018, Munter 2017, Richard 2012) also reported wound closure rates for DFUs. The rates reported varied between 30% and 48%. The RCT by Edmonds 2018 and the pooled data synthesis by Munter 2017 reported similar rates, 48% and 37.4% days respectively. The difference between the rates reported by Edmonds 2018 and the mean time reported by Richard 2012 (58 days) is most likely attributed to the different wound characteristics between these studies (see

above and Table 4). Despite the seemingly favorable wound characteristics in Richard 2012 in comparison with Edmonds 2018, the reported closure rate was the lowest at 30%. However, it should be noted that the study has a follow-up period of only 12 weeks significantly less than the 20 weeks reported by Edmonds 2018 and Munter 2017. Finally, the relative WAR was similar in both Edmonds 2018 and Richard 2012 (72% ± 47% vs. 62.7% ± 49.9%, respectively).

3.9 Ongoing studies

The sponsor referred to 2 ongoing studies ("Retrospective Study of Clinical Outcomes and Resource Use in Chronic Leg Wound Management in the UK" and "Patient Reported Quality of Life Cross-Sectional Study", but the EAC was unable to locate a record of either.

The EAC searched ClinicalTrials.gov, WHO ICTRP, ISRCTN and PROSPERO (see Appendix A for search strategies) and found 1003 records (854 following de-duplication). Of these the EAC identified 12 relevant ongoing studies although none of these are explicitly focusing on UrgoStart.

4 Economic evidence

4.1 Published economic evidence

Critique of the company's search strategy

The sponsor conducted an economic evidence search on PubMed, Medline, Cochrane and Ovid using the search terms (UrgoStart or TLC-NOSF or KSOS) AND ((Resource AND (Use OR Utilisation)) OR Cost) without any restrictions to search dates. Additional searches were also undertaken to retrieve unpublished literature. The economic evidence related to studies that used Urgostart interventions. A total of 10 records were screened and 6 studies were included.

The EAC reviewed the search strategy (Appendix 3 of sponsor's submission) and found it be appropriate. In order to confirm that all relevant evidence has been included, the EAC conducted its own search (see Appendix A). Following application of cost and economic filters, the searches retrieved 53 abstracts related to economic evidence. After reviewing these abstracts, the EAC confirmed that no economic evidence, additional to that included by the sponsor was available for the technology.

Critique of the company's study selection

The sponsor selected studies based on the scope: population included patients with leg ulcers or diabetic foot ulcers; intervention included Urgostart technology compared to neutral dressings and advanced dressings; outcomes included any health economics outcomes (economic outcomes, resource use, cost, ICER, cost per patient, modelling and economic studies). The exclusion criteria applied were: population including paediatric patients (<18 years) and patients with acute wounds (including burns, trauma, surgery). Interventions such as surgical, non- surgical (including electrical stimulation, hyperbaric treatment, vacuum therapy), infection control measures (including silver, iodine or honey), debridement (including, surgical, maggot), bioengineered skin substitutes and offloading were also excluded. Studies with no economic

outcomes reported, non-English language, in vitro studies, reviews and opinion pieces were also excluded. The EAC reviewed the inclusion and exclusion criteria and determined that they were appropriate. The EAC also used the same inclusion and exclusion criteria.

Included and excluded studies

The sponsor included 6 studies, out of which only one was a full peer-reviewed paper (Augustin 2016). Another one was an economic assessment report from York Health Economics Consortium, on Urgostart for the treatment of chronic leg ulcers (Taylor 2011). The sponsor included 4 unpublished studies, which were marked academic in confidence. The EAC could source only one abstract from its literature review (Maunoury 2012). This was a Markov model, set in the French healthcare systems, with no information in the abstract on the source of clinical data, and was excluded by the EAC. Two of the 4 unpublished studies included by the sponsor were updates of the Maunoury 2012 study, and were excluded by the EAC. The EAC received the two electronic unpublished budget impact analysis, which reported cost saving for UrgoStart compared to neutral dressing. The budget impact models extrapolated the cost savings of introducing UrgoStart in the NHS for a 5 year period. The budget impact model reported a cost per patient of £1446 (UrgoStart) vs £1639 (neutral dressing) for diabetic foot ulcers; and £1544 (UrgoStart) vs £3115 (neutral dressing) for leg ulcers. The parameters included were similar to that of the *de novo* model submitted by the sponsor. The EAC thus included only 2 studies for review (Augustin 2016; Taylor 2011).

Overview of methodologies of all included economic studies

Of the two included studies, Augustin 2016 constructed a decision tree model using clinical data from the CHALLENGE study (Meaume 2012) taking the perspective of the German statutory health care system for a time horizon of 8 weeks. Response rate (defined as ≥40% wound size reduction) with UrgoStart was 65·6% versus 39·4% for the comparator (neutral foam dressing) in leg ulcers. There was a cost advantage of €486 for UrgoStart per patient. The

main limitation was the short time duration of 8 weeks, which for most patients would not be long enough to reach wound healing.

Taylor 2011 constructed a one-year Markov model using the CHALLENGE study results (adapted to a UK setting) comparing UrgoStart with neutral foam dressing in patients with chronic leg ulcers. Mean reduction in mean surface area is a surrogate endpoint for healing rate, so the authors converted the outcome data to a weekly healing rate by using a formula based on the modelling of healing observations reported by Cardinal 2008.

[redacted] Though UK NHS costs were used for the study, the clinical data comes from the CHALLENGE study undertaken in France.

Overview and critique of the company's critical appraisal for each study

The sponsor used the suggested tables to summarise each study's location, model and comparators, patient population, costs, patient outcomes, and results for the 6 included studies. Further, the sponsor also completed quality assessment for each health economic study included. The EAC thinks, the critical appraisal for each of the included studies have been appropriately performed.

Does the company's review of economic evidence draw conclusions from the data available?

Though the sponsor has included a critical appraisal of the studies, no specific conclusions were draw from the available data. However, all the included studies showed that a larger proportion of patients reported higher wound area reduction with UrgoStart compared to neutral dressings and UrgoStart was cost saving.

4.2 Company de novo cost analysis

Published economic evidence was available for vascular leg ulcer patients only (Augustin 2016). (Note: the study describes the patient population as of venous and mixed aetiology, but utilises data from the CHALLENGE study

which included only venous leg ulcers.) The scope had requested analysis for both diabetic foot ulcers and leg ulcers. Given that new clinical data was available for diabetic foot ulcers (Edmonds 2018), along with the availability of newer resource used data from UK (Guest 2018a, Guest 2018b), the sponsor has presented separate de novo cost analyses for diabetic foot ulcers and leg ulcers. Two Markov models, each with 1 week cycle length were submitted. Results are presented for a time horizon of 1 year.

Patients

The patient population included in the model are those with leg ulcers and those with diabetic foot ulcers, which is in line with the scope. The data used to parameterize the leg ulcer model is taken predominantly from studies of patients with venous leg ulcers.

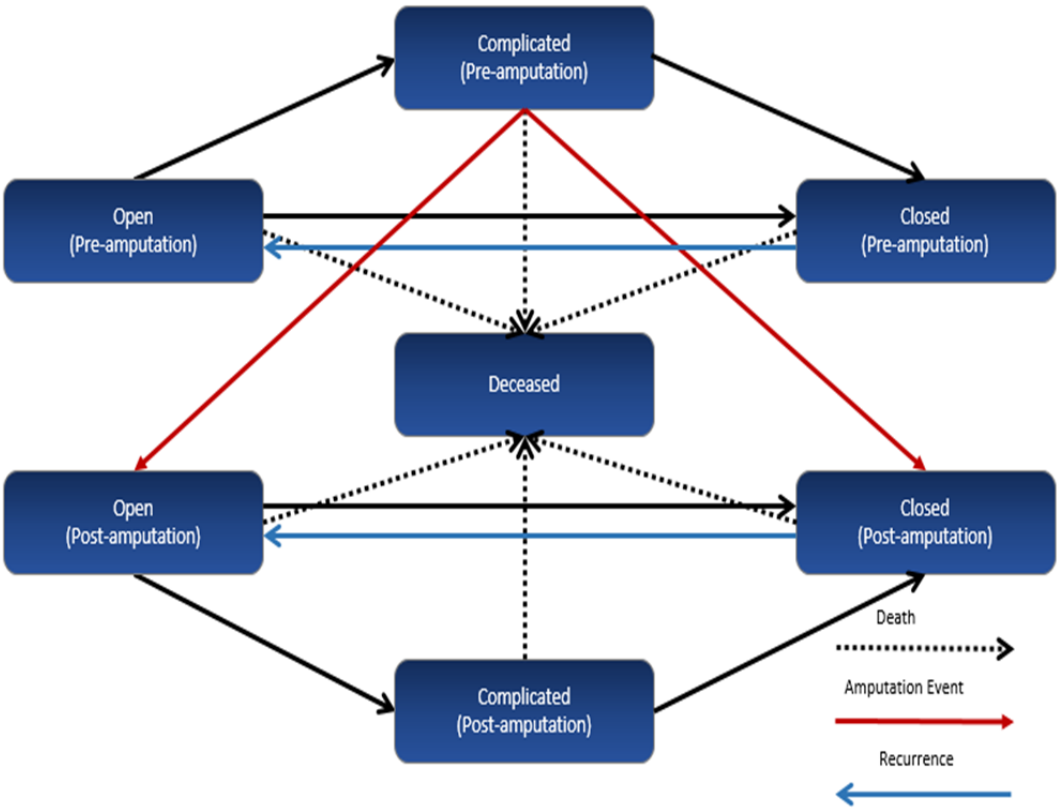
Technology & Comparator(s)

The technology used as the intervention is UrgoStart dressing which contains the TLC-NOSF technology and is aligned with the scope. This is compared with UrgoTul, a neutral dressing manufactured by the same company and for the same indications (leg ulcers and diabetic foot ulcers). UrgoTul was the neutral dressing comparator used in the EXPLORER (Edmonds 2018) and CHALLENGE trials (Meaume , 2012). The EAC thinks that it is a reasonable approach, but notes that other neutral dressings are available which are cheaper and may be equivalent.

Model structure

The sponsor has submitted two Markov models (diabetic foot ulcers and leg ulcers) for estimating the cost-effectiveness of the technology against the comparator from an NHS perspective. The model for diabetic foot ulcers includes the health states: open wound, closed wound and complicated wound for a limb without a previous amputation and a limb post amputation (Figure 1). Patients transition between health states in weekly cycles for a period of one year.

Fig 1: Diabetic foot ulcer model.

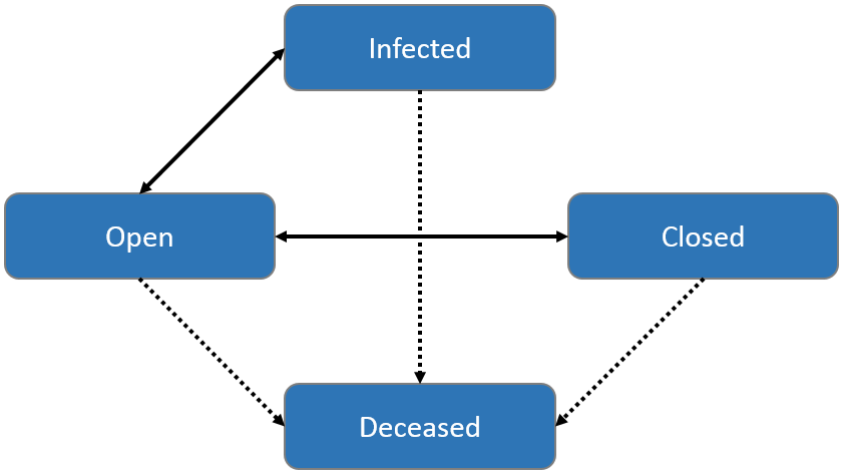


A patient in the diabetic foot ulcer model starts with an open wound (either pre or post amputation) and can transition into a closed (healed) wound or a complicated (infected) wound. Open or complicated wounds pre-amputation can also lead to an amputation. After amputation, patients have a closed wound or their wounds persist as an open wound and would need secondary intervention and could become complicated before healing. In all health states, patients have a risk of death. The EAC is of the opinion that the model structure adequately captures the required health states to examine the costs and consequences of the technology and comparators for patients with diabetic foot ulcers.

The leg ulcer model has 3 states – open, infected or closed (Fig 2). Patients in the model start with an open wound which can become infected. The infection can resolve, in which case the wound is once again open. After healing has occurred, the wound can recur. Patients also transition into the death state

from all other states. The EAC is of the opinion that the model structure adequately captures the health states required to examine the costs and consequences of the technology and comparators for patients with leg ulcer.

Fig 2: Leg ulcer model.



Both models used a number of assumptions which are critiqued below

- The EAC thinks it is reasonable to assume in both the models that all patients begin with an open wound, but notes the possibility that some patients will present with an infected wound.
- The diabetic foot ulcer model assumes that amputation will only occur after patients move to the complicated health state. The EAC thinks this is a reasonable assumption.
- The diabetic foot ulcer model assumes that patients whose ulcer becomes infected either heal or remain infected. They cannot return to the open (uninfected) state. The EAC regards this assumption as acceptable given the data available to parameterise the model.
- The diabetic foot ulcer model allows a maximum of one amputation, which is reasonable to the EAC. In addition, all patients who have an amputation are assumed to require physiotherapy, and a proportion require a prosthesis for a major amputation, which the EAC deems to be reasonable.

- In the diabetic foot ulcer model, a conservative assumption that a closed wound will have the same resource in both pre and post amputation sounds reasonable to the EAC, given that there is no data available to support a difference in health state costs.

- In the leg ulcer model, average infection is assumed to last 2 to 4 weeks and 3 weeks has been used for the base case infection duration. This has been validated by the sponsor's experts. The EAC validated this assumption with NICE experts.

- The EAC notes that key parameters on the healing rate, as well as resource use parameters, for the leg ulcer model are sourced from studies which included patients with venous leg ulcers only.

In summary, the EAC thinks that both model structures adequately captures all the relevant health states and the model assumptions are valid and reasonable.

Summary of the base case

The sponsor's base case results are reported in Table 10 & 11 below.

Table 10. Company's base case results – Diabetic foot ulcer model

	UrgoStart	**Neutral dressing**	**Cost saving per patient/year**
Technology	£390.72	£359.63	-£31.09
Inpatient	£597.61	£811.94	£214.33
Outpatient	£1280.27	£1564.24	£283.97
Medication	£37.95	£44.69	£6.74
Devices (excluding primary dressing)	£734.94	£802.96	£68.02
Amputation event	£142.86	£267.40	£124.54
Total	£3184.35	£3850.86	£666.51

Table 11. Company's base case results – Leg ulcer model

	UrgoStart	Neutral dressing	Cost saving per patient/year
Technology	£157.77	£151.94	-£5.83
Inpatient	£4.60	£4.53	-£0.07
Outpatient	£1140.25	£1370.58	£230.33
Medication	£8.19	£9.78	£1.59
Devices (excluding primary dressing)	£271.78	£320.00	£48.22
Total	£1582.58	£1856.83	£274.25

Clinical parameters and variables

Diabetic foot ulcer model

- The sponsor presents analysis over a time horizon of 1 year which the EAC thinks is appropriate.
- The age of the patients in the model is 65 years and consistent with the EXPLORER study (Edmonds 2018)
- The proportion of patients with a prior amputation is based on the EXPLORER study which reported 50%.
- Seventy-six percent of all amputations are considered to be major, and of these 86% require a prosthesis after amputation (NICE 2015). The EAC regards this as reasonable.
- Transition probabilities have been sourced from the EXPLORER study (Edmonds 2018), National Diabetes Foot Care Audit (CARMS NHS Digital 2018) and the Eurodiale study (Dubský 2013). The EAC checked these probabilities and found those reported from the National Diabetes Foot Care Audit and Eurodiale study to be valid.

- Transition probabilities for healing and infection have been estimated from data collected in the EXPLORER trial. The data was not published in sufficient detail to verify all calculations but the EAC has received raw data from the sponsor which is consistent with the sponsor's model. Weekly probabilities have been estimated via conversion of probabilities over 20 weeks to rates. The EAC regards this as acceptable but notes that this assumes that transition rates are constant over time.

- The transition probability in the comparator arm for transitioning from open wound pre amputation state to complicated wound pre amputation state is 0.0187. This is derived from 16 patients out of 51 patients who became infected over 20 weeks in the EXPLORER study. This is consistent with the Edmonds 2018. However, the EAC notes that the sponsor has included patients with an amputation on the ipsilateral or contralateral foot from this group. The EAC thinks it would have been more appropriate to consider only amputation status for the relevant limb (i.e. to have excluded patients with an amputation of the contralateral limb).

- The transition probability in the comparator arm from open wound pre amputation to closed wound pre amputation is 0.0167. This is derived from 10 patients out of 35 patients with open wound and no prior amputation who healed without becoming infected. The EAC regards this estimation as incorrect. The EAC believes the probability should be calculated using the total number of patients without amputation rather than the subgroup of patients who did not become infected. Accepting the sponsor's definition of amputation (either limb) the number healed is 10 patients from 51, not 35. This generates a weekly probability of 0.0109.

- The transition probability from complicated pre amputation to closed pre amputation is generated from evidence from the EXPLORER trial in which 16 patients became infected, and of these 1 healed. The

sponsor has assumed that the observed transition occurred over an observation period of 20 weeks. In reality, if infections occurred at a steady rate over the trial observation period most patients would have been in the infected state for less than 20 weeks. The EAC believes that an observation period of 10 weeks is a more appropriate estimate of the likely duration of infected ulcers for patients in the trial and should be the basis for the calculation of the weekly probability.

- Transition parameter estimates for patients in the post amputation health states are subject to similar concerns regarding the use of the data reported in Edmonds 2018 and the raw data from the trial provided to the EAC.

- With regard to the transition probabilities for the technology arm, the above issues persist. The EAC notes that patients have been divided into pre-amputation and post-amputation subgroups on the basis of any amputation history rather than amputation in the ipsilateral limb. The EAC believes it would have been more appropriate to classify patients according to amputation history for the relevant limb. Again, the sponsor has subtracted the number of patients becoming infected from the starting population before calculating the probability of healing over 20 weeks. The EAC views this as incorrect; healing probabilities over 20 weeks should be calculated from the proportion of the starting population who heal (and not the subpopulation who do not become infected).

- The sponsor reports that the utility weights for the diabetic foot ulcer model has been sourced from Edmonds 2018. Though the manuscript reports utility weights for UrgoStart and neutral dressing groups, the EAC is unclear on how the sponsor estimated separate utilities for the 6 health states in the model, as this is not reported in Edmonds 2018. It seems that the sponsor has used raw data from the EXPLORER trial to estimate utilities for the specific health states in the model.

Leg ulcer model

- The sponsor presents analysis over a time horizon of 1 year which the EAC thinks is appropriate.

- The age of patients in the model is 73 years and consistent with the CHALLENGE study (Meaume 2012).

- A typical infection is assumed to last 2 to 4 weeks and 3 weeks has been used for the base case infection duration. This has been validated by the sponsor's clinical experts. The EAC also validated this assumption with clinical experts appointed by NICE. The transition probability for resolution of infection (infected to open) for the comparator and technology arms has been estimated as 1/duration of infection, which generates a transition probability of 0.333. The EAC regards this as an acceptable approximation.
- The transition probability of moving from open to infected wound for the comparator and technology arm is sourced from the CHALLENGE study and is consistent with the source.
- The transition probability from closed to open wound (comparator and technology arms) is based on Clarke-Moloney 2012, with 16 patients out of 100 patients having a recurrence over 1 year. The study has been done in Ireland and the EAC thinks it is a valid source for these transition probabilities.
- The CHALLENGE study did not measure wound healing as an endpoint of the study, and measured Relative Wound Area Reduction (RWAR) as a surrogate endpoint for healing. The sponsor has transformed this into a healing rate using an exponential model reported by Cardinal 2008. The EAC has some concerns with this approach. The use of RWAR has been reported to generate a bias towards smaller wounds and to underestimate time to healing (Gilman 2004). It should also be noted that the application of such an exponential model to generate a healing rate is the mathematical equivalent of assuming that the RWAR is equal to the proportion of

patients healed. Despite these reservations the EAC accepts the sponsor's calculation in the absence of more definitive data on healing rates with UrgoStart vs UrgoTul.

- The sponsor failed to convert the healing rates over one week for both the technology and the comparator to a probability before application in the Markov model. The EAC converted the rates to probabilities in its updated model. The impact of this is small.
- The utilities for the leg ulcer model health states have been sourced from a quality of life study in the UK, which the EAC considers as reasonable (Palfreyman 2008).

Resource identification, measurement and valuation

For all health states in the two models, resource data was sourced after a systematic search using the following search strategy

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

Multiple databases, including PubMed, Medline, Cochrane and Ovid were searched. The inclusion criteria restricted studies to DFU or LU management resource use in the UK from 2015. Acute wounds, or a mixed chronic wound population, prevention, diagnostic, decision making tools, not including resource use and studies before 2015 were excluded. The EAC deems this search to be reasonable.

Out of the 71 returned abstracts, only two studies (Guest 2018a, Guest 2018b) included relevant resource use data. Guest 2018a reported on diabetic foot ulcers and Guest 2018b reported on venous leg ulcers. The EAC thinks these are relevant resource use sources for the analysis.

Resource Use

<u>Diabetic foot ulcer model</u>

- Guest 2018a provides data on resource use taken from THIN, an electronic database of records for patients at 562 GP practices across the UK, for 130 patients with a confirmed diabetic foot ulcer. Of these, 35% healed and 17% had an amputation over the 12 month observation period. Evidence on infection is limited but Guest estimates that between 14% and 45% of patients had an infected wound at some point over the 12 months. The EAC regards the study as appropriate as it is a large, representative and recent sample of UK practice.

- Guest 2018a provides data on resource use and cost both overall and by sub-groups. The overall cost is £7800 2015/16 GBP. The sub-groups for which both resource use and costs are tabulated are by outcome: healed, unhealed and amputated. Costs are also reported by subgroup according to evidence of infection: no anti-infective or anti-microbial resource use; anti-microbial dressing only; and anti-infective prescription (with or without anti-microbial dressing). Data is presented on the proportion of patients in most subgroups who healed and the mean time to healing (data on mean time to amputation is not reported for the relevant subgroup). Finally, monthly costs for subgroups according to outcome (healed, unhealed and amputated) are plotted.

- The manufacturer has taken the resource use tabulated by Guest 2018a and applied updated unit costs. Data presented for patients with an unhealed ulcer is used for the open wound (pre-amputation) state. A multiplier of 0.5 is applied to all resource use to recognise the likely lower costs for the subgroup of patients in the data presented by Guest who did not suffer an infection. The same data with a multiplier of 1.5 is used to estimate resource use in the complicated (infected) wound (pre-amputation) state. The multipliers are justified by the data presented according to evidence of infection for which Guest observe that costs are at least 67% lower for patients with no evidence compared to patients in the other subgroups. The resource use data for

patients with an ulcer which heals is used to estimate resource use in the closed wound state (both pre and post amputation).

- A similar approach has been used to estimate resource use in the open wound and complicated (infected) wound post-amputation states. Resource use for both is based on values tabulated for patients with an ulcer leading to amputation. Again, multipliers of 0.5 and 1.5 are applied to estimate resource use for patients with and without an infection, respectively.

- For secondary dressing, the sponsor has assumed that open DFU and infected DFU require 57% and 30% less secondary dressings than the respective primary dressings required for each wound type. This assumption is based on the Urgo Medical chart extraction study, which the EAC did not have access to. However, the assumption seems reasonable and the sponsor has tested the uncertainty surrounding this parameter in the sensitivity analysis.

- The EAC has a number of concerns regarding the application of this data in the sponsor's submission. All data presented by Guest 2018a is for patients with a DFU; for some patients the ulcer heals and for others it leads to amputation. The proportion healed, and hence the mean number of months with a DFU over the 12 month observation period, varies by subgroup; only for the unhealed subgroup is this 12 months. For the other subgroups an assumption of 12 months duration will underestimate weekly costs attributable to DFU.

- Data presented for the 'healed DFU' subgroup represents resource use for patients with an ulcer which heals over the 12 month observation period. Mostly this will be associated with the ulcer prior to healing rather than post. This is evident from the plot of monthly costs in the paper (Figure 5) where costs tend to zero by month 12. (In contrast, costs for unhealed ulcers are fairly constant over the 12 month period.) Consequently the EAC thinks that zero is a better estimate of resource use after healing of a DFU.

- The derivation of the multipliers of 0.5 and 1.5 to represent the relative impact of infection is problematic. The data in table 6 of the paper on which this is based also notes that 70% of patients with no evidence of infection healed in a mean of 2.3 months. The corresponding figure for patients prescribed an anti-infective are 16% and 6.1 months. From this data we can calculate the mean duration of the ulcer for patients in the two subgroups; it is 5.2 months for patients in the former subgroup and 11.1 months for patients in the latter subgroup. If we assume zero costs post healing of the ulcer, the costs for patients prescribed an anti-infective are incurred over a period twice as long as those without. Failing to account for this will overestimate the difference in weekly costs caused by infection.

- There are further concerns regarding the use of this data to estimate the impact of infection on costs. Only 25% of patients received no anti-infective or anti-microbial prescription suggesting that the use of these treatments was sometimes prophylactic. The data on healing proportions might indicate the use of prophylactic anti-infective measures on more serious DFUs. Hence the subgroups identified may be only modestly correlated with infection status and the cost differences may be confounded by ulcer severity. For these reasons, and those outlined above, the EAC regards the application of the 0.5 and 1.5 multipliers to adjust for infection to be insufficiently evidenced. There is an absence of evidence in the literature on the impact of infection on cost per week. EAC applied a multiplier of 1.2 in the base case and explored a wide range of multipliers in sensitivity analysis.

- The EAC also has concerns regarding the use of data from Guest 2018a to estimate resource use for the open and complicated wound post amputation health states. The sponsor has based estimates on resource use tabulated for patients whose outcome is amputation. The resource use relating to the ulcer (rather than the amputation) will have preceded the amputation. Whilst the resource use for the amputation itself can be subtracted from the data tabulated it is unclear how much

of the £4261 of costs attributable to hospital admissions relate to the amputation and how much to the actual ulcer. For these reasons the EAC regards the data tabulated in Guest (2018a) on patients with an amputation endpoint as inappropriate to estimate the resource use for patients with an ulcer post amputation. Instead, it would be more appropriate to assume that the weekly costs are the same as those for patients without a previous amputation. The EAC also believes that the use of a 0.5 and 1.5 multiplier on costs to adjust for infection status is not supported by Guest 2018a for the reasons outlined above.

Leg ulcer model

- Data on resource use for the leg ulcer model has been taken from the publication by Guest 2018b. This is the sister publication to that of Guest 2018a and provides the corresponding data for 505 patients from the THIN database with a confirmed venous leg ulcer. Resource use and costs are tabulated according to outcome: healed (53% of patients), and unhealed and monthly costs for the subgroups are plotted. Costs for unhealed ulcers are stable at approximately £1,100 a month over 12 months. Monthly costs for healed ulcers fall from approximately £750 in the first month to approximately £50 at 12 months.

- Guest 2018b also reports costs by subgroup according to evidence on infection: no infection (53%); patients only received antimicrobial (6%); patients were prescribed anti-infective (with and without antimicrobial) (40%). Costs rise and the proportion of patients who heal falls as evidence of infection increases.

- The sponsor has derived the resource use associated with an open wound from the data in Guest 2018b for patients with an ulcer which does not heal, and the resource associated with a healed ulcer from the data for patients who heal. A multiplier has been applied to the

resource use reported in Guest 2018b for patients who do not heal to differentiate costs in the open wound and infected wound states of 0.475 and 1.525, respectively. The ratio is derived from the observation in Guest that costs are at least 69% lower for patients with no evidence of infection.

- The EAC has concerns regarding the use of the data in Guest 2018b to estimate resource use in the leg ulcer model by the sponsor. The data has been utilised in a very similar fashion to the application of data in Guest 2018a to estimate resource use in the DFU model, and the concerns regarding the use of that data, outlined earlier apply here. In brief, evidence in Guest 2018b suggests that costs for leg ulcer tend to zero as the ulcer heals; costs for patients whose ulcer eventually heals are inappropriate to estimate resource use in the healed ulcer state. Estimation of the impact on weekly resource use of infection on the basis of the ratio of costs for patients with and without infection in Guest 2018b takes no account of the differing duration of ulcers in the different subgroups, as well as the possibility of confounding by severity of ulcer and the misclassification of infections due to prophylactic use. For these reasons the EAC considers the multipliers to be insufficiently supported by the evidence in Guest 2018b. Consistent with the DFU model the EAC applied a multiplier of 1.2 in the base case and varied the multiplier across a wide range in sensitivity analysis.

- For secondary dressing, as with the DFU model the sponsor has assumed that open LU and infected LU require 57% and 30% less secondary dressings than the respective primary dressings required for each wound type, based on Urgo Medical chart extraction study, which the EAC did not have access to. However, the assumption seems reasonable and the sponsor has tested the uncertainty surrounding this parameter in the sensitivity analysis.

Unit costs

Diabetic foot ulcer model

- The cost of hospital admission of £ 2,330 has been sourced from the NHS reference costs (DOH 2016) and the valid codes (KB03C, KB03D, KB03E) for diabetes and lower limb complications have been used.

- The unit costs for GP consultation (£38), hospital outpatient (£138), Podiatrist (£45) have been taken from an appropriate source (Curtis & Burns 2017).

- Unit cost (£20) for a community nurse is based on an assumed 30 minutes visit by a band 6 nurse (Curtis & Burns 2017) and is acceptable to the EAC.

- The unit cost (£50) for a practice nurse is taken from NHS Reference Costs as the weighted average cost of an appointment for a Tissue Viability Nurse (DOH 2016). The EAC has consulted with clinical experts and understands that patients are more likely to be seen at home by community nurses if immobile, or by the practice nurse/GP or a DFU clinic depending on local policy. The EAC thinks that an appropriate unit cost would be that of a band 5 GP practice nurse (£36 per hour). Assuming a contact time similar to that of a community nurse would generate a cost of £18.

- The cost of Antibiotics (1 course of Cefalexin 28 tablets) is reported as £1.57 (BNF 2018). The EAC notes the cost is £1.47 on the BNF. The cost of analgesics (1 course of gastro-resistant Diclofenac Sodium 28 tablets) is reported at £2.07 consistent with the source (BNF 2018).

- The cost of minor amputation used in the model is £4,440, sourced from the national schedule of costs (DOH 2016). This is the weighted average of amputation codes (YQ23B, YQ24B, YQ25B, YQ26B, and YQ26C). The cost of major amputation (£9,269) is the weighted

average of amputation codes (YQ23A, YQ24A, YQ25A, YQ26A). Both are appropriate estimates.

- Follow up physiotherapy after amputation cost is £532, and the cost for prosthesis after major amputation is £2,876. These one off costs are sourced from the NICE Costing report on diabetic foot problems (NICE 2015) and are appropriate. As a part of the economic analysis for NICE guidance (NG19) for Diabetic foot problems: prevention and management, ongoing monthly post amputation care for minor amputation (£64) and major amputation (£418) have been estimated (NICE 2016). In its updated model, the EAC used these estimates of ongoing post amputation care cost (regardless of ulcer status). The EAC used a weighted average of weekly cost of £34.26 based on the sponsor's assumption that 76% of amputations are minor.

Leg ulcer model

- The cost of hospital admission (£452) has been sourced from the NHS reference costs using the codes (JD07A - K) for skin disorders with and without interventions (DOH 2016). However, the weighted average of these codes is £1,586 and needs to be updated in the model.
- The unit cost for GP consultation (£38), and hospital outpatient (£138) have been taken from an appropriate source (Curtis & Burns 2017).
- The unit cost (£20) for a community nurse is based on an assumed 30 minutes visit by a band 6 nurse (Curtis & Burns 2017) and is acceptable to the EAC.
- Similar to the diabetic foot ulcer model, a unit cost (£50) for a practice nurse is derived from the weighted average of the NHS reference costs for Tissue Viability Nursing (DOH 2016). The EAC believes it is unlikely that most patients with leg ulcers would be seen by a specialist Tissue Viability Nurse. For reasons listed in the section describing the diabetic foot model, the EAC believes a band 5 GP practice nurse should be assumed, generating a cost of £18 for a 30 minute appointment.

- The cost of Antibiotics (1 course of Cefalexin 28 tablets) is reported as £1.57 (BNF 2018). The EAC notes that the cost is £1.47 on the BNF. The cost of analgesics (1 course of gastro-resistant Diclofenac Sodium 28 tablets) is reported at £2.07 consistent with the referenced source (BNF 2018).
- Compression system (£6.96) and hosiery (£11.73) have been sourced from Urgo Medical price list. The EAC checked them on the BNF and the sources cited by the sponsor and found them to be valid.

Technology and comparators' costs

The technology price is the sponsor's list price of £4.28. A mean value of 2.08 dressings used per week based on Guest 2018 has been used. The comparator (neutral dressing) has a price of £3.13. This is based on UrgoTul Absorb dressing 10cm x 10cm product. The EAC notes that the UrgoTul dressing is listed as £2.38 on the BNF (2018). The EAC also notes that there are several other products used in place of UrgoTul in the UK which are likely to be equivalent and may be cheaper.

Sensitivity analysis

Uncertainty around assumptions and variables has been tested using one-way deterministic and probabilistic sensitivity analyses. Deterministic sensitivity analysis was used to identify the key cost drivers. If variation of a parameter caused more than a 5% change in the base-case cost it was deemed a cost driver. The remaining parameters were not varied in the probabilistic sensitivity analysis, which was conducted using 1000 runs of the model.

The inference that UrgoStart is cost saving compared with UrgoTul was robust to all deterministic analysis undertaken for the DFU model. The PSA varied all parameters which generated a minimum 5% change in the

incremental cost). The mean cost saving was £664 (range: -£1352 to -£1). When looking at the ICER, UrgoStart is dominant, saving cost and generating health gains.

When varying parameters on the leg ulcer model, resource use during the open wound health state caused the largest variance in costs. With community nurse visits at £0; UrgoStart incurs £24.59 per patient and with primary dressing use at maximum of 208.36 dressings per year in the closed wound health state, UrgoStart incurs £9.57 per patient cost. The PSA varied all parameters deemed to be cost drivers (parameters whose variation generated a minimum 5% change in the incremental cost of UrgoStart) and generated a mean cost saving of £340 (range: -£1723 to £423). UrgoStart is dominant; that is it is cost saving and generates health gains.

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

The EAC is of the opinion that the deterministic sensitivity analyses are appropriate. The PSA excluded parameters whose variation generated less than 5% change in the incremental cost in the deterministic analysis. As a standard practice, it is good to include all the parameters in the PSA. However, this issue is not a major concern.

4.3 Interpretation of economic evidence

The sponsor compares the results of the diabetic foot ulcer and leg ulcer models to published literature (Guest 2018a; Guest 2018b). The diabetic foot ulcer paper highlights a cost range of £2140 - £16,900 dependent on the wound status (Guest 2018a). The sponsor notes that the results of the diabetic foot ulcer model is within these bounds.

For the leg ulcer results, the published literature (Guest 2018b) show a cost range of £3000 - £13,500 for VLUs dependent on the wound healing status. The sponsor's model shows a more modest cost and is attributed to higher healing rates (CHALLENGE study) applied in the model compared to the Guest 2018b.

The EAC notes that the sponsor's estimates of cost over one year are lower than those estimated in the recent literature for a relevant UK population. The EAC believes this reflects a greater propensity for patients in the EXPLORER and CHALLENGE trials to heal compared with routine clinical practice, regardless of the trial arm. The EAC broadly accepts the company's model structure but made a number of changes to both unit cost and transition parameters. The overall effect of these changes is to reduce the estimated cost saving attributable to the technology for DFUs and to increase it for leg ulcers.

4.4 Results of EAC analysis

Given the issues listed above with the sponsor's model, the EAC made a number of changes to model parameters, and estimated new cost savings. The following changes were made to the DFU model:

- Transition probabilities for healing for all subgroups (pre and post amputation in the technology and comparator arm) were re-estimated

using the entire subgroup as the relevant population rather than excluding patents who became infected.

- Transition probabilities for healing following an infection (for all subgroups) were re-estimated assuming a mean observation time of 10 weeks rather than 20 weeks to represent the variable duration of infections for patients in the EXPLORER trial.

- The resource use associated with an open DFU was modified to match resource use reported in Guest 2018a for a healed DFU over a period of 4.4 months, which is the mean healing duration. This was applied to resource use relating to ulcer treatment for both the pre and post amputation states.

- Resource use for a healed ulcer pre amputation was assumed to be minimal on the basis of data reported in Figure 5 of Guest 2018a (costs at 12 months when all ulcers have healed); only the cost of an offloading device (orthotic) was included.

- Resource use relating to ulcer treatment for a healed ulcer post amputation was assumed to be zero apart from the cost of an offloading device (orthotic). (Costs relating to post amputation ongoing care were included.)

- All post amputation states were assumed to accrue ongoing amputation management costs of £34.26 a week representing a weighted average of ongoing costs for patients with a major and a minor amputation.

- Costs for infected ulcers (both pre and post amputation) were assumed to be 20% higher than those for uninfected ulcers. This multiplier was tested in sensitivity analysis.

- The following unit costs were changed: cost of a practice nurse visit (changed from £50 to £18); cost of a prescription of antibiotics (from

£1.57 to £1.47); cost of UrgoTul (from £3.13 to £2.38 based on the price in the BNF).

- The EAC calibrated the model to match the proportion of patients healing with UrgoTul in the model after 1 year to the proportion of patients reported to heal after 1 year in Guest 2018a (35%). The EAC did this by assuming that a subpopulation of those treated would not heal. It fixed the proportion of this subpopulation to ensure the model predicted healing for 35% of the entire cohort with UrgoTul after 12 months. The EAC assumed 20% of the population would not heal. It assumed that treatment for these patients would proceed for 1.4 months (6.09 weeks) on average before the dressing was changed to a different product based on data reported in Guest 2018. During this period patients treated with UrgoStart would accrue additional costs to those treated with UrgoTul reflecting purely the additional dressing costs; all over costs would remain the same. Hence these patients would accrue additional costs of £32.69 (£5.37 per week for 6.09 weeks) when treated with the technology rather than the comparator.

The following changes were made to the leg ulcer model:

- Weekly healing rates for the technology and the comparator calculated from data on the median RWAR reported in the CHALLENGE trial were converted to weekly probabilities before application in the model.

- The resource use associated with an open leg ulcer was modified to match resource use reported in Guest 2018b for a healed venous leg ulcer over a period of 3.0 months, which is the mean healing duration.

- Resource use for a healed ulcer was assumed to be zero on the basis of data reported in Figure 5 of Guest 2018b.

- Costs for infected ulcers were assumed to be 20% higher than those for uninfected ulcers. This multiplier was tested in sensitivity analysis.

- The following unit costs were changed: cost of a practice nurse visit (changed from £50 to £18); cost of a prescription of antibiotics (from £1.57 to £1.47); cost of a hospital admission (from £452 to £1,586); cost of UrgoTul (from £3.13 to £2.38 based on the price in the BNF).

- The EAC calibrated the model to match the proportion of patients healing with UrgoTul in the model after 1 year to the proportion of patients reported to heal after 1 year in Guest 2018b (53%). The EAC did this by assuming that a subpopulation of those treated would not heal. It fixed the proportion of this subpopulation to ensure the model predicted healing for 53% of the entire cohort with UrgoTul after 12 months. The EAC assumed 37.6% of the population would not heal. It assumed that treatment for these patients would proceed for 1.9 months (8.26 weeks) on average before the dressing was changed to a different product based on the data reported in Guest 2018b. During this period patients treated with UrgoStart would accrue additional costs to those treated with UrgoTul reflecting purely the additional dressing costs; all over costs would remain the same. Hence these patients would accrue additional costs of £31.81 (£3.85 per week for 8.26 weeks) when treated with the technology rather than the comparator.

The base case results and sensitivity analyses are reported in the sections below.

Base-case analysis results

Table 12: Diabetic Foot Ulcer

	Expected cost per patient (healed population, £)	Cost saving over 1 year (healed population, £)	Cost saving after calibration for patients who don't heal
Comparator (UrgoTul)	£3,102		
Technology (UrgoStart)	£2,667	£435	£342

Table 13: leg Ulcer

	Expected cost per patient (healed population, £)	Cost saving over 1 year (healed population, £)	Cost saving after calibration for patients who don't heal
Comparator (UrgoTul)	£1,813		
Technology (UrgoStart)	£927	£886	£541

Sensitivity analysis results

Deterministic sensitivity analysis was performed for the key model parameters for diabetic foot ulcer and leg ulcer models. Results are reported in table 14 for DFU and table 15 for leg ulcer as the annual cost saving attributable to the technology after calibration adjustment for the proportion of patients who do not heal.

For the DFU model, UrgoStart was cost saving in all sensitivity analyses with the exception of the analysis in which healing rates with UrgoStart estimated from the Explorer trial were reduced by 50%. In this scenario UrgoStart generated a modest cost increase compared to UrgoTul.

For the leg ulcer model, UrgoStart was cost saving in all sensitivity analyses.

Table 14: Diabetic Foot Ulcer

	Cost saving from UrgoStart per patient
Base case	£342
Weekly cost of ulcer care 50% higher	£458
Weekly cost of ulcer care 50% lower	£225
Cost increase due to infection 5%	£316
Cost increase due to infection 50%	£392
Cost increase due to infection 100%	£476
Proportion of patients who don't heal 50% (in calibration)	£201
Proportion of patients who don't heal 30% (in calibration)	£295
Proportion of patients who don't heal 10% (in calibration)	£388
Cost of neutral dressing £3.13	£422
Healing rates for pre and post amputation ulcers with UrgoStart reduced by 50%	-£13
Healing rates for pre and post amputation ulcers with UrgoStart reduced by 25%	£181
Healing rates for pre and post amputation ulcers with UrgoStart increased by 25%	£477
Healing rates for pre and post amputation ulcers with UrgoStart increased by 50%	£591

Table 15: leg Ulcer

Cost saving from UrgoStart per patient	
Base case	£541
Weekly cost of ulcer care 50% higher	£812
Weekly cost of ulcer care 50% lower	£271
Cost increase due to infection 5%	£540
Cost increase due to infection 50%	£544
Cost increase due to infection 100%	£549
Proportion of patients who don't heal 50% (in calibration)	£427
Proportion of patients who don't heal 30% (in calibration)	£611
Proportion of patients who don't heal 10% (in calibration)	£794
Cost of neutral dressing £3.13	£575
Median relative wound area reduction at 8 weeks for UrgoStart 35%	£41
Median relative wound area reduction at 8 weeks for UrgoStart 45%	£297
Median relative wound area reduction at 8 weeks for UrgoStart 55%	£488
Median relative wound area reduction at 8 weeks for UrgoStart 65%	£635

Subgroup analysis

The NICE scope requested subgroup analysis based on wound types. Venous/arterial and mixed aetiology wounds were included in the pooled analysis undertaken reported in Munter 2017. However, the CHALLENGE study included only patients with venous leg ulcers. The EAC considers the DFU model to be representative of diabetic foot ulcers. The EAC analysis excludes pressure ulcers and arterial leg ulcers due to the lack of data.

Model validation

The original models submitted by the sponsor were validated by clinical experts, technical experts and academics at Manchester Metropolitan

University. The EAC checked the electronic model for errors, and ascertained that the model was valid before updating the parameters.

4.5 EAC Interpretation of economic evidence

The sponsor used clinical data from the Explorer and CHALLENGE studies to populate the DFU and leg ulcer models. The sponsor's analysis showed that Urgostart was cost saving over a 1 year time horizon for diabetic foot ulcers and leg ulcers. The EAC detected some anomalies with parameter estimation, particularly with the use of data from Guest 2018a and Guest 2018b in the estimation of resource use associated with health states in the models. The EAC retained the structure of the models submitted by the sponsor but made a number of changes to parameters for resource use, unit costs and transitions. The EAC also calibrated the models using an assumption that a proportion of the population would not see sufficient wound progression with either the technology or the comparator and would be switched to a different product after a period of time.

Following these changes the EAC also found Urgostart to be cost saving. This finding was robust to all sensitivity analysis undertaken on the leg ulcer model and nearly all the sensitivity analysis undertaken for the DFU model. Only when the true healing rates with UrgoStart are half of those reported in the EXPLORER trial is the overall cost of UrgoStart higher than that of the comparator.

The EAC estimated lower cost savings for DFUs compared with analysis using the sponsor's model and higher cost savings for leg ulcers. The EAC's changes to the estimates of resource use associated with the different model states is likely to have increased the cost saving attributable to UrgoStart. The EAC's changes to unit costs (especially the cost of the comparator but also the cost of a practice nurse) are likely to have decreased the cost saving attributable to UrgoStart. The calibration undertaken by the EAC also reduces the cost saving attributable to UrgoStart. The changes the EAC made to

transition parameters is unlikely to have had much impact on estimations of cost savings.

Impact on the cost difference between the technology and comparator of additional clinical and economic analyses undertaken by the External Assessment Centre

As a result of changes to parameters and calibration, the final base case cost savings estimated by the EAC differed from those estimated by the sponsor for DFUs (Table 16) and leg ulcers (Table 17)

Table 16: Diabetic Foot Ulcer

	Sponsor's estimates			EAC's estimates (before calibration)		
	UrgoStart	Neutral dressing	Difference	UrgoStart	Neutral dressing	Difference
Technology	£390.72	£359.63	-£31.09	£348.47	£251.32	-£97.15
Inpatient	£597.61	£811.94	£214.33	£0	£0	£0
Outpatient	£1280.27	£1564.24	£283.97	£1052.29	£1365.09	£312.80
Medication	£37.95	£44.69	£6.74	£46.39	£60.18	£13.79
Devices*	£734.94	£802.96	£68.02	£220.44	£278.50	£58.06
Amputation event	£142.86	£267.40	£124.54	£137.24	£272.14	£134.09
Post amputation care	£0	£0	£0	£862.32	£875.11	£12.79
Total	£3184.35	£3850.86	£666.51	£2667.15	£3102.34	£434.38

*excluding primary dressing

	EAC's model	Sponsor's model	Difference
Saving before calibration	£435	£667	-£232
Saving after calibration	£342	£667	-£325

Table 17: leg Ulcer

	Sponsor's estimates			EAC's estimates (before calibration)		
	UrgoStart	Neutral dressing	Difference	UrgoStart	Neutral dressing	Difference
Technology	£157.77	£151.94	-£5.83	£86.64	£98.27	£11.63
Inpatient	£4.60	£4.53	-£0.07	£12.19	£24.87	£12.68
Outpatient	£1140.25	£1370.58	£230.33	£627.06	£1279.29	£652.23
Medication	£8.19	£9.78	£1.59	£5.20	£10.60	£5.40
Devices*	£271.78	£320.00	£48.22	£196.17	£400.20	£204.03
Total	£1582.58	£1856.83	£274.25	£927.26	£1813.23	£885.97

*excluding primary dressing

	EAC's model	Sponsor's model	Difference
Saving before calibration	£886	£274	£612
Saving after calibration	£541	£274	£267

The EAC estimates lower costs of treatment than those estimated by the sponsor. This is driven primarily by the changes the EAC has made to the resource use associated with treating unhealed and healed ulcers. The costs associated with unhealed leg ulcers have risen; in contrast the costs associated with healed leg ulcers and infected leg ulcers have fallen. The costs associated with DFUs have generally fallen although the cost of treating unhealed DFUs prior to amputation has risen modestly. The changes have had the biggest impact on the estimates for leg ulcers where the EAC estimates much lower costs attributable to treatment with UrgoStart than those in the sponsor's submission. However, the impact of calibration is greater for the leg ulcer model. After calibration, the EAC estimates cost savings for leg ulcers of roughly twice those estimated by the sponsor for leg ulcers and half of those estimated by the sponsor for DFUs.

5 Conclusions

5.1 Conclusions on the clinical evidence

The sponsor provided a submission that included all available clinical evidence on UrgoStart. Three of the studies did not include UrgoStart as the intervention and were excluded by the EAC. The final list of evidence included by the EAC consisted of 3 RCTs (Edmonds 2018 EXPLORER, Meaume 2012 CHALLENGE, Schmutz 2008) and 2 non-comparative studies (Munter 2017, Richard 2012). One RCT (Edmonds 2018) and 2 non-comparative studies (Munter 2017, Richard 2012) analysed people with DFUs and 2 RCTs (Meaume 2012, Schmutz 2008) and 1 non-comparative study analysed people with mixed aetiology LUs (Munter 2017). The comparative studies submitted by the sponsor compared the intervention with UrgoTul or UrgoTul Absorb (non-advanced dressing) and with Promogran (advanced dressing).

Because of high dropout rates the RCT by Schmutz 2008 was underpowered. As a result the main evidence for DFUs are based on Edmonds 2018 and for VLUs on Meaume 2012. Based on Meaume 2012 in people with VLUs use of UrgoStart results in statistically significant higher relative WAR rates. Based on Edmonds 2018 in people with DFUs use of UrgoStart results in higher healing rates in comparison with the control. The level of benefit in terms of healing rates for DFUs and VLUs was also broadly supported by evidence from a pooled analysis of non comparative data (Munter 2017). Edmonds 2018 recruited patients from UK sites, therefore, the results should be generalisable to the UK setting.

There are no evidence to support improved quality of life with the intervention, however, there are some evidence to support non-inferiority in both DFUs and VLUs. Although the re-analysis of the CHALLENGE trial resulted in higher QoL with UrgoStart in some of the dimensions (pain/discomfort and anxiety/depression) there was no overall improvement in QoL. The patient acceptance and safety profile in terms of local adverse events was similar between UrgoStart and the comparators in the CHALLENGE and EXPLORER

trials. None of the included studies were adequately powered to detect differences in the secondary outcomes such as QoL, acceptability and safety.

The majority of the included evidence refers to venous leg ulcers, however, the clinical experts consulted as part of the assessment report, were of the opinion that findings on the efficacy of UrgoStart in venous leg ulcers are generalisable to the broader category of leg ulcers. If this is the case then the EAC believes that the findings on the impact on costs will also be generalisable.

5.2 Conclusions on the economic evidence

As a part of the economic submission, the sponsor performed a systematic review of economic evidence. They included 6 studies of which 4 were unpublished studies. After confirmation with its own systematic review, the EAC included only two studies on leg ulcers, which were both based on the CHALLENGE study results. One was for a time horizon of 8 weeks and the other one adapted to the UK context was for 1 year. Both the studies reported that UrgoStart was cost savings compared to neutral dressing. The sponsor submitted cost analysis based on two Markov models; for diabetic foot ulcers and leg ulcers. The EAC reviewed the models and found the model structure to be appropriate. However, the EAC disagreed with the sponsor on the appropriate utilization of the relevant literature in the estimation of model parameters. The EAC retained the literature used by the sponsor but made a number of changes to parameter estimates.

The sponsor's model results showed that UrgoStart was cost saving compared to UrgoTul. The EAC updated the clinical and cost parameters, and re-estimated the cost savings. The EAC estimated lower cost savings for DFUs but higher cost savings for leg ulcers compared with the sponsor's estimates. The EAC found UrgoStart to be cost saving for diabetic foot ulcers and leg ulcers. The EAC concludes that UrgoStart provides a cost saving of £342 per patient with a diabetic foot ulcer over 1 year and a cost saving of £541 per patient with a leg ulcer over 1 year. Sensitivity analysis performed by

the EAC supported the inference that UrgoStart is cost saving compared to UrgoTul.

6 Summary of the combined clinical and economic sections

The efficacy of UrgoStart is supported by evidence provided by randomised comparative studies, mainly the CHALLENGE for VLUs and the EXPLORER for DFUs, and the magnitude of the effect is supported by evidence from single-armed observational data. The results should be generalisable to the UK setting. Economic evidence and *de novo* model analysis results show that UrgoStart technology compared to neutral dressings (UrgoTul) results in cost savings for diabetic foot ulcers and leg ulcers.

7 Implications for research

Future comparative studies should be adequately powered to use complete wound closure as a primary endpoint rather than outcomes associated with measures of wound area reduction as the former is more clinically relevant and has not been investigated in people with leg ulcers. Adequately powered comparative evidence on the effect of UrgoStart on quality of life for both leg ulcers and DFUs are missing. Finally, further studies should focus on other subgroups of leg ulcers as the current evidence is mainly focused on venous leg ulcers.

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Appendix A: Search strategies

The search strategy was created following scoping of search terms from a reference set comprising the studies included in the UrgoStart medtech innovation briefing (MIB82) (https://www.nice.org.uk/advice/mib82). The CDSR was searched using the term "urgostart" and the search strategies of relevant reviews also contributed to scoping free-text and keyword terms.

The following searches are broken down into 2 parts to aid the sifting process. The first part of the search focuses on terms specific to the technology (brand name variation, UrgoStart specific technology etc.), while the second part of the search was structured around elements of the PICO (omitting the comparator element). For the second part of the search the date limits were set at 2008 to present and animal studies were excluded.

The searches for ongoing trials and economic evidence are simplified and less restrictive to reflect the smaller amount of evidence on these topics.

Clinical evidence

UrgoStart specific search (no date limits): 310 before de-duplication, 209 unique references.

Generic search on wound care dressings (2008-present): 7080 before de-duplication, 4109 unique references.

Combined total (including 5 from reference set): 4323 before de-duplication, 4257 unique references.

First sift excluded 4210 references leaving 47 for full-text review.

- Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
- Search date: 19th March 2018

1	(urgostart* or urgo-start* or urgo start*).mp.	6
2	(nano-oligosaccharide factor or nanooligosaccharide factor or NOSF).tw.	23
3	(technology adj1 (lipido-colloid or lipido colloid or lipidocolloid)).tw.	7
4	(Protease Inhibitor adj3 dressing*).tw.	2
5	TLC-NOSF.tw.	8
6	or/1-5	31

1	ulcer/	13346
2	exp diabetic foot/	7425
3	exp Leg Ulcer/	20320
4	pressure ulcer/	11222
5	exp skin ulcer/	40811
6	((varicose or venous or foot or feet or toe or leg or stasis or crural or cruris or diabet* or pressure) adj3 ulc*).tw.	21711
7	((pressure or bed) adj (sore or sores)).tw.	3116
8	chronic wound*.tw.	4702
9	((non-healing or non healing or nonhealing) adj3 wound).tw.	390
10	or/1-9	63405
11	exp bandages/	22630
12	dressing*.tw.	19925
13	bandag*.tw.	5270
14	gauze*.tw.	3864
15	or/11-14	39868
16	((time or rate or minute* or second*) adj5 wound healing).tw.	2497
17	((time or rate or minute* or second*) adj5 wound clos*).tw.	1052
18	wound area reduction.tw.	84
19	wound area progression.tw.	1
20	exp wound healing/	113314
21	or/16-20	114686
22	10 and 15 and 21	2452
23	(case report or editorial or letter).pt.	1432819
24	22 not 23	2397

25	animals/ not (animals/ and humans/)	4401096
26	24 not 25	2322
27	limit 26 to yr="2008-Current"	1086

- Embase 1974 to 2018 Week 12
- Search date: 19th March 2018

1	(urgostart* or urgo-start* or urgo start*).mp.	12
2	(nano-oligosaccharide factor or nanooligosaccharide factor or NOSF).tw.	35
3	(technology adj1 (lipido-colloid or lipido colloid or lipidocolloid)).tw.	9
4	(Protease Inhibitor adj3 dressing*).tw.	2
5	TLC-NOSF.tw.	11
6	or/1-5	45

1	diabetic foot/	12571
2	leg ulcer/	13314
3	exp decubitus/	18727
4	buruli ulcer/ or foot ulcer/ or leg ulcer/ or plantar ulcer/ or trophic ulcer/	19498
5	ulcerogenesis/	2420
6	((varicose or venous or foot or feet or toe or leg or stasis or crural or cruris or diabet* or pressure) adj3 ulc*).tw.	27672
7	((pressure or bed) adj (sore or sores)).tw.	3791
8	chronic wound*.tw.	6271
9	((non-healing or non healing or nonhealing) adj3 wound).tw.	537
10	or/1-9	62291
11	hydrocolloid dressing/ or hydrogel dressing/ or silicone dressing/ or transparent dressing/ or wound dressing/ or occlusive dressing/ or foam	15981

	dressing/ or biological dressing/ or pressure dressing/ or silver dressing/ or gauze dressing/	
12	bandage/ or elastic adhesive bandage/ or adhesive bandage/ or compression bandage/	12708
13	(dressing* or bandag*).tw.	31046
14	gauze*.tw.	5061
15	or/11-14	48073
16	((time or rate or minute* or second*) adj5 wound healing).tw.	3471
17	((time or rate or minute* or second*) adj5 wound clos*).tw.	1414
18	wound area reduction.tw.	94
19	wound area progression.tw.	1
20	wound healing/ or ulcer healing/ or tissue regeneration/	128004
21	or/16-20	129204
22	10 and 15 and 21	3519
23	(case report or editorial or letter).pt.	1562955
24	22 not 23	3416
25	animals/ or animal experiment/ or (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep or ovine).ti,ab,sh.	6074841
26	exp human/ or human experiment/	19336688
27	25 not (25 and 26)	4765368
28	24 not 27	3297
29	limit 28 to yr="2008-Current"	1956

- Cochrane (CDSR, CENTRAL, DARE, Cochrane Methodology Register, HTA Database and NHSEED)
- Search date: 19th March 2018

ID	Search	Hits
#1	(urgostart* or urgo-start* or "urgo start*")	7
#2	("nano-oligosaccharide factor" or "nanooligosaccharide factor" or NOSF)	8
#3	(technology near/1 (lipido-colloid or lipido colloid or lipidocolloid))	2
#4	(Protease Inhibitor near/3 dressing*)	0
#5	TLC-NOSF	4
#6	{or #1-#5}	10

ID	Search	Hits
#1	[mh ^ulcer]	175
#2	[mh "diabetic foot"]	603
#3	[mh "leg ulcer"]	1467
#4	[mh ^"pressure ulcer"]	707
#5	[mh "skin ulcer"]	2280
#6	(varicose or venous or foot or feet or toe or leg or stasis or crural or cruris or diabet* or pressure) near/3 ulc*	4315
#7	(pressure or bed) next (sore or sores)	457
#8	chronic wound*	466
#9	(non-healing or "non healing" or nonhealing) near/3 wound	19
#10	{or #1-#9}	5215
#11	[mh bandages]	2806
#12	dressing*	4510
#13	bandag*	3105
#14	gauze*	1028
#15	{or #11-#14}	6948
#16	(time or rate or minute* or second*) near/5 "wound healing"	1180
#17	(time or rate or minute* or second*) near/5 wound clos*	983
#18	wound area reduction	47
#19	wound area progression	1
#20	[mh "wound healing"]	5036
#21	{or #16-#20}	6092
#22	#10 and #15 and #21 Publication Year from 2008	324

- PubMed
- Search date: 19th March 2018

Search	Query	Items found
#12	Search (#4 or #8 or #9 or #10 or #11)	115
#11	Search TLC-NOSF[Title/Abstract]	8
#10	Search Protease Inhibitor dressing*	88
#9	Search ("nano-oligosaccharide factor"[Title/Abstract] OR "nanooligosaccharide factor"[Title/Abstract] OR NOSF[Title/Abstract])	23

#8	Search (technology lipido-colloid[Title/Abstract] OR technology lipido colloid[Title/Abstract] OR technology lipidocolloid[Title/Abstract])	5
#4	Search ((urgostart* or urgo-start* or "urgo start*"))	6

Search	Query	Items found
#24	Search (#10 and #15 and #21) Filters: published in the last 10 years; Humans Sort by: [pubsolr12]	1000
#23	Search (#10 and #15 and #21) Filters: Humans Sort by: [pubsolr12]	2251
#22	Search (#10 and #15 and #21)	2391
#21	Search (#16 or #17 or #18 or #19 or #20)	125009
#20	Search wound healing[MH]	113337
#19	Search "wound area progression"	1377
#18	Search "wound area reduction"	82
#17	Search wound closure time	6243
#16	Search wound healing time	33707
#15	Search (#11 or #12 or #13 or #14)	39966
#14	Search gauze*[tiab]	3873
#13	Search bandag*[tiab]	5888
#12	Search dressing*[tiab]	20306
#11	Search bandages[MH]	22633
#10	Search (#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9)	61080
#9	Search non-healing wound	1168
#8	Search "chronic wound*"[tiab]	1671
#7	Search (pressure sore*[Title/Abstract] OR bed sore*[Title/Abstract])	3134
#6	Search (varicose ulc*[Title/Abstract] OR venous ulc*[Title/Abstract] OR foot ulc*[Title/Abstract] OR feet ulc*[Title/Abstract] OR toe ulc*[Title/Abstract] OR leg ulc*[Title/Abstract] OR stasis ulc*[Title/Abstract] OR crural ulc*[Title/Abstract] OR cruris ulc*[Title/Abstract] OR diabetic ulc*[Title/Abstract] OR pressure ulc*[Title/Abstract])	20675
#5	Search skin ulcer[MH]	40820
#4	Search pressure ulcer[mesh:noexp]	11227
#3	Search leg ulcer[MH]	20320
#2	Search diabetic foot[MH]	7425
#1	Search ulcer[mesh:noexp]	13348

- Web of Science
- Search date: 19th March 2018

# 6	24	#5 OR #4 OR #3 OR #2 OR #1 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2018

# 5	7	TS=(TLC-NOSF) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2018
# 4	0	TS=(Protease Inhibitor NEAR3 dressing*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2018
# 3	0	TS=(technology NEAR1 (lipido-colloid or lipido colloid or lipidocolloid)) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2018
# 2	24	TS=("nano-oligosaccharide factor" or "nanooligosaccharide factor" or NOSF) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2018
# 1	5	TS=(urgostart* or urgo-start* or "urgo start*") Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2018

# 11	591	#10 AND #9 AND #8 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2008-2018
# 10	13,112	TS=(wound healing time or wound closure time or wound area reduction or wound area progression) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2008-2018
# 9	18,640	TS=(bandag* or dressing* or gauze*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2008-2018
# 8	29,699	#7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2008-2018
# 7	663	TS=(non-healing wound)

		Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2008-2018
# 6	9,069	TS=(chronic wound*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2008-2018
# 4	13	TS=((pressure or bed) NEXT (sore or sores)) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2008-2018
# 3	18,347	TS=((varicose or venous or foot or feet or toe or leg or stasis or crural or cruris or diabet* or pressure) AND ulc*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2008-2018
# 1	13,950	TS=(diabetic foot OR leg ulcer OR decubitus OR buruli ulcer or foot ulcer or leg ulcer or plantar ulcer or trophic ulcer) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2008-2018

- CINAHL
- Search date: 19-20th March 2018

Search ID#	Search Terms	Search Options	Actions
S6	S1 OR S2 OR S3 OR S4 OR S5	Search modes - Boolean/Phrase	(18)
S5	TLC-NOSF	Search modes - Boolean/Phrase	(10)
S4	Protease Inhibitor dressing*	Search modes - Boolean/Phrase	(2)
S3	technology lipido-colloid OR technology lipido colloid OR technology lipidocolloid	Search modes - Boolean/Phrase	(6)
S2	"nano-oligosaccharide factor" OR "nanooligosaccharide factor" OR NOSF	Search modes - Boolean/Phrase	(13)

S1	urgostart	Search modes - Boolean/Phrase	(5)

#	Query	Limiters/Expanders	Last Run Via	Results
S17	S6 AND S9 AND S15	Limiters - Published Date: 20080101-20181231 Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	976
S16	S6 AND S9 AND S15	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	1,972
S15	S10 OR S11 OR S12 OR S13 OR S14	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	14,096
S14	MW wound healing	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	13,710
S13	TX wound area progression	Search modes - Boolean/Phrase	Interface - EBSCOhost	4

			Research Databases Search Screen - Advanced Search Database - CINAHL	
S12	TX wound area reduction	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	148
S11	TX (time or rate or minute* or second*) N5 wound clos*	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	310
S10	TX (time or rate or minute* or second*) N5 wound healing	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	842
S9	S7 OR S8	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	14,641
S8	TX dressing* OR bandag* OR gauze*	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases	14,641

			Search Screen - Advanced Search Database - CINAHL	
S7	MW bandages	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	7,867
S6	S1 OR S2 OR S3 OR S4 OR S5	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	26,740
S5	TX non-healing wound	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	205
S4	TX chronic wound*	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	4,149
S3	TX (pressure OR bed) N1 (sore OR sores)	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search	2,526

			Database - CINAHL	
S2	TX (varicose OR venous OR foot OR feet OR toe OR leg OR stasis OR crural OR cruris OR diabet* OR pressure) N3 ulc*	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	19,600
S1	TX diabetic foot OR leg ulcer OR decubitus OR buruli ulcer OR foot ulcer OR leg ulcer OR plantar ulcer OR trophic ulcer	Search modes - Boolean/Phrase	Interface - EBSCOhost Research Databases Search Screen - Advanced Search Database - CINAHL	11,776

- British Nursing Index
- Search date: 19-20th March 2018

Set	Search	Results
S7	(urgostart* or urgo-start* or "urgo start*") OR ("nano-oligosaccharide factor" or "nanooligosaccharide factor" or NOSF) OR (technology lipido-colloid OR technology lipido colloid OR technology lipidocolloid) OR "Protease Inhibitor dressing*" OR TLC-NOSF	34°
S6	TLC-NOSF	9°
S5	"Protease Inhibitor dressing*"	1°
S3	technology lipido-colloid OR technology lipido colloid OR technology lipidocolloid	17°
S2	("nano-oligosaccharide factor" or "nanooligosaccharide factor" or NOSF)	21°
S1	(urgostart* or urgo-start* or "urgo start*")	11°

Set	Search	Results
S10	((diabetic foot OR leg ulcer OR decubitus OR buruli ulcer OR foot ulcer OR leg ulcer OR plantar ulcer OR trophic ulcer) OR ((varicose OR venous OR foot OR	751°

Set	Search	Results
	feet OR toe OR leg OR stasis OR crural OR cruris OR diabet* OR pressure) AND ulc*) OR ((pressure sore*) OR (bed sore*)) OR "chronic wound*" OR "non-healing wound") AND (dressing* OR bandag* OR gauze*) AND (wound healing time OR wound closure time OR wound area reduction OR wound area progression) **Limits applied: 2008-current**	
S9	((diabetic foot OR leg ulcer OR decubitus OR buruli ulcer OR foot ulcer OR leg ulcer OR plantar ulcer OR trophic ulcer) OR ((varicose OR venous OR foot OR feet OR toe OR leg OR stasis OR crural OR cruris OR diabet* OR pressure) AND ulc*) OR ((pressure sore*) OR (bed sore*)) OR "chronic wound*" OR "non-healing wound") AND (dressing* OR bandag* OR gauze*) AND (wound healing time OR wound closure time OR wound area reduction OR wound area progression)	**1,762°**
S8	wound healing time OR wound closure time OR wound area reduction OR wound area progression	**8,281°**
S7	dressing* OR bandag* OR gauze*	**14,700***
S6	(diabetic foot OR leg ulcer OR decubitus OR buruli ulcer OR foot ulcer OR leg ulcer OR plantar ulcer OR trophic ulcer) OR ((varicose OR venous OR foot OR feet OR toe OR leg OR stasis OR crural OR cruris OR diabet* OR pressure) AND ulc*) OR ((pressure sore*) OR (bed sore*)) OR "chronic wound*" OR "non-healing wound"	**20,882***
S5	"non-healing wound"	**47°**
S4	"chronic wound*"	**1,933°**
S3	(pressure sore*) OR (bed sore*)	**7,275°**
S2	(varicose OR venous OR foot OR feet OR toe OR leg OR stasis OR crural OR cruris OR diabet* OR pressure) AND ulc*	**14,565***
S1	diabetic foot OR leg ulcer OR decubitus OR buruli ulcer OR foot ulcer OR leg ulcer OR plantar ulcer OR trophic ulcer	**9,415°**

- Internurse
- Search date: 19-20th March 2018

All: "tlc-nosf" (12)

All: "protease inhibitor dressing" (0)

All: technology lipido-colloid (23)

All: nano-oligosaccharide factor (13)

All: urgostart (8)

Combined and de-duplicated: **31 results**

Search string:

((diabetic foot OR leg ulcer OR decubitus OR buruli ulcer OR foot ulcer OR leg ulcer OR plantar ulcer OR trophic ulcer) OR ((varicose OR venous OR foot OR feet OR toe OR leg OR stasis OR crural OR cruris OR diabet* OR pressure) AND ulc*) OR ((pressure sore*) OR (bed sore*)) OR "chronic wound*" OR "non-healing wound") AND (dressing* OR bandag* OR gauze*) AND (wound healing time OR wound closure time OR wound area reduction OR wound area progression)

[[[All: diabetic] AND [[All: foot] OR [All: leg]] AND [[All: ulcer] OR [All: decubitus] OR [All: buruli]] AND [[All: ulcer] OR [All: foot]] AND [[All: ulcer] OR [All: leg]] AND [[All: ulcer] OR [All: plantar]] AND [[All: ulcer] OR [All: trophic]] AND [All: ulcer]] OR [[[All: varicose] OR [All: venous] OR [All: foot] OR [All: feet] OR [All: toe] OR [All: leg] OR [All: stasis] OR [All: crural] OR [All: cruris] OR [All: diabet*] OR [All: pressure]] AND [All: ulc*]] OR [All: pressure sore*] OR [All: bed sore*] OR [All: "chronic wound*"] OR [All: "non-healing wound"]] AND [[All: dressing*] OR [All: bandag*] OR [All: gauze*]] AND [All: wound healing] AND [[All: time] OR [All: wound]] AND [All: closure] AND [[All: time] OR [All: wound]] AND [All: area] AND [[All: reduction] OR [All: wound]] AND [All: area progression] (505)

Pre-2008 results removed: **303 results**

- Global Health 1973 to 2018 Week 10
- HMIC Health Management Information Consortium 1979 to January 2018
- Search date: 19th March 2018

1	(urgostart* or urgo-start* or urgo start*).mp.	0
2	(nano-oligosaccharide factor or nanooligosaccharide factor or NOSF).tw.	2
3	(technology adj1 (lipido-colloid or lipido colloid or lipidocolloid)).tw.	0
4	(Protease Inhibitor adj3 dressing*).tw.	0
5	TLC-NOSF.tw.	0
6	or/1-5	2

1	ulcer/	0

2	exp diabetic foot/	0
3	exp Leg Ulcer/	0
4	pressure ulcer/	0
5	exp skin ulcer/	0
6	((varicose or venous or foot or feet or toe or leg or stasis or crural or cruris or diabet* or pressure) adj3 ulc*).tw.	1687
7	((pressure or bed) adj (sore or sores)).tw.	166
8	chronic wound*.tw.	413
9	((non-healing or non healing or nonhealing) adj3 wound).tw.	32
10	or/1-9	2147
11	exp bandages/	120
12	dressing*.tw.	3109
13	bandag*.tw.	404
14	gauze*.tw.	516
15	or/11-14	3832
16	((time or rate or minute* or second*) adj5 wound healing).tw.	322
17	((time or rate or minute* or second*) adj5 wound clos*).tw.	141
18	wound area reduction.tw.	10
19	wound area progression.tw.	1
20	exp wound healing/	5161
21	or/16-20	5260
22	10 and 15 and 21	65
	Re-run in HMIC	28

Grey literature

- www.greylit.org/

- www.opengrey.eu/
- www.oaister.org/
- ntrl.ntis.gov/NTRL/
- http://webarchive.nationalarchives.gov.uk/adv_search/
- http://www.opendoar.org/
- https://patents.google.com/
- https://www.orcha.co.uk
- Search date: 19th March 2018

Search term "urgostart" – 0 records found

Ongoing studies

Total records retrieved: 1003

Total following de-duplication: 854

- ClinicalTrials.gov
- Search date 11th April 2018

urgostart OR urgo OR "nano-oligosaccharide factor" OR NOSF OR technology lipido colloid OR protease inhibitor dressing OR TLC-NOSF OR sucrose octasulfate	with results	0
	without results	17
("diabetic foot" OR "leg ulcer" OR "foot ulcer" OR "pressure ulcer" OR "chronic wound" OR "non-healing wound") AND (dressing OR bandage OR gauze OR "wound healing" OR "wound closure")	with results	77
	without results	551

- WHO ICTRP
- Search date 11th April 2018

urgostart OR urgo OR nano-oligosaccharide factor OR NOSF OR technology lipido colloid OR protease inhibitor dressing OR TLC-NOSF OR sucrose octasulfate	9
wound healing AND dressing* AND diabetic foot OR leg ulcer*	304

- ISRCTN
- Search date 11th April 2018

Searched: "urgo", "urgostart" – 1 result

- PROSPERO
- Search date 11th April 2018

Line	Search for	Hits

#1	urgo OR urgostart	4
#2	NOSF OR nano-oligosaccharide factor OR technology lipido colloid	1
#3	sucrose octasulfate	0
#4	protease inhibitor dressing	0
#5	#1 OR #2 OR #3 OR #4	4
#6	diabetic foot	79
#7	leg ulcer	23
#8	foot ulcer	42
#9	pressure ulcer	59
#10	chronic wound	25
#11	non-healing wound	2
#12	#6 OR #7 OR #8 OR #9 OR #10 OR #11	166
#13	dressing OR bandage OR gauze	145
#14	#12 AND #13	40
#15	#5 OR #14	42

Economics searches

Total records retrieved: 62

Total following de-duplication: 53

- Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
- Embase 1974 to 2018 Week 16
- Search date: 20th April 2018

1	(urgostart* or urgo-start* or urgo start*).mp.	6
2	(nano-oligosaccharide factor or nanooligosaccharide factor or NOSF).tw.	23
3	(technology adj1 (lipido-colloid or lipido colloid or lipidocolloid)).tw.	7
4	(Protease Inhibitor adj3 dressing*).tw.	2

5	TLC-NOSF.tw.	8
6	urgo.mp.	26
7	or/1-6	53
8	quality-adjusted life years/ or exp economics/ or exp economic aspect/ or (cost* or econ* or reimburs* or payment* or copayment* or icer or icers or qaly* or quality adjusted life year* or payer* or fee or fees or price or prices or pricing or technology assessment* or hcfa or health care finance administration*).mp.	1132281
9	7 and 8	3
	Re-run in Embase	21

- Cochrane (CDSR, CENTRAL, DARE, Cochrane Methodology Register, HTA Database and NHSEED)
- Search date: 20th April 2018

ID	Search	Hits
#1	(urgostart* or urgo-start* or "urgo start*" or urgo)	33
#2	("nano-oligosaccharide factor" or "nanooligosaccharide factor" or NOSF)	8
#3	(technology near/1 (lipido-colloid or lipido colloid or lipidocolloid))	2
#4	(Protease Inhibitor near/3 dressing*)	0
#5	TLC-NOSF	4
#6	{or #1-#5}	36
#7	cost* or econ* or reimburs* or payment* or copayment* or icer or icers or qaly* or "quality adjusted life year*" or payer* or fee or fees or price or prices or pricing or "technology assessment*" or hcfa or "health care finance administration*"	109249
#8	#6 and #7	27

- PubMed
- Search date: 20th April 2018

Search	Query	Items found
#10	Search (#6 and #9)	9
#9	Search (#7 or #8)	1295177
#8	Search (quality-adjusted life years[MH] or economics[MH] or economic aspect[MH])	559488
#7	Search (cost* or econ* or reimburs* or payment* or copayment* or icer or icers or qaly* or "quality adjusted life year*" or payer* or fee or fees or price or prices or pricing or "technology assessment*" or hcfa or "health care finance administration*")	1147511
#6	Search (#1 or #2 or #3 or #4 or #5)	160

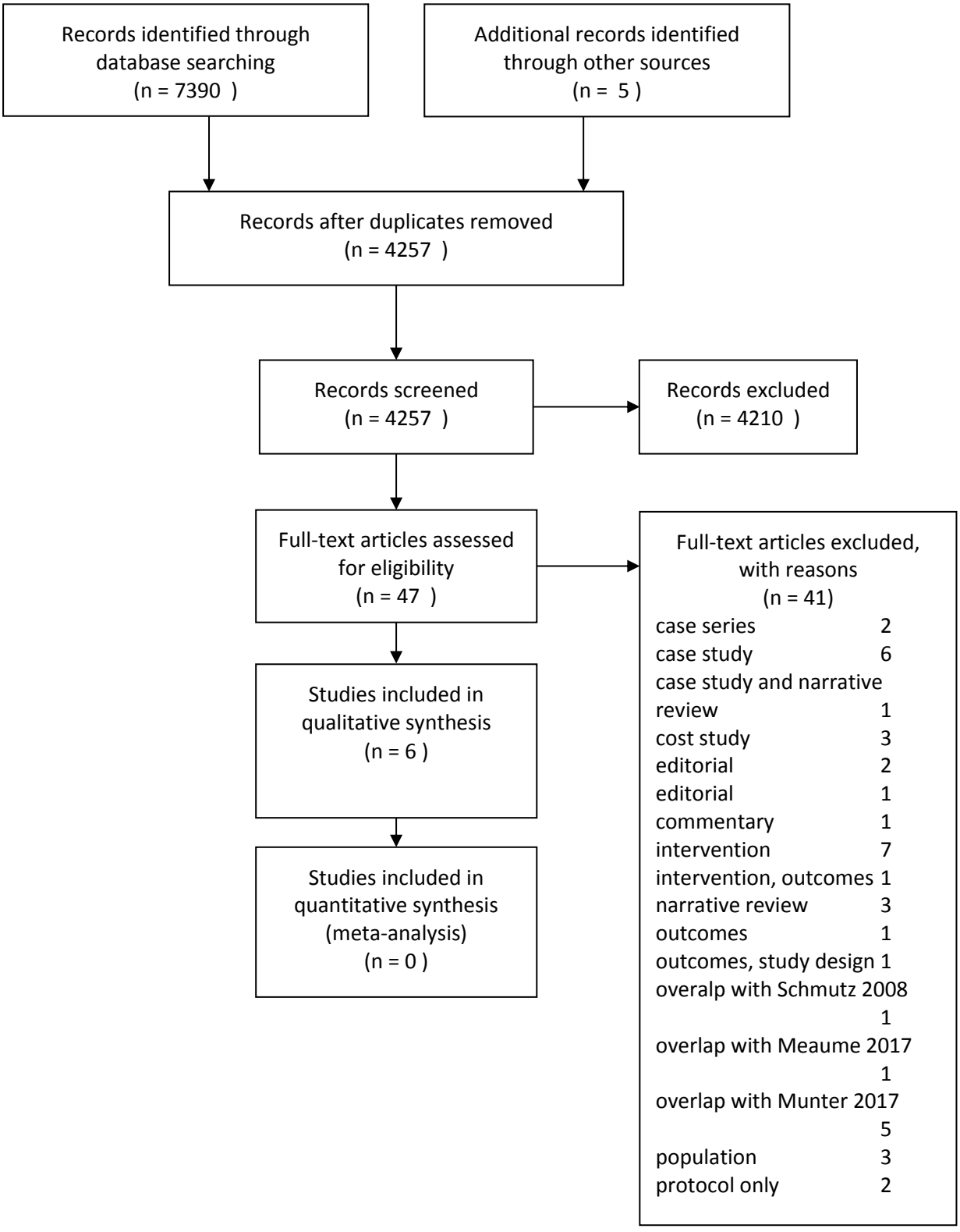
#5	Search TLC-NOSF[Title/Abstract]	8
#4	Search Protease Inhibitor dressing*	88
#3	Search ("nano-oligosaccharide factor"[Title/Abstract] OR "nanooligosaccharide factor"[Title/Abstract] OR NOSF[Title/Abstract])	23
#2	Search (technology lipido-colloid[Title/Abstract] OR technology lipido colloid[Title/Abstract] OR technology lipidocolloid[Title/Abstract])	5
#1	Search ((urgostart* or urgo-start* or "urgo start*" or urgo))	53

- Web of Science
- Search date: 20th April 2018

# 9	2	#7 and #8 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2018
# 8	2,569,381	TS=(cost* or econ* or reimburs* or payment* or copayment* or icer or icers or qaly* or "quality adjusted life year*" or payer* or fee or fees or price or prices or pricing or "technology assessment*" or hcfa or "health care finance administration*") Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2018
# 7	50	#6 OR #5 OR #4 OR #3 OR #2 OR #1 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2018
# 6	28	TS=(urgo) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2018
# 5	7	TS=(TLC-NOSF) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2018
# 4	0	TS=(Protease Inhibitor NEAR3 dressing*) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2018
# 3	0	TS=(technology NEAR1 (lipido-colloid or lipido colloid or lipidocolloid)) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2018

# 2	24	TS=("nano-oligosaccharide factor" or "nanooligosaccharide factor" or NOSF) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2018
# 1	5	TS=(urgostart* or urgo-start* or "urgo start*") Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=1900-2018

EAC PRISMA 2009 Flow Diagram



Appendix B: Methodological quality template

Study identification					
Include author, title, reference, year of publication					
Guideline topic:		**Review question no:**			
Checklist completed by:					
		Circle or highlight one option for each question			
A. Selection bias (systematic differences between the comparison groups)					
A1	An appropriate method of randomisation was used to allocate participants to treatment groups (which would have balanced any confounding factors equally across groups)	Yes	No	Unclear	N/A
A2	There was adequate concealment of allocation (such that investigators, clinicians and participants cannot influence enrolment or treatment allocation)	Yes	No	Unclear	N/A
A3	The groups were comparable at baseline, including all major confounding and prognostic factors (patient and lesion characteristics)	Yes	No	Unclear	N/A
A4	Are the patient inclusion/exclusion criteria clearly defined?	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was selection bias present? If so, what is the likely direction of its effect?					
Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
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B. Performance bias (systematic differences between groups in the care provided, apart from the intervention under investigation)					
B1	The comparison groups received the same care apart from the intervention(s) studied	Yes	No	Unclear	N/A

B2	Participants receiving care were kept 'blind' to treatment allocation	Yes	No	Unclear	N/A
B3	Individuals administering care were kept 'blind' to treatment allocation	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was performance bias present? If so, what is the likely direction of its effect?					
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Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
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C. Attrition bias (systematic differences between the comparison groups with respect to loss of participants)					
C1	All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)	Yes	No	Unclear	N/A
C2	a. How many participants did not complete treatment in each group?				
	b. The groups were comparable for treatment completion (that is, there were no important or systematic differences between groups in terms of those who did not complete treatment)	Yes	No	Unclear	N/A
C3	a. For how many participants in each group were no outcome data available?				
	2 (1 in each group)				
	b. The groups were comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available).	Yes	No	Unclear	N/A

Based on your answers to the above, in your opinion was attrition bias present? If so, what is the likely direction of its effect?					
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Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
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D. Detection bias (bias in how outcomes are ascertained, diagnosed or verified)					
D1	The study had an appropriate length of follow-up	Yes	No	Unclear	N/A
D2	The study used a precise definition of outcome	Yes	No	Unclear	N/A
D3	A valid and reliable method was used to determine the outcome	Yes	No	Unclear	N/A
D4	Investigators were kept 'blind' to participants' exposure to the intervention	Yes	No	Unclear	N/A
D5	Investigators were kept 'blind' to other important confounding and prognostic factors	Yes	No	Unclear	N/A
D6	Is an independent clinical events committee involved with outcomes assessment?	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?					
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Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
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E. Other					
E1	Does the trial have any disclosures of potential conflicts of interest?	Yes	No	Unclear	N/A
E2	Is there a sample size calculation for the primary endpoint?	Yes	No	Unclear	N/A
E3	Did the study used time to wound healing as the primary endpoint?	Yes	No	Unclear	N/A
Based on your answers to the above, in your opinion was detection bias present? If so, what is the likely direction of its effect?					
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Low risk of bias	Unclear/unknown risk	High risk of bias			
Likely direction of effect:					
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Appendix C: Excluded studies

REASON	AUTHOR	TITLE	JOURNAL	CITATION
Intervention outside the scope	Vin et al. 2002	The healing properties of Promogran in venous leg ulcers.	Journal of Wound Care	11(9), pp. 335-41
Intervention outside the scope	Veves et al. 2002	A randomized, controlled trial of Promogran vs standard treatment in the management of diabetic foot ulcers.	Archives of Surgery	137(7), pp. 822-7
Intervention outside the scope	PRO study	Unpublished	Unpublished	Unpublished
exclude case series	Cardenal, et al. (2009)	Healing post traumatic wounds with URGOCELLReg. START.	Journal of Community Nursing	23:02
exclude case series	Hinojosa Caballero, D., et al. (2016)	[Clinical Cases-Treated with Technology Lipid Colloidal (Tlc)].	Revista de Enfermeria	39: 4 (8-16)
exclude case study	Turns, M. (2012)	Evaluation of NOSF in neuropathic diabetic foot ulcers.	Wounds UK	8: 1 (100-106)
exclude case study	Timmons, J. (2010)	Evaluating a new foam dressing with a healing accelerator.	Wounds UK	6: 3 (88-92)
exclude case study	Powell, G. (2009)	The new Start dressing range – Urgotul Start, UrgoCell Start.	British Journal of Nursing	18: Sup2 (S30-S36)
exclude case study	Kelly, J., et al. (2013)	UrgoClean: a new dressing for desloughing exuding wounds.	British Journal of Community Nursing	(S42-49)
exclude case study	Downe, A. (2013)	Use of Urgotul SSDÂ® to reduce bacteria and promote healing in chronic wounds.	British Journal of Community Nursing	(S32-38)
exclude case study	Blasco Garcia, C., et al. (2012)	[Clinical cases about the therapeutic use of debriding dressing hidrodetersive polyacrylate fibers with TLC and foam dressings TLC-NOSF polyurethane in chronic wounds]. [Spanish].	Revista de enfermeria (Barcelona, Spain)	35: 10 (9-14)
exclude case study and narrative review	Dowsett, C. (2017)	Using TLC-NOSF advanced wound dressing to improve outcomes for patients with leg and diabetic foot ulcers.	Wounds UK	13: 4 (113-117)
exclude cost	Maunoury, F., et al. (2012)	Cost-effectiveness of the TLC-NOSF dressing in venous leg ulcers.	Value in Health	15 (7): (A353)
exclude cost	Augustin, M., et al. (2016)	Cost-effectiveness of treating vascular leg ulcers with UrgoStart® and UrgoCell® Contact.	International Wound Journal	13: 1 (82-87)

exclude cost	Arroyo Ana, A., et al. (2012)	[Cost-effectiveness of a TLC-NOSF polyurethane foam dressing].	Revista de Enfermeria	35: 11 (27-32)
exclude editorial	-2008	Bulletin board.	Journal of Wound Care	17: 11 (493-493)
exclude editorial	Shanahan, D. R. (2013)	The Explorer study: the first double-blind RCT to assess the efficacy of TLC-NOSF on DFUs.	Journal of Wound Care	22: 2 (78-82)
exclude editorial	-2011	Bulletin board.	Journal of Wound Care	20: 3 (142-143)
exclude commentary	Sandner, F. (2012)	UrgoStart with nano-oligosaccharide factor shows significant advantages in chronic wounds. [German].	Perfusion (Germany)	25: 4 (135)
exclude intervention	Benbow, M. and G. Iosson (2004)	A clinical evaluation of Urgotul to treat acute and chronic wounds.	British Journal of Nursing	13: 2 (105-109)
exclude intervention	Lopez, J. R., et al. (2005)	LCT (lipocolloid technology) in lesions of venous etiology. [Spanish].	Revista de enfermeria (Barcelona, Spain)	28: 2 (52-56)
exclude intervention	Krejner, A. and T. Grzela (2015)	Modulation of matrix metalloproteinases MMP-2 and MMP-9 activity by hydrofiber-foam hybrid dressing - relevant support in the treatment of chronic wounds.	Central European Journal of Immunology	40: 3 (391-394)
exclude intervention	Kordestani, S., et al. (2008)	A randomised controlled trial on the effectiveness of an advanced wound dressing used in Iran.	Journal of Wound Care	17: 7 (323-327)
exclude intervention	Jeffcoate, W. J., et al. (2009)	Randomised controlled trial of the use of three dressing preparations in the management of chronic ulceration of the foot in diabetes.	Health Technology Assessment (Winchester, England)	13: 54 (1-86, iii-iv)
exclude intervention	-2011	The clinical evidence for dressings with TLC technology.	Journal of Wound Care	20: Sup1 (11-21)
exclude intervention	Ubbink, D. T., et al. (2014)	Systemic wound care: a meta-review of cochrane systematic reviews.	Surgical Technology International	24: (99-111)
exclude intervention, outcomes	Tamayol, A., et al. (2016)	Flexible pH-Sensing Hydrogel Fibers for Epidermal Applications.	Advanced Healthcare Materials	5: 6 (711-719)
exclude narrative review	-2011	Dressings with TLC-NOSF Technology.	Journal of Wound Care	20: Sup1 (27-32)
exclude narrative review	Mietzelfeld, G. (2003)	New treatment options with modern lipido-colloid technology.	European Journal of Trauma	29: 4 (250)

exclude narrative review	Game, F. L. and W. J. Jeffcoate (2016)	Dressing and Diabetic Foot Ulcers: A Current Review of the Evidence.	Plastic & Reconstructive Surgery	138: 3 Suppl (158S-164S)
exclude outcomes	Meyer, F. J., et al. (2008)	Effect of collagen turnover and matrix metalloproteinase activity on healing of venous leg ulcers.	British Journal of Surgery	95: 3 (319-325)
exclude outcomes, study design	Couty, L., et al. (2009)	A NOSF (nano-oligosaccharide factor) lipido- colloid dressing stimulates MMPs/TIMPs complexes formation leading to MMPs inhibition in an in vitro dermal equivalent model.	Wound Repair and Regeneration	17 (4): (A64)
exclude overalp with Schmutz 2008	Fays, S., et al. (2005)	Leg ulcers and the Urgocell Non-Adhesive wound dressing.	British Journal of Nursing	14: 11 (S15-S16,S18-S20)
exclude overlap with Meaume 2017	-2017	A research roundup of recent papers relevant to wound care.	Wounds UK	13: 3 (98-99)
exclude overlap with Munter 2017	Sollner, B. (2015)	For all chronic wounds without infection: UrgoStart wound dressing with TLC-NOSF Wundheilungsmatrix.	Journal fur Pharmakologie und Therapie	24: 2 (52-53)
exclude overlap with Munter 2017	Keriheul, J., et al. (2017)	PRACTICAL MANAGEMENT OF CHRONIC WOUNDS WITH TLC-NOSF DRESSINGS: AN EVALUATION BASED ON MORE THAN 13 000 WOUNDS TREATED BY FRENCH AND GERMAN HEALTH PROFESSIONALS.	Journal of Wound Care	26: Sup6b (1-518)
exclude overlap with Munter 2017	Bischoff, A. (2012)	Faster healing of chronic wounds: Nano-oligosaccharide factor (NOSF)-containing lipid colloid wound dressing. [German].	Haut	23: 4 (160)
exclude overlap with Munter 2017	Anonymous (2008)	UrgoCell for leg ulcers and delayed wound healing: Superiority of the NOSF lipid colloid matrix. [German].	Phlebologie	37: 2 (103)
exclude overlap with Munter 2017	Allaert, F. A. (2014)	[Observational study on the efficacy of TLC-Ag and TLC-NOSF on chronic wounds]. [French].	Soins; La Revue de Reference Infirmiere	785 (15-18)
exclude population	Coulomb, B., et al. (2008)	A NOSF (Nano-Oligosaccharide Factor) lipido-colloid dressing inhibits MMPs in an in vitro dermal equivalent model.	Wound Repair and Regeneration	16: 6 (A74-A74)

exclude population	Coulomb, B., et al. (2010)	EVALUATION OF A NOSF (NANO-OLIGOSACCHARIDE FACTOR) LIPIDO-COLLOID MATRIX, IN AN IN VITRO DERMAL EQUIVALENT MODEL.	Journal of Wound Ostomy and Continence Nursing	37: 3 (S128-S128)
exclude population	Bisson, J. F., et al. (2013)	Effects of TLC-Ag dressings on skin inflammation.	Journal of Dermatology	40: 6 (463-470)
exclude protocol only	Anonymous (2013)	Assessing efficacy of a TLC-NOSF dressing on DFUs: The explorer study.	Wounds UK	9: 1 (7)
exclude protocol only	Joyce, P., et al. (2016)	Organisation of health services for preventing and treating pressure ulcers.	Cochrane Database of Systematic Reviews	DOI: 10.1002/14651858.CD012132