A clinical and economic evaluation of protease-modulating matrix interventions for diabetic foot and leg ulcers: Towards the development of treatment guidelines in the United Kingdom

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A clinical and economic evaluation of protease-modulating matrix interventions for diabetic foot and leg ulcers: Towards the development of treatment guidelines in the United Kingdom

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A thesis submitted in partial fulfilment of the requirements of Manchester Metropolitan University for the degree of Doctor of Philosophy

Department of Health Professions
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Abstract

Background: Wounds such as Diabetic foot ulcers (DFU) and leg ulcers (LU) are burdensome, reduce a patient's quality of life (QoL) and require a lot of time, money, and resources to heal. Patients have access to many types of dressing, but no guidance exists identifying a preferred dressing regimen, in part due to lack of data supporting clinical and cost-effectiveness. This research investigates treatment of DFU and LU with protease-modulating matrix interventions with the intent of creating treatment guidelines.

Methods: A multi-method research protocol was designed to include; systematic literature reviews; Delphi methodology expert panel; patient reported outcomes study; retrospective real-world data analysis; and a collection of economic modelling. Economic models include budget impact modelling, cost-consequence analysis, cost-utility and cost-effectiveness analysis, supported by data collected in the four previous studies. Statistical and sensitivity analysis have been performed where necessary and external guidelines and best practice followed to assure high-quality research.

Results: The studies showed the variance in care; the efficacy of the sucrose-octasulfate dressing and the burden of DFU and LU. Economic modelling found that the sucrose-octasulfate dressing was both a clinically and cost-effective option; improving time to healing and reducing the cost of care; whilst the incidence of adverse events such as infection or amputation was less. The results of this research have been included in guidance published by the National Institute for Health and Care Excellence (NICE).

Discussion: The most cost-effective dressing is not the one with the lowest acquisition cost. Scenario analysis showed the sucrose-octasulfate dressing as cost-saving when a comparator was zero cost; demonstrating the impact of improved healing time on reducing overall costs. Patients, healthcare professionals and payers should be aware of the newly published NICE guidance; to accelerate healing, reduce cost and improve QoL for patients with DFU or LU.

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To my family for always encouraging me to search for answers; or to create them if I found none.

And to Adam; for everything.

Outputs and dissemination

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Conference presentations

- **Betts, A**; Odeyemi, I; Yeowell, G; Fatoye, F; Devlin, N. 2017. Addressing Uncertainty in Wound Management Using A Modified Delphi Methodology. *Value in Health*, Volume 20, A794. Presented at ISPOR Glasgow November 2017.

- Fatoye, F; **Betts, A;** Gebrye, T; Odeyemi, I: Yeowell, G. 2018. A Systematic Review of Economic Outcomes Associated with Use of Topical Interventions for Treatment of Chronic Wounds. *Value in Health*, Volume 21, S174. Presented at ISPOR Baltimore May 2018.

- Yeowell, G; **Betts, A**; Odeyemi, I: Fatoye, F. 2018. l A Systematic Review of Clinical Efficacy Associated with use of Protease-Modulating Interventions with Diabetic Foot Ulcer or Venous Leg Ulcer. *Value in Health*, Volume 21, S163. Presented at ISPOR Baltimore May 2018.

- **Betts, A**; Odeyemi, I; Fatoye, F; Yeowell, G; Tadej, M; Lant, C. 2018 Real Life Use of Dressings in the Treatment of Leg Ulcers and Diabetic Foot Ulcers. *Value in Health*, Volume 21, S174 - S175. Presented at ISPOR Baltimore May 2018.

- **Betts, A**; Fatoye, F; Odeyemi, I; Yeowell, G. 2018. Using EQ-5D to measure quality of life in patients with diabetic foot ulcers and venous leg ulcers. *Value in Health*, Volume 21, S241. Presented at ISPOR Barcelona November 2018.

- **Betts, A**; Yeowell, G; Odeyemi, I; Fatoye, F. 2018. The budget impact and cost-consequence of treating diabetic foot ulcers with UrgoStart. *Value in Health*, Volume 21, S249. Presented at ISPOR Barcelona November 2018.

- **Betts, A;** Yeowell, G; Fatoye, F; Odeyemi, I. 2018. The budget impact and cost-consequence of treating leg ulcers with UrgoStart. *Value in Health*, Volume 21, S249. Presented at ISPOR Barcelona November 2018.

- Betts, A; Odeyemi, I; Fatoye, F; Yeowell, G; Tye, A. 2018. Cost-effectiveness and cost-utility analysis of treating diabetic foot ulcers with UrgoStart compared to a neutral dressing. *Value in Health*, Volume 21, S260. Presented at ISPOR Barcelona November 2018.

- Betts, A; Odeyemi, I; Yeowell, G; Fatoye, F; Tye, A. 2018. Cost-effectiveness and cost-utility analysis of treating leg ulcers with UrgoStart compared to a neutral dressing. *Value in Health,* Volume 21, S260. Presented at ISPOR Barcelona November 2018.

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List of abbreviations

ABPI	Ankle brachial pressure index
BIM	Budget-impact mode
BNF	British National Formulary
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CI	Confidence Interval
CRD	Centre for Review and Dissemination
CUA	Cost-utility analysis
CWIS	Cardiff Wound Impact Schedule
CXVUQ	Charing Cross Venous Ulcer Questionnaire
DFS	Diabetic Foot Ulcer Scale
DFU	Diabetic foot ulcer
DPA	Data Protection Act
DSA	Deterministic sensitivity analysis
DVT	Deep vein thrombosis
EAC	External assessment centre
EQ-5D	EuroQol 5 dimension
GDPR	General Data Protection Regulation
GP	General Practitioner
GRADE	Grades of Recommendation Assessment, Development and Evaluation
HCP	Health care provider
HEOR	Health economics and outcomes research
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ISOQOL	International Society for Quality of Life Research
ISPOR	International Society of Pharmacoeconomics and Outcomes Research
ITT	Intention to treat
KiTEC	King's Technology Evaluation Centre
LoE	Level of evidence
LU	Leg ulcer

Manchester Met	Manchester Metropolitan University
MMP	Matrix metalloproteinase
MTEP	Medical Technologies Evaluation Process
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
ONS	Office of National Statistics
ORC	Oxidized regenerated cellulose
PICO	Population, intervention, comparator, outcome
PMCPA	Prescriptions Medicines Code of Practice Authority
PMM	Protease-modulating matrix
PP	Per-protocol
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRO	Patient reported outcome
PROM	Patient reported outcome measure
PSA	Probabilistic sensitivity analysis
PUSH	Pressure ulcer scale for healing
QALY	Quality adjusted life year
QOF	Quality and Outcomes Framework
QoL	Quality of life
RCT	Randomised controlled trial
RWAR	Relative wound area reduction
SAT-II	Self-Assessment of Treatment, version 2
SIGN	Scottish Intercollegiate Guidelines Network
SLR	Systematic literature review
SO	Sucrose octasulfate
THIN	The Health Improvement Network
TLC-NOSF	Lipido-colloid technology Nano-oligosaccharide factor
UK	United Kingdom
VAS	Visual analogue scale
VBA	Visual basic application
WAR	Wound area reduction

Chapter 1 Introduction and background

1.1 Introduction

Diabetic Foot Ulcers (DFU) and Leg Ulcers (LU) are examples of chronic wounds which fail to follow a normal healing pattern and are caused by an underlying aetiology such as diabetes or venous/arterial disease (Frykberg and Banks, 2015). Chronic wounds have been shown to have high levels of Matrix Metalloproteinases (MMPs) enzymes expressed during the inflammatory phase of healing that play a role in cell proliferation, and it has been shown that persistent elevated MMPs in a wound are linked to slow healing (Olzyck et al., 2014). MMPs are expressed at higher levels in the wounds of patients with diabetes or venous insufficiency and are thought to contribute to impaired wound healing (Lazaro et al., 2016). High levels of MMPs in the wound, can be changed by using protease-modulating matrix (PMM) interventions to create an environment more amenable to healing.

Wounds that do not heal, consume substantial healtchcare resources and are a significant burden for the patient, for the healthcare system, and to society as a whole. In the United Kingdom (UK) a study in 2012-3 found that DFUs and venous LUs accounted for 8% and 13% of all wounds; this study also recorded unspecified LUs which accounted for a further 19% of wounds seen in the National Health Service (NHS) (Guest et al., 2015). Guest et al., (et al., (2015) did not solely focus on chronic wounds, also including surgical wounds, burns, trauma and abscesses. Nonetheless, it is evident that chronic wounds create a large burden on the health system; considering that a wound will need regular monitoring and the dressing will need changing by a health care provider (HCP), so a patient is in frequent contact with HCPs for a potentially long period of time.

Clarity on optimal treatment strategies for chronic wounds, both in terms of clinical and cost-effectiveness, is sought by the studies within this PhD thesis given that current UK guidelines do not provide specific advice to HCPs with regards to dressings.

The primary aim of this thesis is to evaluate the clinical and economic impact of PMM interventions in DFU and LU to inform the development of treatment guidelines in the UK. The research has several objectives to achieve this, as presented in section 1.4.

1.2 Background

1.2.1 Diabetic foot ulcers (DFU)

Patients with diabetes are at an increased risk of foot ulcers (Kerr, 2017). The risk is partly due to diabetic neuropathy that affects over 50% of type 1 and type 2 diabetic patients (Tesfaye et al., 2013). Diabetic neuropathy is the degeneration of the nervous system caused by high blood glucose levels and up to 75% of diabetic neuropathy is categorized as distal polyneuropathy; presenting as sensory or motor, affecting the feet, legs, hands, and arms (Bansa et al., 2006). Another presentation of diabetic neuropathy, autonomic neuropathy, affects internal processes in the body connected with ulceration, causing reduced sweating, leading to dry skin at risk of abrasion (Pendsey, 2010). Patients suffer weakness and a loss of sensation, frequently starting in the lower legs, so a small cut or scrape can be exacerbated by usual day-to-day activities and go unnoticed by the patient until it has fully ulcerated. To mitigate these processes, patients are advised to maintain good blood glucose control; however, this will not reverse any existing damage (Inzucchi et al., 2012).

Diabetes is also a risk factor for peripheral vascular disease which occurs earlier and in greater severity than a non-diabetic population (Huysman & Mathieu, 2009). Metabolic changes caused by diabetes impacts the vascular system, including the structure and functionality of the arteries; initially presenting as fatigue in the lower extremities (American Diabetes Association, 2003). Further developments of vascular disease can include pain, tissue loss, and gangrene. Ischaemia (defined as inadequate blood supply) is a consequence of peripheral vascular disease and impairs wound healing and tissue reformation. As with diabetic neuropathy, patients are advised to maintain control of their blood glucose levels to mitigate the negative impact of peripheral vascular disease, but again this will not reverse any damage or heal any DFUs present (Diabetes.co.uk, 2019). Higher than expected levels of MMPs, linked to slow healing, are found from the very first emergence of a DFU (Lazaro et al., 2016). As a result steps to prevent ulcers should be observed in the first instance and if a patient does become ulcerated then controlling MMP expression using interventions such as a PMM dressing may improve healing.

The growth of the diabetic population in the UK (NHS Digital, 2017) indicates that the incidence of DFU is set to rise. In the 20-year period between 1998 and 2018 the number of people diagnosed with type 1 or type 2 diabetes in the UK has more than doubled, from 1.8 million to

3.7 million, with nearly another 1 million people thought to be undiagnosed (Diabetes UK, 2018). DFUs often precede amputation; a last resort after unsuccessful prior treatment of an ulcer impacted by diabetic neuropathy, peripheral arterial disease, or critical ischaemia.

Given these dramatic consequences, it is unsurprising that DFU is associated with a high cost to the healthcare system. A Diabetes UK report states that in 2014-15 the NHS spent approximately £1 billion, or £1 in every £140, on foot ulcers or amputations (Kerr, 2017). In addition to the economic consequences associated with DFUs and amputations, the clinical burden is high to the patient; with mortality at 5 years post amputation reported at 62.2% (Stern et al., 2017). Typically, DFUs are located on the foot or lower leg and can prevent patients from walking, driving, and getting about independently; leading to an increased reliance on others. Further to this, patients are often pre-retirement age and a persistent ulcer may prevent them from working, causing a burden to families and the state due to productivity costs and social care requirements (Coffey et al., 2019).

1.2.2 Leg ulcers (LU)

Leg ulcers are a sore or break in the skin that takes more than 2 weeks to heal; they can be triggered by underlying aetiologies such as venous and arterial disease both of which cause an increased likelihood of ulceration. LUs are more common in older individuals, with the annual prevalence for individuals aged 65- 95 reported at 1.69% (Alavi et al., 2016). LUs are the most frequently reported wound (Guest et al., 2015) and are a significant contributor to the 7 billion USD per year spent on chronic wounds worldwide (Alavi et al., 2016).

LUs can be a complication of venous disease where valves inside the veins in the leg do not adequately prevent backwards flow when returning blood to the heart. Backwards flow results in venous stasis, high pressure, swelling in the legs and consequently, blood vessels can become damaged (British Association of Dermatologists, 2017). Structural changes in the veins and valves controlling blood flow is often a result of aging, presenting with deteriorated function in the lower legs and wounds forming from broken blood vessels (Kelechi et al., 2015). Venous leg ulcers usually develop on the lower leg above the ankle and can cause pain, itching, swelling, changes in the skin, and produce an odorous exudate (NHS, 2019).

In addition to vascular disease, arterial disease can also cause ulcers. Atherosclerosis, caused by smoking, obesity, hypertension or diabetes, is the leading cause of arterial LU when the

arteries fail to provide adequate oxygen and nutrients resulting in tissue breakdown (Moffatt, 2001). Arterial ulcers can occur anywhere on the lower leg and compared with venous LU are often deeper wounds that are more rounded with clear borders, and the limb appears pale in colour and there is often a reduction in hair (Newton, 2011).

The diagnosis of LU and the corresponding causal aetiology can be helped by a doppler ultrasound to measure ankle brachial pressure index (ABPI), the ratio of blood pressure in the ankle compared with the arm (Al-Qaisi et al., 2009). The 'unspecified' ulcers reported by Guest et al., (et al., (2015) are potentially patients who did not have an ABPI measurement thus preventing a more specific diagnosis. 'Unspecified' ulcers account for 19% of the wounds presenting to the NHS and is an important subgroup to consider.

LUs are often slow to heal due to the inevitable poor blood supply resulting from venous or arterial disease; these wounds are also debilitating for a patient, causing pain or discomfort. Quality of life (QoL) outcomes are reduced in patients with LUs due to the ulcer, the dressing, or the resulting self-isolation because of pain, odour or exudate; patients also report depression, anxiety and low mood (Green et al., 2014).

The aetiology of LUs is not always established by a clinician in a treatment setting and therefore the data and literature relating to LUs can include ulcers of either, mixed, or unknown origin. For the purposes of this PhD thesis all references are made to LUs of any aetiology. This is because of similar treatment patterns and the large number of wounds (around 19%), that would have to be excluded by following a narrower definition including only wounds that have had further diagnostic tests to establish aetiology.

1.2.3 Treatment guidelines regarding dressings for DFU and LU

The National Institute for Health and Care Excellence (NICE) DFU guidelines state that dressings should be offered to patients with a DFU (NICE, 2016). Section 1.5.10 addressed wound dressings directly; instructing HCPs to consider the clinical assessment and patient preference, but to use appropriate devices with the lowest acquisition cost (NICE, 2016). A NICE Evidence Summary published in 2016 identified little high-quality evidence to support the use of advanced dressings for chronic wounds (NICE, 2016).

The Scottish Intercollegiate Guidelines Network (SIGN) has published a national guideline for the management of chronic venous LU in 2010. SIGN identified compression as the mainstay of treatment and found no evidence to support a single type of dressing above the others, recommending that a simple non-adherent dressing be used (SIGN, 2010).

1.3 Evidence gap and rationale for research

Analysis of the literature for wound care has highlighted a gap within the current body of evidence in reaction to new clinical trials of wound care dressings. The data gap provides the rationale for this PhD and informs the design of this research study.

In December 2017, Urgo Medical Ltd reported the first double-blind randomised controlled trial (RCT) of patients with neuro-ischaemic DFU; the Explorer study (Edmonds et al., 2018). This RCT tested two dressing types: a sucrose octasulfate dressing which is a PMM dressing, and a neutral dressing which was identical but without the active ingredient (Edmonds et al., 2018). The Explorer study offered valuable high-quality evidence in the field of wound care, as both this, and a previous trial in LU, managed to achieve double blinding due to Urgo Medical Ltd being the manufacturer of both the study and comparator dressings (Meaume et al., 2012). With the efficacy of this intervention being demonstrated in clinical trials it now important to examine the evidence for the clinical and cost-effectiveness specific to the UK, using a broad evidence base, including real world evidence and economic modelling.

With the publication of Meaume et al., (2012) and Edmonds et al., (2018) there is now evidence to counter the claims of low-quality evidence in the field of dressings for wound care. A review by the Cochrane Collaboration in 2016 explored the use of PMM dressings for venous LU, with no single dressing shown as superior, thus no specific dressing protocol has been adopted into any subsequent published guidance. The Cochrane review did not include DFUs and the publication of newer studies of these interventions (Westby et al., 2016). A further review to incorporate new evidence is thus required to include observational studies of clinical outcomes across the two aetiologies of interest, DFU and LU. The economic burden of having and managing a chronic wound is also a topic that has not previously been subject to a systematic review and will be investigated.

Validation by clinical and health economic experts of the methods used, and results produced by the research in this thesis is also required, given that recommendations for treatment

guidelines would seek to change clinical practice. A change of clinical practice is an ambitious goal, but this could be achieved if this research compels NICE to produce new guidance.

NICE recommended guidelines are amongst the most respected source of clinical guidance, in the UK and worldwide, due to the robust process and methodology followed, which includes consultation with experts (NICE, 2016). This thesis hopes to produce guidance that could be recommended according to this world-class method, so this process must be emulated. As a result, this thesis will include repeated consultation with a multidisciplinary group of experts to anticipate any potential issues regarding adoption of a new technology.

Existing data on patient QoL has broadly been collected using qualitative methods, including interviews and focus groups. A few RCTs have collecting data using Patient Reported Outcome (PRO) tools were also identified (Green et al., 2014). Utility scores for patients with DFUs have been reported using the SF Health Surveys (SF-12) and EuroQol 3-dimension (EQ-5D-3L) instruments; these studies took place in the Netherlands and Sweden (Ragnarson-Tennvall and Apelqvist, 2000; Redekop et al., 2004). QoL scores can differ across geographies, health care systems and treatment practices. In addition, a difference in society and culture has been shown to cause divergence in how QoL dimensions are scored by patients from different countries (Feng et al., 2017).

Considering these factors, it is asserted that QoL studies require updating with patients from the UK to provide data most reflective of the UK population. Utility scores for DFU and LU have not been reported since early in the century, for DFU never in the UK, and never in an observational setting using validated tools. There is also the possibility that reported utility scores will change over time. For example, the recent focus on mental health by many charities and public health bodies may mean patients are more comfortable to reveal the burden of anxiety/depression, whereas in the past this may have gone unsaid.

Health Technology Assessment (HTA) bodies such as NICE prefer data from patients within their countries to ensure generalisability of the outcomes to their locale; and given the ambition of this thesis to meet the standard set by NICE this preference will be observed. Therefore, an observational real-world study to collect QoL data from UK patients using validated PRO tools would add to the body of knowledge on the burden of DFU and LU, generalisable to the wider UK population.

Further supporting the rationale for the need for up to date QoL research is that since the publication of the previous studies, the EuroQol questionnaire has advanced, from the EQ-5D-3L to the EQ-5D-5L, there are now five levels of answer in each of the five dimensions where previously there were only three. By using the new five level version, the utility scores collected are more sensitive to changes in QoL (Janssen et al., 2018).

Real-world data is available in the form of pooled observational studies and database studies using electronic records such as the THIN database. A large pooled observational analysis published in 2017 showed improved healing outcomes were associated with use of the sucrose octasulfate dressing in 10,220 patients and identified various risk factors for impaired healing (Munter et al., 2017). Further analysis in a multidisciplinary setting, to better reflect UK treatment practice, would aim to establish treatment patterns and behaviours, healing outcomes and resource use. Previous analysis of the cost of DFU and LU to the UK NHS when treated in primary care, showed that they cost £7800 and £7600, respectively, to treat for 12 months, as per data from The Health Improvement Network (THIN) database (Guest et al., 2018a; Guest et al., 2018b).

The collection of the data regarding DFU and LU provides an opportunity to inform accurate health care modelling using concurrent contemporary data. Models could then compare the outcomes reported in clinical trials with real-world practice and use these comparisons to help determine quality standards for treating chronic wounds.

1.4 Aims

The primary aim of this thesis is:

To evaluate the clinical and economic impact of PMM interventions in DFU and LU to inform the development of treatment guidelines in the United Kingdom.

To achieve the primary aim, this thesis has the following objectives served by the individual studies:

A. To evaluate current treatment guidelines.
    - Addressed by studies 1, 3, 4, and 5.
B. To gain consensus on guidelines, and treatment strategies for chronic wounds.

- Addressed by study 2.

C. To quantify QoL for DFU and LU patients
    - Addressed by study 3.

D. To assess clinical and economic impact of PMM interventions in wound management.
    - Addressed by studies 1, 2, 4, 5

E. To assess the clinical and economic impact of the proposed recommendations.
    - Addressed by study 5.

The findings of this PhD thesis will create a new body of evidence to provide answers not found in current literature, thereby improving current knowledge and providing an evidence base for guidance recommendations. It is hoped that this research will result in a change in treatment practice, with the goal of improving outcomes for patients. An optimal guideline would enable the delivery of maximum benefit to patients using the resources available.

To address the gaps in the current research, this thesis has undertaken a series of studies to address the primary aim and objectives. Desk research consisting of two systematic reviews performed on interlinking topics within the management of DFU and LU have been performed. The reviews adhere to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, which provide a framework for SLRs relating to health care interventions.

Qualitative methods have been used to illicit individual opinions in the expert consensus study. The statements developed using thematic analysis of existing literature were tested using a Delphi methodology (Braun, 2006). Patient views regarding their wound and QoL were collected using a questionnaire pack consisting of validated PRO tools and a demographic information sheet developed by the researcher (AB). Current treatment pathways have been examined using quantitative methods and the economic evaluation has modelled the data to investigate the budget-impact and cost-utility associated with the proposed recommendations.

A multi methods approach to data collection and analysis in this thesis allows for a greater understanding of the complexities and nuances of wound care. By understanding experiences and opinions of an individual and relating this to measured variables and outcomes the results provide a clear illustration of the issues at hand (Braun, 2006).

1.5 Thesis structure

There are five studies in total that constitute this thesis, each using a different method to examine the impact of DFU and LU on clinical, economic and QoL outcomes. The PhD researcher (AB) has driven the conception, design and execution of all studies that make up this programme. AB carried out and led all elements of studies 1 and 2, and informed data collection and performed all data analysis and economic modelling for studies 3-5.

Chapter 1 of this study is the introduction to this body of knowledge and has presented information on DFU and LU, the rationale for the research and the thesis primary aim and objectives. Chapter 2 presents two systematic literature reviews (SLR) that constitute study 1, the first a clinical SLR that investigates the efficacy of PMM dressings and the second an economic SLR of topical chronic wound care interventions more broadly. Chapter 3 will present the Delphi methodology expert consensus panel, study 2, highlighting areas of uncertainty upon which a consensus will be sought from a multidisciplinary panel of experts.

Chapter 4 presents two studies, study 3 and study 4, both examples of real-world evidence studies. Collecting data from patients in practice; study 3 seeks to evaluate patient QoL using standardized tools whilst study 4 investigates the real-world incidence and causes of treatment switching for patients with a DFU or LU. Chapter 5 presents the economic evaluation of the PMM intervention for patients with a DFU and LU using multiple methods of cost-modelling. Chapter 6 presents the overall discussion of the body of knowledge presented here whilst Chapter 7 puts forth the recommendations and conclusions drawn.

The studies are not performed in isolation, rather they each will inform the design and development of the final economic modelling and subsequent recommendations. Figure 1.1 shows the relationships and interdependencies of the studies. This figure is shown repeatedly throughout the thesis, with the relevant sections highlighted in colour to illustrate the multi-methods approach that this research has taken towards achieving the primary aim.

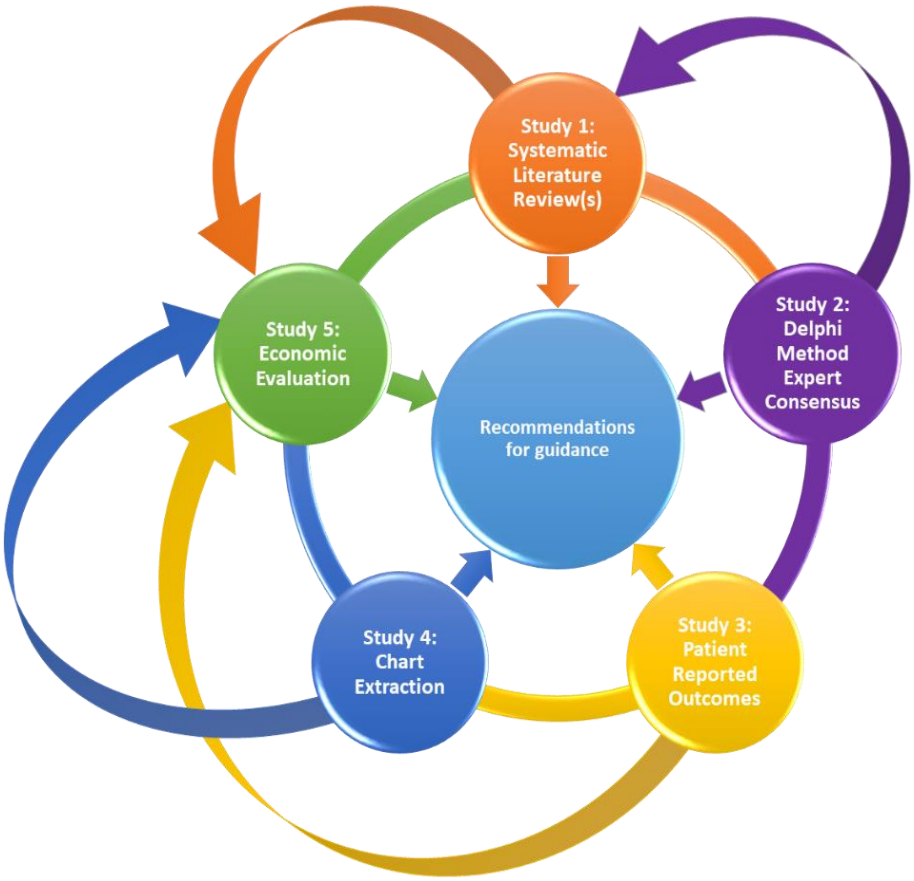


Figure 1.1. Overall PhD framework

All five studies focus on DFU and LU patients when considering chronic wounds. Pressure ulcers and acute wounds were deemed out of scope for this thesis, due to different treatment strategies, and the fact they occur in diverse patient populations. Pressure ulcers are often found in patients who are immobile for long periods of time whilst acute wounds can happen to anyone with little predisposition.

The overarching design of the thesis is a multi-method study; with projects that can either be interpreted on their own; or be viewed together as part of this overall PhD thesis. Whilst some researchers make no distinction between multi-method and mixed methods studies (Stange, 2006) this thesis is aligned with the definition provided by Pat Bazeley where multi-method research consists of different approaches or methods that are used in parallel or sequence but are not integrated until inferences are made (Johnson et al., 2007). Multi-methods in this instance refers to the different ways of collecting data demonstrated in this thesis; but also to the different approaches of each study; looking at varied perspectives (the patient, a care provider or health care budget holder). The intent of this approach is to provide a holistic

overview of all issues regarding wound care in order to develop optimal recommendations for treatment guidance.

The Delphi panel was the first study performed. The broad systematic search of literature used to develop the evidence-based statements for the Delphi panel informs the development of the subsequent SLRs that comprise study 1. The clinical SLR in study 1 informed the economic modelling with regards to which PMM intervention was of most interest and had the strongest evidence from RCTs and observational studies, and the outcomes associated with the use of this dressing in patients with DFU and LU.

The economic SLR informed the data analysis of the chart extraction, study 4. The economic SLR highlighted variance in the application of standard care in the literature and this then became a research priority for the chart extraction; to understand treatment switching, in addition to reporting on healing outcomes. Patient utility scores collected using EQ-5D-5L in study 3 were used directly in the economic modelling as a core component of the cost-utility analysis. Study 4 confirmed the suspicion that standard care incorporated a large variance when considering DFU and LU. By not using a variable standard care protocol and instead relying on the RCTs identified in study 1, the modelling can be asserted to show the difference powered only by the sucrose octasulfate dressing. Should another standard care protocol be substituted into the model; the results should remain consistent as the only difference between the treatment arms was the sucrose octasulfate dressing as a replacement for a neutral dressing.

1.6 Organisational setting

The partnership between Manchester Metropolitan University (Manchester Met) and Urgo Medical Ltd, a wound care medical device manufacturer, has facilitated this PhD. Urgo Medical Ltd commissioned Manchester Met to manage data generation and the subsequent submission of evidence to NICE. NICE produces guidance, briefings and knowledge summaries to guide HCPs in England where NICE guidance is mandatory. Medical device manufacturers such as Urgo Medical Ltd can participate in the Medical Technologies Evaluation Process (MTEP) with NICE, to obtain guidance for their products. Upon the completion of a successful clinical trial, Urgo Medical Ltd wished to submit their product to NICE for MTEP review (Edmonds et al., 2018). A project was commissioned to develop a robust evidence portfolio of clinical, economic, and patient related outcomes. This PhD thesis has been developed concurrently, to complement this project with aims that were broader than the MTEP sought to address.

1.7 Chapter summary

This chapter contextualises the PhD thesis; by providing an overview of the conception and context of the research, an introduction to the disease areas, LU and DFU, and current guidelines that dictate the treatment of these wounds with dressings. The chapter also provides a critical review of current research in this area and highlights evidence gaps that have shaped the development of this thesis. The PhD structure has been discussed, giving an insight into the five constituent studies and their methodologies, whilst exploring the linkages between the studies and how together they address the primary aim and thesis objectives.

The next chapter in this thesis discusses the SLRs, first the clinical review of PMM interventions and then the SLR focused on economic outcomes associated with topical interventions for wounds. The SLRs highlight the current research in existence on this subject and inform the subsequent studies.

Chapter 2 Clinical and economic systematic literature reviews

2.1 Introduction

This chapter presents two systematic literature reviews (SLRs), that have been carried out to understand the current body of work that surrounds the economic analyses of topical wound care interventions and the clinical efficacy of protease-modulating matrix (PMM) interventions. A literature review becomes systematic when it is based on a clear question and performed according to an explicit methodology that includes pre-defined inclusion and exclusion criteria, an appraisal of evidence quality and a summary of the evidence. The Cochrane Handbook for Systematic Reviews highlights that SLRs are conducted with a view to minimize bias, to provide reliable and generalizable findings that can inform evidence-based conclusions and guide decision making (The Cochrane Collaboration, 2011).

These reviews were carried out independently of each other, to address separate aims. The aims were informed by the SLR that was carried out in advance of the Delphi Methodology expert panel (study 2) presented in chapter 3, as shown in Figure 2.1. The first SLR is a focussed SLR on PMM interventions and their clinical effectiveness. This is followed by a review pertaining to economic outcomes of a broader range of topical interventions for chronic wounds.

This chapter presents each SLR in turn, exploring the background relating to each topic, setting out the methodology used, presenting the results and a discussion of the findings. A critical review of both SLRs follows to explore the synergies between the two reviews and illustrate the strengths and limitations of the reviews when presented together.

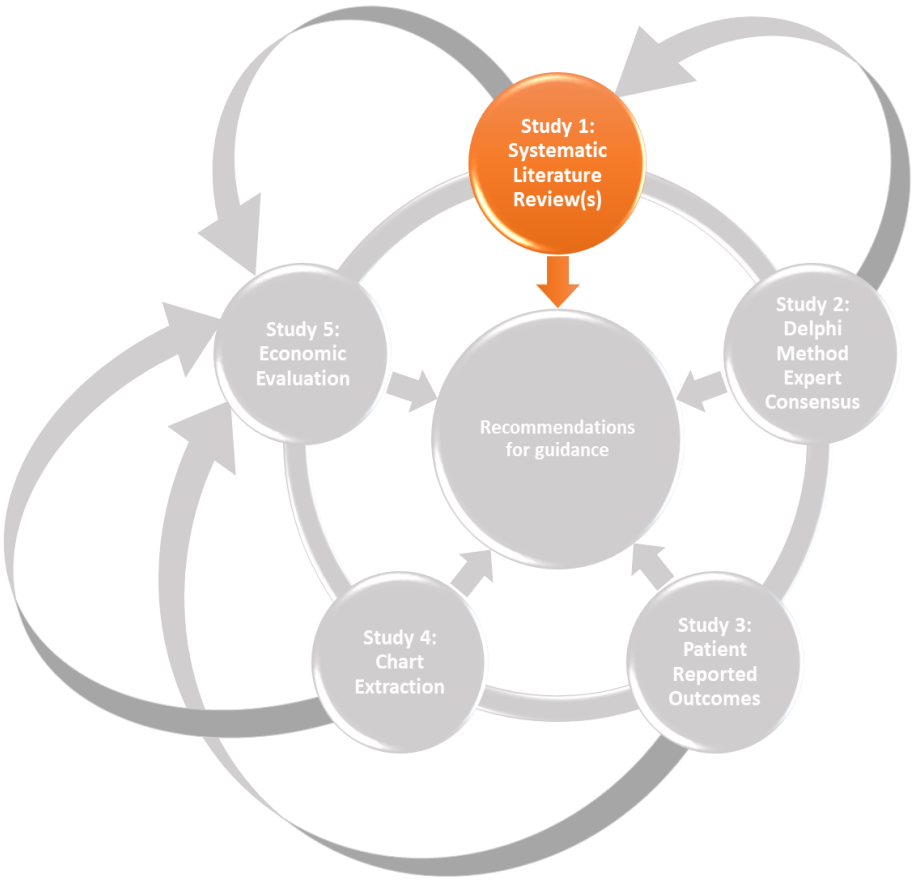


Figure 2.1. SLRs within the PhD framework

2.2 A systematic review of clinical efficacy of PMM interventions for treating DFU or LU

2.2.1 Introduction

Diabetic foot ulcers (DFUs) or Leg Ulcers (LUs) can cause a considerable burden to a patient and health care provider (HCP), taking a long time to heal and requiring frequent interventions. Dressings are a mainstay of treatment with countless options for an HCP. PMM interventions are an alternative to basic or other advanced dressings. A systematic review was undertaken to assess the clinical effectiveness of PMM interventions for DFUs and LUs.

2.2.2 Background

DFU and LU are examples of wounds that fail to follow a normal healing pattern (Russell et al., 2018). These wounds frequently present as a symptom of an underlying chronic comorbidity such as diabetes, venous or arterial disease (Frykberg & Banks, 2015). They may last for many months or even years, causing a burden felt by patients, the healthcare system and the wider economy. DFU and LU caused by venous or arterial disease can, without appropriate

treatment, become long lasting wounds. Treatment pathways for these patients are complicated, with a wide variation in practice found in recent retrospective studies (Guest et al., 2018a; Guest et al., 2018b). Variance in treatment is explored in this thesis in the following economic SLR (see section 2.3), and in study 4 presented in chapter 4.

Wound dressings are a mainstay treatment applied as part of a wider treatment strategy, which may also include compression, debridement, offloading and infection control to achieve full wound closure (SIGN, 2010; NICE, 2016). PMM dressings or interventions act on the matrix-metalloproteases (MMPs) present in DFU and LU. These interventions are intended to rebalance MMPs, enzymes that play a role in cell proliferation expressed during the inflammatory state of healing (Olzyck et al., 2014). Studies show higher levels of MMPs in DFU and LU from onset in comparison with acute wounds (Lazaro et al., 2016).

Given traditional low levels of evidence associated with wound care studies due to the difficulty in blinding there is often uncertainty concerning the validity of wound care studies. The National Institute for Health and Care Excellence (NICE) provides only limited guidance on the use of dressings, with a focus on the "least costly dressing" that meets the needs of the patient (NICE, 2019). The vast array of dressings available poses a challenge to clinicians and decision makers regarding dressing selection (BNF, 2015).

An earlier systematic review of PMM dressings looking solely at venous LUs did not find conclusive evidence for the use of PMM dressings (Westby et al., 2016). In recent years, new high-quality evidence has become available for the use of PMM dressings. A pooled analysis of observational trials (Munter et al., 2017) and a double-blinded randomised controlled trial (RCT) (Edmonds et al., 2018) highlights the need to review the evidence. No review has included these new high-quality studies.

The new high-quality evidence in this field and the fact that these interventions are offered in multiple indications, including DFU and LU of all aetiologies, drives the need to perform a systematic review to provide evidence on which PMM interventions which could offer improved clinical outcomes for patients with DFU and LU.

2.2.3 Study aims

The aim of study 1a was:

- To establish the clinical effectiveness of PMM interventions in the treatment of DFU and LU.

The objectives of study 1a were:

- To document all studies of PMM interventions in the treatment of DFU.
- To analyse and critically appraise the included studies.

2.2.4 Methods

A systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines was undertaken (Moher et al., 2009). An electronic database search, and consultation with experts and manufacturers identified the literature. Two researchers (AB and PhD supervisor, IO) independently performed data extraction with a third (PhD supervisor, FF) consulted in case of any discrepancies. A narrative synthesis of results and critical appraisal of included studies was performed. Further detail about the search strategy is described in this section.

Search strategy

The following electronic databases were searched: Centre Reviews and Dissemination (CRD) York Database; Cochrane Library (all databases); Medline (PubMed); NICE Evidence; Science Direct/Scopus. The databases were searched in April 2018 with no date stipulation, given that the search criteria of protease-modulating matrix interventions itself would restrict the results. Relevant ongoing research was accessed using the World Health Organisation International Trial Registry and ClinicalTrials.gov. Other sources included citation searches of included studies, contact with relevant manufacturers and experts. The search string used can be found in Appendix A.

Eligibility criteria

The inclusion and exclusion criteria for this review are shown in Table 2.1. There were no restrictions with respect to the date of publication due to PMM interventions being a relatively recent innovation. Methods to diagnose a venous, arterial or diabetic ulcer may vary and this review accepted any as described by the included studies.

Table 2.1. Clinical SLR inclusion and exclusion criteria

Inclusion criteria	
Population	Diabetic foot ulcer, leg ulcer, or a study of chronic wounds
Interventions	Protease modulating matrix interventions
Outcomes	Wound area reduction, wound closure.
Study design	Randomised controlled trials, observational studies
Language	English language
Exclusion criteria	
Population	Paediatrics (<18), acute wounds
Interventions	N/A
Outcomes	N/A
Study design	In vitro studies, review or discussion articles, treatment pathway/guidelines, systematic/lliterature reviews or meta analyses, epidemiology studies, Modelling, case studies, economic studies, database studies
Language	Non-English language

Data extraction (selection and coding)

Two researchers (AB and PhD supervisor, IO) independently assessed titles and abstracts retrieved by the searches for relevance (.ris files were extracted to EndNote using Excel database for review). Access to the full text files was obtained for titles appearing relevant at initial screening.

The researchers then independently assessed the eligibility of the text against this study's inclusion and exclusion criteria shown in Table 2.1. The researchers applied the pre-defined criteria independently to produce a final list of included studies. Data was extracted into tables with different information extracted for RCTs and observational studies.

Risk of bias (quality) assessment

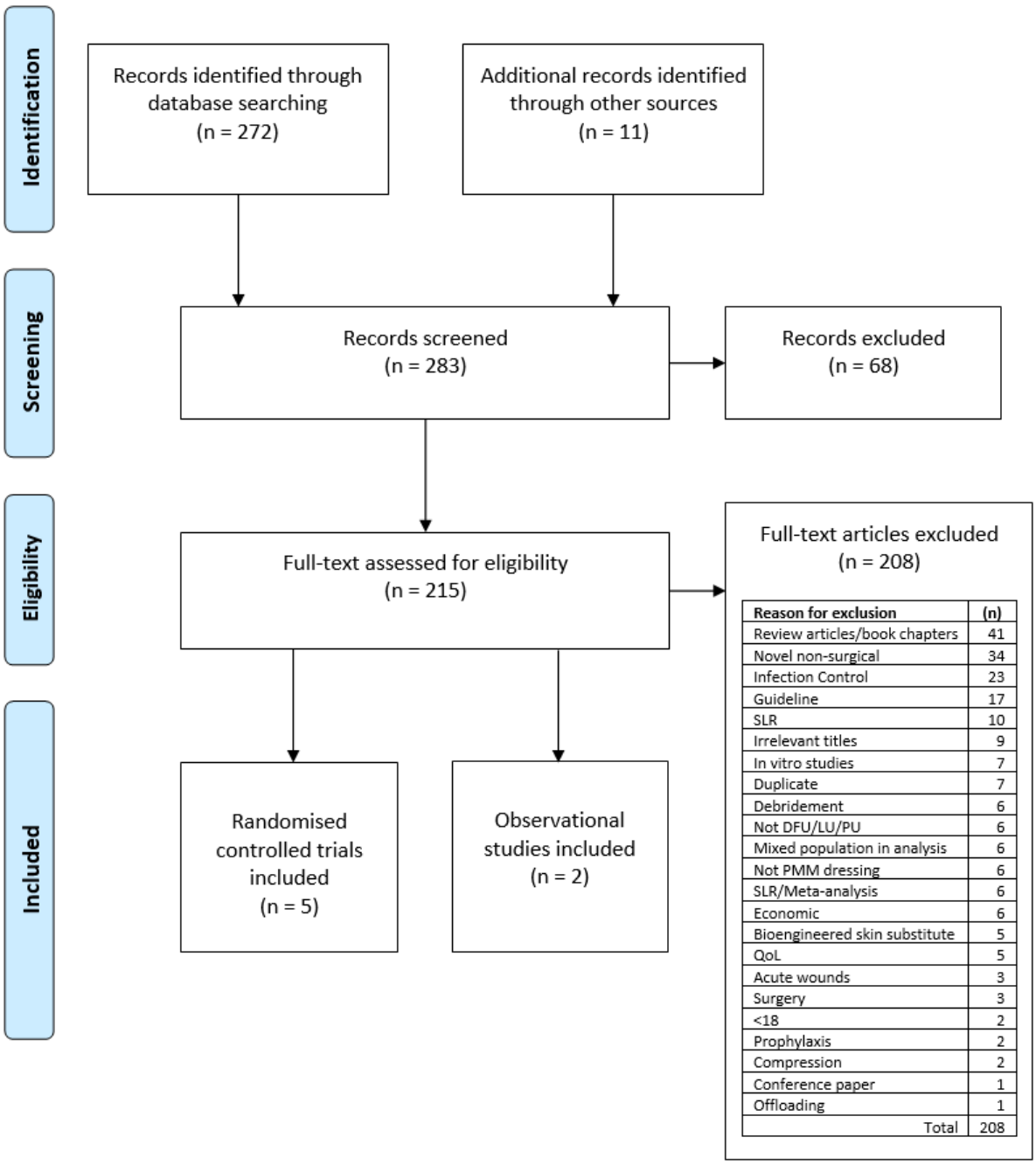
A critical appraisal of studies was carried out on the studies as per the NICE submission templates for Medical Technologies Evaluation Programme (MTEP); which is derived from York University CRD (NICE, 2017). The templates are different for RCT and observational studies.

Strategy for data synthesis

A structured narrative synthesis of the data was constructed using the completed data tables; stratified according to wound type, and then by intervention. As the included studies were not homogenous with regards to population, comparator or outcome measurements; a meta-analysis was not able to be performed (Sedgwick, 2015).

2.2.5 Results

From searching the databases, 272 results were returned. Discussion with experts and manufacturers provided 11 further titles. After initial screening of the 283 titles and abstracts, 68 were excluded due to lack of relevance to the research question. The remaining 215 texts were judged against the inclusion and exclusion criteria in Table 2.1. Two hundred and eight titles were excluded, with 7 being included as per the PRISMA flow chart in Figure 2.2.



Reason for exclusion	(n)
Review articles/book chapters	41
Novel non-surgical	34
Infection Control	23
Guideline	17
SLR	10
Irrelevant titles	9
In vitro studies	7
Duplicate	7
Debridement	6
Not DFU/LU/PU	6
Mixed population in analysis	6
Not PMM dressing	6
SLR/Meta-analysis	6
Economic	6
Bioengineered skin substitute	5
QoL	5
Acute wounds	3
Surgery	3
<18	2
Prophylaxis	2
Compression	2
Conference paper	1
Offloading	1
Total	208

Figure 2.2. Clinical SLR PRISMA reporting diagram

The list of included studies can be found in Table 2.2. Data extraction tables for study methodology were completed; the two DFU RCTs are detailed in Table 2.3 and the three LU RCTs in Table 2.4; and observational studies for both indications are shown in Table 2.5.

Table 2.2. Clinical SLR included studies

Study	Study Title	Population	Intervention	Comparator
Veves et al., 2002	A randomized, controlled trial of Promogran vs standard treatment in the management of DFU	DFU	ORC	Moistened gauze
Vin et al., 2002	The healing properties of Promogran in LU	LU	ORC	Silicone dressing
Schmutz et al., 2008	Evaluation of the TLC-NOSF matrix in the local management of LU: results of a randomised, controlled trial	LU	SO dressing	ORC
Meaume et al., 2012	A randomized, controlled, double-blind prospective trial with a TLC-NOSF wound dressing in the local management of LU	LU	SO dressing	Neutral dressing
Richard et al., 2012	Management of DFU with a TLC-NOSF wound dressing	DFU	SO dressing	N/A
Munter et al., 2017	The reality of routine practice: a pooled data analysis on chronic wounds treated with TLC-NOSF wound dressings	Mixed	SO dressing	N/A
Edmonds et al., 2018	Sucrose octasulfate dressing versus control dressing in patients with neuroischaemic DFU (Explorer): an international, multicentre, double-blind, randomised, controlled trial	DFU	SO dressing	Neutral dressing

Abbreviations: DFU: diabetic foot ulcer, LU: leg ulcer, ORC: oxidized regenerated cellulose. SO: sucrose octasulfate. TLC-NOSF: lipido-colloid technology nano-oligosaccharide factor.

Table 2.3. Clinical SLR summary of methodology of DFU RCTs

Study	Veves et al., 2002	Edmonds et al., 2018
Objectives	To evaluate healing rates of DFU treated with ORC compared with saline-moistened gauze	To demonstrate superiority of SO compared with control for the treatment of neuro-ischemic DFU
Location	United States	UK, Spain, Germany, France, Italy
Design	Multi-centre randomised, prospective, controlled trial	Multicentre, randomised, prospective, **double blind** controlled trial
Duration	12 weeks	20 weeks
Sample	276	240
Inclusion criteria	–> 18 years –DFU present for **> 30 days**. –Area **>1cm^2**. –Wagner grade 1 to 2. –Adequate circulation –No necrotic tissue	–> 18 years –HbA1c level ≤ 10%. –**Neuro-ischemic DFU** –Area **1-30 cm^2** –Confirmed neuropathy –No local clinical infection
Exclusion	–Allergy to study dressing. –Infection. –Ulcer extending to bone. –Severe comorbidity, poor health, immunosuppressant or corticosteroid use. –Unwillingness to comply with offloading. –Multiple ulcers on one foot.	–Surgery/revascularization (1month). –Acute ischemic event (3 months) –Dialysis for renal failure. – >20% necrotic tissue or extending to bone. –Neoplastic condition. –Severe comorbidity, poor health, immunosuppressant or corticosteroid use. –Inter-digital, heel or posterior.
Randomisation	Stratified by wound size	Stratified by wound size
Blinding	Unclear in publication	Double blind confirmed by 2 blinded reviewers

Study	Veves et al., 2002	Edmonds et al., 2018
Intervention/ comparator	ORC (n = 138) Moistened Gauze (n = 138)	SO (n=126) Neutral dressing (n=114)
Baseline differences	No significant difference at baseline. Verified using appropriate tests	No significant difference at baseline. Verified using appropriate tests
Follow-up	12 weeks. No information available regarding patients lost to follow up	20 weeks. 37 patients did not complete. (SO n=18, comparator n=19)
Statistical tests	Random-effects mixed model. Linear logistic regression. Odds ratio.	ITT. Regression logistic analysis. 4 sensitivity analyses on ITT, and 1 on PP
Primary outcomes	**Complete healing**. 100% reepithelialisation, no draining confirmed by blinded assessor	**Wound closure** at 20 weeks. 100% reepithelialisation, no draining confirmed after 2 weeks later
Secondary outcomes	**Relative WAR** **Time to complete ulcer healing**	**Time to complete wound closure** **Relative and absolute WAR** Adverse events/Quality of Life
Abbreviations: DFU: diabetic foot ulcer, ITT: intention to treat, ORC: oxidized regenerated cellulose, PP: per protocol, SO: sucrose octasulfate, WAR: wound area reduction.		

Table 2.4. Clinical SLR summary of methodology of LU RCTs

Study	Meaume et al., 2012	Schmutz et al., 2008	Vin et al., 2002
Objectives	To assess efficacy of the SO in LU	To assess SO relative to ORC in LU	To evaluate LU healing rate using ORC
Location	France	France & UK	France
Design	Multi-centre, randomised, two-arm **double blind** controlled	Multi-centre randomised, two-arm, **open label,** controlled	Multi-centre, randomised, two-arm **open label**, controlled
Duration	8 weeks	12 weeks	12 weeks
Sample	187	117	73
Inclusion criteria	– > 18 years – ABPI of ≥0.8 – 1.3 – Using compression – 5-50 cm^2 & 6-36 months – 50% granulation	– > 18 years – ABPI of ≥0.8 – Using compression – 5-25cm^2 & 3–24 months.	– LU with ABPI of ≥0.8 – Free from infection – Wound at least 30 days. – Wound ≥2cm^2 .≤10cm^2
Exclusion criteria	– Suspicion of infection – Malignant wound –Severe comorbidity, poor health, immunosuppressant or corticosteroid use – CMC contact dermatitis. – Recent surgery/DVT	– Suspicion of infection – Malignant wound – Severe comorbidity, poor health, immunosuppressant or corticosteroid use – Necrotic/devitalised. – Recent surgery/DVT	– No compression – Immobile patients and/or unable to care for themselves – Severe comorbidity, poor health, immunosuppressant or corticosteroid use
Randomisation	Blocks of 2 by centre	Unclear	Unclear
Method of blinding	Dressings identical. Blinded clinicians.	N/A Open label	N/A Open label

Study	Meaume et al., 2012	Schmutz et al., 2008	Vin et al., 2002
Intervention/ comparator	SO (n = 93) Standard care (n = 94)	SO (n = 57) ORC (n = 60)	ORC (n=37) Silicone dressing (n=36)
Baseline differences	No significant difference at baseline. Verified using appropriate tests	No significant difference at baseline. Verified using appropriate tests	No significant difference at baseline. Verified using appropriate tests
Follow up	8 weeks. Withdrawals: SO (n = 4) Control (n = 6)	12 weeks. One lost to follow-up	12 weeks. 5 were lost to follow-up
Statistical tests	Nonparametric Mann–Whitney test	Non-inferiority using confidence interval.	Student's t-test, Mann-Whitney & chi-square
Primary outcomes	**Relative WAR** of last available wound tracing	**Relative WAR** of last available planimetry	**Completely healed** and **relative WAR**
Secondary outcomes	**Absolute WAR** **Healing rate** **RWAR** 40% & 60% **Tolerance/ Acceptability**	**Absolute WAR** 12-week **wound closure** rate **40% WAR**	**Resource use** **Tolerability**: Pain and ease of removal.
Abbreviations: ABPI: Ankle-brachial pressure index, DVT: Deep vein thrombosis, LU: leg ulcer, ORC: Oxidized regenerated cellulose, SO: Sucrose octasulfate, WAR: Wound area reduction			

Table 2.5. Clinical SLR summary of methodology of observational studies

Study	Munter et al., 2017	Richard et al., 2012
Objective	Study real-world efficacy of SO	Estimate efficacy, tolerability and acceptability of SO in DFUs
Location	France and Germany	France
Design	Pooled observational studies	Open-label single arm pilot study
Duration	4-20 weeks	12 weeks
Population	Chronic wounds	DFU
Sample size	10,220 (1306 DFU, 7903 LU)	34
Inclusion	–Use of the sucrose octasulfate dressing	– >18 years –Neuropathic, non-ischaemic DFU. –1–15cm^2, –Located on the forefoot or midfoot. –Texas University classification 1A –> 50% granulation tissue.
Exclusion	–N/A	–Clinical signs or symptoms of infection
Follow-up	Date of inclusion, latest visit and calculation of follow-up duration.	Analysis of the last evaluation. One patient excluded due to missing data.
Statistical tests	Binary logistic regression analysis. OR calculated for covariates with 95 % CI. Mean estimate of time to closure calculated using Kaplan-Meier method.	The statistical analysis, purely descriptive, without any test, was performed on an ITT basis for both the primary and secondary endpoints of the study
Primary outcome	**Wound closure.**	**Relative WAR** (%)
Secondary outcomes	Time to **50 % reduction of the PUSH** score.	**Healing rate** and mean **healing time**, **Tolerability** and **acceptability**.
Abbreviations: CI: confidence interval, DFU: diabetic foot ulcer, ITT: intention to treat, LU: leg ulcer, OR: odds ratio, PUSH: pressure ulcer scale for healing, SO: sucrose octasulfate, WAR: wound area reduction.		

Study interventions

The two PMM interventions used in the included studies, were the sucrose octasulfate dressing (marketed in the United Kingdom (UK) under the brand name UrgoStart and manufactured by Laboratoires Urgo) and the oxidized regenerated cellulose (ORC) dressing (marketed in the UK under the brand name Promogran and manufactured by Acelity). These dressings both claim to inhibit MMPs in a wound and have this as part of a registered mode of action. In the sucrose octasulfate dressing, the potassium salt of sucrose octasulfate acts at the tissue level and has been shown to inhibit excess MMPs and interacts with growth factors restoring their biological functions contributing to tissue formation (White et al., 2015). Oxidized regenerated cellulose (ORC) has been shown to bind and inactivate damaging MMPs present within the wound, also binding with naturally occurring growth factors preventing them from being broken down by damaging proteases (Cullen & Ivins, 2010).

Study demographic data

The seven studies included 9859 patients in total; 1822 of these with a DFU and 8037 with a LU, Munter et al., (2017) did not include sex data for all included patients, and also included pressure ulcers but these have been excluded from this analysis. DFUs were more common in males, with only 32% of the recorded population being female. Conversely the LU population was predominantly female (62.1%). Patients with LU were on average approximately 10 years older than patients with DFU. Of 9859 patients included in this systematic review, 9.1% (n = 893) were from RCTs and the remaining 90.9% (n =8966) were from the observational studies. The three LU RCTs included 377 patients, and the two DFU RCTs included 516 patients.

Table 2.6. Clinical SLR pooled study demographic data

Patient characteristics	Total population	DFU	LU
Included patients	9859	1822	8037
Male	4286 (43.5%)	1239 (68.0%)	3047 (37.9%)
Female	5573 (56.5%)	583 (32.0%)	4990 (62.1%)
Mean age	65.4 years*	61.2 years*	71.6 years*
*Mean age excludes patients in Munter et al., 2017 as this data was not available.			

DFU RCTs

The DFU RCTs included in this review tended to have a longer follow up than the studies for LU; with Veves et al., (2002) being 12 weeks, and Edmonds et al., (2018), 20 weeks. The inclusion and exclusion criteria appear similar between the two studies, despite not being well described in Veves et al., (2002), resulting in patients with similar baseline characteristics. Veves et al., (2002), mandated that the ulcer be larger than $1cm^2$ and Edmonds et al., (2018), stipulated a size range, from $1cm^2$ - $30cm^2$. DFUs tend not to be as large as LUs, with their size less considered as a marker of severity.

Edmonds et al., (2018), required the DFUs to be confirmed as neuro-ischaemic, a category of ulcers that are considered more difficult to heal than ulcers without neuropathy or ischaemia (Yotsu et al., 2014). These RCTs have exclusion criteria affecting patients with a weakened immune response, or with comorbidities or concomitant medication that could influence healing. This may not be reflective of a real-world treatment population; however, allows for greater control of confounding within the RCTs. Both DFU studies have a primary outcome measure that addressed full wound healing, or closure.

LU RCTs

The inclusion and exclusion criteria for all LU studies were comparable, all excluding patients with concomitant illnesses or medications that may impair healing. Vin et al., (2002), was most restrictive in terms of ulcer size, stipulating that it must be between $2cm^2$ and $10cm^2$, whilst Schmutz et al., (2008), had a broader range of 5-$25cm^2$. Meaume et al., (2012), had no restriction on ulcer size or age. All the studies included compression as part of standard care for both treatment arms.

Wound care trials are usually difficult to achieve blinding however, Meaume et al., (2012), was a double blinded study with the others being open label. Double blinding was achieved as Laboratoires Urgo manufactured both study dressings used in the trial; one impregnated with the sucrose octasulfate matrix and one without. This is the same methodology as in the DFU RCT carried out on the sucrose octasulfate dressing.

The primary outcome was wound area reduction (WAR) in 2 out of 3 LU studies, with only Vin et al., (2002), capturing full wound healing. Full wound healing is a more relevant endpoint for patients and caregivers as this reflects the goal of treatment, whereas WAR is a surrogate

measure that does not guarantee full closure; and does not account for wound depth. It is likely that these surrogate endpoints were used instead of complete wound closure as the study follow up periods of 8 weeks (Meaume et al., 2012) and 12 weeks (Vin et al., 2002: Schmutz et al., 2008) would not be long enough to record wound closure.

Observational studies

The two observational studies include data from 10,254 patients, with Munter et al., (2017), being a pooled analysis of 10,220 patients, including patients with both LU (n = 7903) and DFU (n = 1785), amongst other wounds. Munter et al., (2017) intended to understand real-world treatment patterns with the sucrose octasulfate dressing, using a large patient cohort pooled from 8 other observational studies. The included studies have not been assessed for risk of bias and appear all to be manufacturer driven and led. Length of follow up ranges from 4 weeks to 20 weeks and the outcome measure reported by Munter et al., (2017) was wound closure or proportion of patients with a 50% reduction in the PUSH score; reaching this in 29.8% and 37.4% of LU and DFU patients respectively. Richard et al., (2012) was a prospective pilot study on 34 DFU patients, with primary objective assessing relative WAR of the wounds within 12 weeks.

Primary outcomes

The results of the primary outcomes are shown in Table 2.7, structured to show the LU, DFU RCTs and observational studies separately, with the results of Munter et al., (2017) stratified by wound type, LU or DFU. Of the total 7 studies included, 3 had a primary outcome of relative WAR and 4 assessed healing or closure outcomes. The studies provide evidence that not all PMM dressings offer the same clinical benefit to patients, with only the sucrose octasulfate dressing recording statistically significant outcomes, Edmonds et al., (2018) demonstrated an odds ratio of 2.6 ($p = 0.002$) of healing at 20 weeks when using the sucrose octasulfate dressing on DFUs. Looking at the total population Munter et al., (2017) show a 30.8% benefit when a treatment regime included the sucrose octasulfate dressing, broken down as a 29.8% (CI: 28.8%-30.9%) benefit for LU patients and 37.4% (CI: 34.8%-40.1%) for DFUs. For ORC, Veves et al., (2002) did not reach statistical significance improving wound healing versus control for DFU, nor did Vin et al., (2002) when studying LU; an improvement was noted but this result failed to reach significance ($p = 0.184$). Overall, there is a stronger evidence base for the clinical benefit of the sucrose octasulfate dressing compared to ORC.

Table 2.7. Clinical SLR results of included studies

		LU RCT			DFU RCT		OBSERVATIONAL STUDIES		
Study name		Meaume et al., 2012	Schmutz et al., 2008	Vin et al., 2002	Edmonds et al., 2018	Veves et al., 2002	Richard et al., 2012	Munter et al., 2017	
								DFU	LU
(n=)	Active	93	57	36	126	138	34	1273	7660
	Control	94	60	37	114	138	N/A	N/A	N/A
Duration	Weeks	8	12	12	20	12	12	4-20	4-20
Analysis		ITT	ITT	ITT	ITT	N/A	ITT	N/A	N/A
Primary outcome	Name	Relative WAR	Relative WAR	Complete closure	Complete closure	Complete closure	Relative WAR	Complete closure	Complete closure
	Unit	%	%	%	OR and %	%	%	% and days	% and days
Effect size	Value	SO 58.3% Control 31.6%	SO 54.4% ORC 12.9%	ORC 49% Control 33%	SO 48% Control 30% OR 2.6	ORC 37% Control 28.3%	Mean 62.7%	37.4% 98.1	29.8% 112.5
	95% CI	-38.3 to -15.1%	n/a	-0.7 to +38%	1.43% - 4.73%	n/a	±49.9%	34.8-40.1% 88.8-107.5	28.8-30.9% 105.8-119.3
Test	Type	Mann-Whitney	Wilcoxon	Mann-Whitney	Binary logistic regression	Linear logistic regression		Kaplan-Meier and log-rank	Kaplan-Meier and log-rank
	p value	P = 0.002	P = 0.0286	P = 0.184	P = 0.002	P = 0.12	n/a	n/a	n/a

Risk of bias (quality) assessment

The NICE submission template (as relevant to each design) for MTEP were used to assess quality and risk of bias (NICE, 2017) as presented in Tables 2.8 and 2.9. The assessment of RCTs had 7 questions to report from the studies in the following categories: randomisation, concealment, baseline similarity, blinding, withdrawal imbalances, unreported outcomes, ITT analysis. A scoring method was applied, giving a point for each dimension the study could satisfy- giving a maximum of 7 points. One study scored 7 points (Edmonds et al., 2018) one study scored 6 points (Meaume et al., 2012), and one each scored 5, 4, 3, and 2 points, giving an average score of 5.4. There are no defined criteria for interpreting the scoring; however it

is to be assumed that the more points scored; the more robust the study can be considered. The critical review of the observational studies also had 7 questions, asking about recruitment, exposure, outcome measurement, confounding factors, follow up and precision of results. A scoring method of assigning a point per category satisfied was applied, and both studies scored only 1 point, showing that these studies did not report enough data to be considered high quality. The methodological assessment of the studies is in Table 2.8 for the RCTs and Table 2.9 for the observational studies.

Table 2.8. Clinical SLR risk of bias assessment of RCTs (NICE 2017)

Study name	Meaume et al., 2012	Schmutz et al., 2008	Vin et al., 2002	Veves et al., 2002	Edmonds et al., 2018
Appropriate randomisation	Yes, stratified by centre	Not clear	Not clear	Yes, stratified by wound area	Yes, stratified by wound area
Concealment of allocation?	Yes, double-blind	No, open label	No, open label	Not clear	Yes, double-blind
Groups similar at baseline?	Yes	Yes	Yes	Not clear	Yes
Allocation blinded?	Yes	No	No	Not clear	Yes
Imbalances in dropouts?	No	Yes, more ORC	Not clear	No	No
Outcomes all reported?	No	No	No	Not clear	No
ITT analysis? Missing data?	Yes	Yes	Not clear	Not clear	Yes
Score	6	3	2	2	7

Table 2.9. Clinical SLR risk of bias assessment of observational studies (NICE 2017)

	Richard et al., 2012.	Munter et al., 2017
Acceptable recruitment?	Yes, consecutive patients	Not clear, pooled studies
Exposure measured?	Not clear	Not clear
Outcome measured?	Not clear, relative WAR	Not clear, wound closure
Confounders Identified?	Not clear	Not clear
Confounders mitigated?	Not clear	Not clear
Follow-up of complete?	No, 1 missing & 8 withdrawn	Yes, at least 1 follow up
Results precise?	No, CI of ± 49.9%.	Yes, p=<0.001
Score	1	2

2.2.6 Discussion

A systematic search of the literature was undertaken to investigate whether PMM interventions are clinically effective treatment for DFUs and/or LUs. This review has found evidence that some PMM interventions were clinically effective in the management of DFU and LU, compared to control.

For patients with a DFU, Edmonds et al., (2018) measured wound closure and achieved this endpoint in 48% of patients using the sucrose octasulfate dressing versus 30% of patients using control, with an odds ratio of 2.6 in favour of the intervention; subgroup analysis also showed that the earlier that treatment is initiated, the better the outcomes. For ORC, Veves et al., (2002) also achieved a positive result for the PMM intervention, however this study did not reach the threshold for statistical significance. The result suggests that the sucrose octasulfate dressing is more likely to result in better healing outcomes for these patients.

For patients with a LU, the most measured endpoint in the RCTs was WAR; perhaps because LUs can take a very long time to heal and clinical studies that measured full healing would need to be long in duration: and thus very expensive. Instead, studies rely on the proven statistical link between the rate of initial wound area reduction and eventual closure (Cardinal et al., 2008). All studies included showed the superiority of the PMM intervention, however the ORC study as reported by Vin et al., (2002), did not reach statistical significance. Meaume et al., (2012) found a statistically significant benefit for the sucrose octasulfate dressing with 26.7%

difference between the groups, in favour of the study dressing; repeated in Schmutz et al., (2008); where patients using this dressing had a WAR of 54.4% versus only 12.9% of those using control, a statistically significant result. The LU RCTs may suggest that the sucrose octasulfate dressing is not only better than control but is also superior to the ORC matrix in treating these wounds.

There is also some evidence of benefit for patients in a real-world setting, with Munter et al., (2017) aiming to understand if the efficacy demonstrated in clinical studies is effectively translated to a real-life patient; with 37.4% and 29.8% of DFU and LU patients reaching the endpoint of either wound closure or 50% reduction in PUSH score. However, there is difficulty in observing real-world trends; this pooled analysis of observational studies is without a critical appraisal of included studies and scored low in the critical assessment.

Both Meaume et al., (2012) and Edmonds et al., (2018) compared two wound care products by the same manufacturer. The studies achieved double blinding by producing both the intervention and control dressing with the same material, packaging and colours as one another; with the sole difference of the sucrose octasulfate dressing having the active healing matrix to inhibit excess metalloproteases and restore local angiogenesis. By performing double blinded RCTs, high-quality evidence has now been produced in the field of wound care; setting a new standard for manufactures.

The risk of bias (quality) assessment of the evidence scored the RCTs as being of an overall moderate quality when considered as a collective, however Meaume et al., (2012) and Edmonds et al., (2018) both individually scored highly, reflecting the robust double-blinded nature of these studies. The observational studies both were of low quality when evaluated by the critical review. Uncertainty of evidence undermines the data produced; and in an external environment of manufacturer led studies, the open-label studies score poorly on risk-of-bias scoring methodologies due to the practicalities of wound care products. Due to the high-quality of the studies by Meaume et al., (2012) and Edmonds et al., (2018) there is limited uncertainty when assessing the positive results in these RCTs. To balance RCTs with real-world practice, expert opinion and real-world data could be sought inform best treatment practice.

This systematic review highlights the need for further research into the efficacy of PMM treatments; given the use of the proxy endpoint WAR in many RCTs. Future studies could follow

the example of Meaume et al., (2012) and Edmonds et al., (2018) which demonstrate the feasibility of double blinding when examining wound care devices. More research into the patient perspective of ulceration and living with treatment would help to understand quality of life (QoL) factors. Secondary outcomes of tolerance and adverse events reported in the studies here give insight into patient issues, however using validated tools such as EQ-5D-5L and SF-36 allows for greater transferability of results. A review of patient level data to examine the treatment practices used by HCPs would be useful to establish treatment pathways; or to highlight how RCTs differ from 'real-life' in terms of patient characteristics, treatment plans and outcomes. A dressing, by its nature is frequently changed, and a treatment switch at dressing change is speculated by this author to be more likely in a real-life setting opposed to a protocolised clinical study setting. All the studies stipulate using the study dressing for the duration of follow-up (from 8 to 20 weeks) and treatment patterns applied by HCPs in a clinic may deviate from this; perhaps having an impact on efficacy.

2.2.7 Conclusions

This review provides some evidence that PMM interventions have a clinical benefit on wound healing outcomes; however, there were several methodological issues with the studies included. New evidence shows promising results for the treatment of DFUs involving inhibition of excess metalloproteases and restoration of local angiogenesis by sucrose octasulfate dressings.

The findings of this systematic review can inform clinical decision making concerning the use PMM interventions. The evidence collected shows the superiority of the sucrose octasulfate dressing over the ORC matrix, highlighting that not all PMM interventions are the same. The evidence suggests that the sooner a patient is treated with the sucrose octasulfate dressing, the better the healing outcomes. Early intervention combined with reducing healing time in general, could help to alleviate burden of DFU and LU on patients, clinicians, and the healthcare system.

2.3 A systematic review of economic outcomes associated with use of topical interventions for treatment of chronic wounds

2.3.1 Introduction

Chronic wounds such as DFU and LU are burdensome for patients, their caregivers, the healthcare system, and wider society. They can last a long time, often for more than a year. Chronic wounds are more prevalent in older people, due to the impact aging has on the wound repair processes and the increased incidence of diabetes and cardiovascular disease (Gould et al., 2018). Patients diagnosed with a chronic comorbidity such as diabetes or venous insufficiency are at a higher risk of developing a chronic wound (Frykberg & Banks, 2015; Kerr, 2017). The prevalence and incidence of diabetes is rising in the United Kingdom (UK), as too is the size of the elderly population (Zghebi et al., 2017; Office for National Statistics, 2018). The growth of these populations suggests that there will also be a growth in the financial and economic cost of their co-morbidities; including chronic wounds. A retrospective database study suggests that 2.2 million people, or 4.5% of the adult population presented with a chronic wound in the study year (Guest et al., 2015). Chronic wounds also contribute to a significant portion of healthcare spending in the UK, with an estimated 5.5% of National Health Service (NHS) expenditure on chronic wound care (Phillips et al., 2016).

2.3.2 Background

Treating chronic wounds involves a range of standard care interventions, including debridement, infection control, offloading, surgery, compression, and use of dressings (Jones et al., 2018). A combination of these strategies may be appropriate for a patient presenting with a chronic wound. The optimal treatment pathway is still uncertain; with many products offering a variety of evidence as to their clinical and cost-effectiveness. Wound dressings and topical interventions are a key component of treatment strategies to achieve wound closure for a range of wounds. Dressings have been categorised by the British National Formulary (BNF) as being either basic, advanced, antimicrobial, or specialised; spending on wound-care dressing prescriptions in England was almost £106 million in the year ending August 2017 (NICE, 2019).

The uncertainty surrounding the clinical and cost-effectiveness of interventions impacts the benefits felt by patients and the wider economy. In terms of dressings, the National Institute for Health and Care Excellence (NICE) states that HCPs should "routinely choose the least costly dressing" (emphasis added) unless a specific dressing can be justified on clinical grounds (NICE,

2016). This instruction demonstrates a preference for cost-containment; rather than assessing the cost-effectiveness or cost-dominance of a dressing; contrary to standard NICE technology appraisal processes (NICE, 2016). The choice of dressing is thus left to an individual HCP; theorised to cause a variance in treatment practices, given the lack of standardised guidance on specific products and the abundance of products available.

A series of SLRs on different types of wound dressings performed by the Cochrane Collaboration found no superior intervention when looking at clinical outcomes of wound care dressings, largely because of a high risk of bias and low-quality clinical studies (Dumville et al., 2011; Dumville et al., 2012; Westby et al., 2016). Meta-analysis is often impossible in wound care studies due to the heterogeneity of studies and an unclear and often varied standard care protocol. Standard care can vary by wound aetiology, geographical location and clinician discipline. To the knowledge of the present researcher no SLR looking at economic outcomes associated with dressings was identified in current literature. To address this current gap, a systematic review was undertaken to examine the economic impact of topical interventions for chronic wounds and the variance associated with standard care.

2.3.3 Study aims

The aim of study 1b was:

- To explore the economic impact of interventions for chronic wounds and estimate the cost of standard care in the UK.

The objectives of study 1b were:

- To establish a definition of standard care.
- To document economic evaluations of topical interventions for chronic wounds.
- To establish if more expensive wound care products are cost-effective.

2.3.4 Methods

A systematic review was carried out following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009). This review searched several databases and included discussion with experts and manufacturers to identify the literature. Two researchers (AB and a research associate) performed data extraction, with a third (PhD supervisor, IO) consulted where there were disagreements. Economic endpoints

were extracted, including incremental cost-effectiveness ratio (ICER), cost-per Quality Adjusted Life Year (QALY) and disease related resource use. A narrative synthesis of results and critical appraisal using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement were performed (Husereau et al., 2013).

Search strategy

In line with recommendations by the Cochrane Collaboration, search terms were identified according to the Population, Intervention, Comparator and Outcome (PICO) framework to retrieve literature pertinent to the search topic (The Cochrane Collaboration, 2019). The search terms were used to obtain literature relating to chronic wounds, specifically DFU and LU and their management, treatment or care using a dressing, compression, or standard care. These wound aetiologies were selected as they have been shown to be the most common chronic wounds in a recent study of UK real-world data (Guest et al., 2015). Further terms were used to identify economic outcomes. Table 2.10 shows a full list of search terms. No comparator was determined as the interventions included were deemed broad enough to capture a range of studies.

Table 2.10. Economic SLR search terms used

Search terms	Item
(Wound (*) and chronic) or (ulcer and (or diabetic foot or leg))	Population
Management or treatment or care	Intervention
Dressing (*)	Intervention
Resource and (use or utilisation) or cost	Outcome
Quality of life or patient outcomes or burden or impact	Outcome
Effectiveness or efficacy	Outcome

Data sources

Electronic databases (Science Direct, NICE Evidence database, Medline (PubMed), Centre of Reviews and Dissemination/NHS Economic Evaluation Database (University of York), and the Cochrane Database) were searched using these terms and a citation search of included articles was performed. Further relevant titles were identified through discussions with manufacturers and experts.

Table 2.11. Economic SLR inclusion and exclusion criteria

Inclusion criteria	
Population	Chronic wounds- DFU or LU
Interventions	Topical dressings or applications
Outcomes	Economic outcomes
Study design	Randomised controlled trials with economic evaluation, economic modelling
Language	English Language
Search dates	After 1987
Exclusion criteria	
Population	Paediatrics (<18), acute wounds (including Burns, Trauma, Surgery) pressure Ulcers.
Interventions	Surgical, novel non-surgical, infection control measures, debridement, bioengineered skin substitutes, offloading
Outcomes	Not meeting inclusion criteria
Study design	In vitro studies, review or discussion articles
Language	Non-English language
Search dates	Before 1987

Types of study included

This study reviewed economic analyses of randomised controlled trials (RCTs), and other examples of economic modelling. All other study designs, review articles, expert opinion and guidance documents were excluded. Searches were limited to 30 years, from 1987-2017, to ensure that included articles were not outdated.

Interventions

Topical applications and standard care were the interventions of interest, to understand the variance in standard care methods and costs. Standard care did not need to fit any pre-specified criteria, as this review would accept any definition as provided by a study. Surgery was excluded, as were novel non-surgical interventions such as vacuum assisted closure, hyperbaric oxygen therapy and electric stimulation as these were deemed to be procedures and not comparable with a dressing or topical intervention.

Population

This review included studies of patients with chronic wounds. Chronicity is defined as a wound caused by an underlying aetiology, such as diabetes or vascular insufficiency; or as a wound with a duration of over 4 weeks (Russell et al., 2018). Non-healing surgical wounds, burns, and acute trauma wounds were excluded due to their lack of underlying aetiology. Pressure ulcers were excluded as these occur in a different population; predominantly in immobile or hospitalised patients and have different treatment methods. Methods to diagnose a venous, arterial or diabetic wound may vary and this review accepted any as described by the included the studies.

Data extraction (selection and coding)

The first reviewer (AB) undertook initial screening of titles and available abstracts exported to EndNote. The initial screening removed duplicate articles, irrelevant titles, foreign language, and letters, editorials or other discussion texts. The database stored bibliographic information, abstracts, and the link to the full text. If the full text was unavailable, then an effort was made to retrieve it, if the abstract indicated that the article met the inclusion and exclusion criteria.

The titles exported to the Excel database were then reviewed against the pre-determined inclusion and exclusion criteria, shown in Table 2.11. Two researchers (AB and a research associate) undertook the review, applying the inclusion and exclusion criteria independently of each other.

Risk of bias (quality) assessment

Studies were judged using the CHEERS statement, which includes parameters for methods, assumptions, results, and discussion as per the standards set by the International Society of Pharmacoeconomic and Outcomes Research (ISPOR) (Husereau et al., 2013). Two researchers (AB and a research associate) completed an independent review of the quality assessment.

Strategy for data synthesis

A structured narrative synthesis of the data was constructed using data tables, stratified according to wound type, and then by intervention. A meta-analysis using standard statistical methods was considered, however the studies were not sufficiently homogenous to perform this analysis (Sedgwick, 2015).

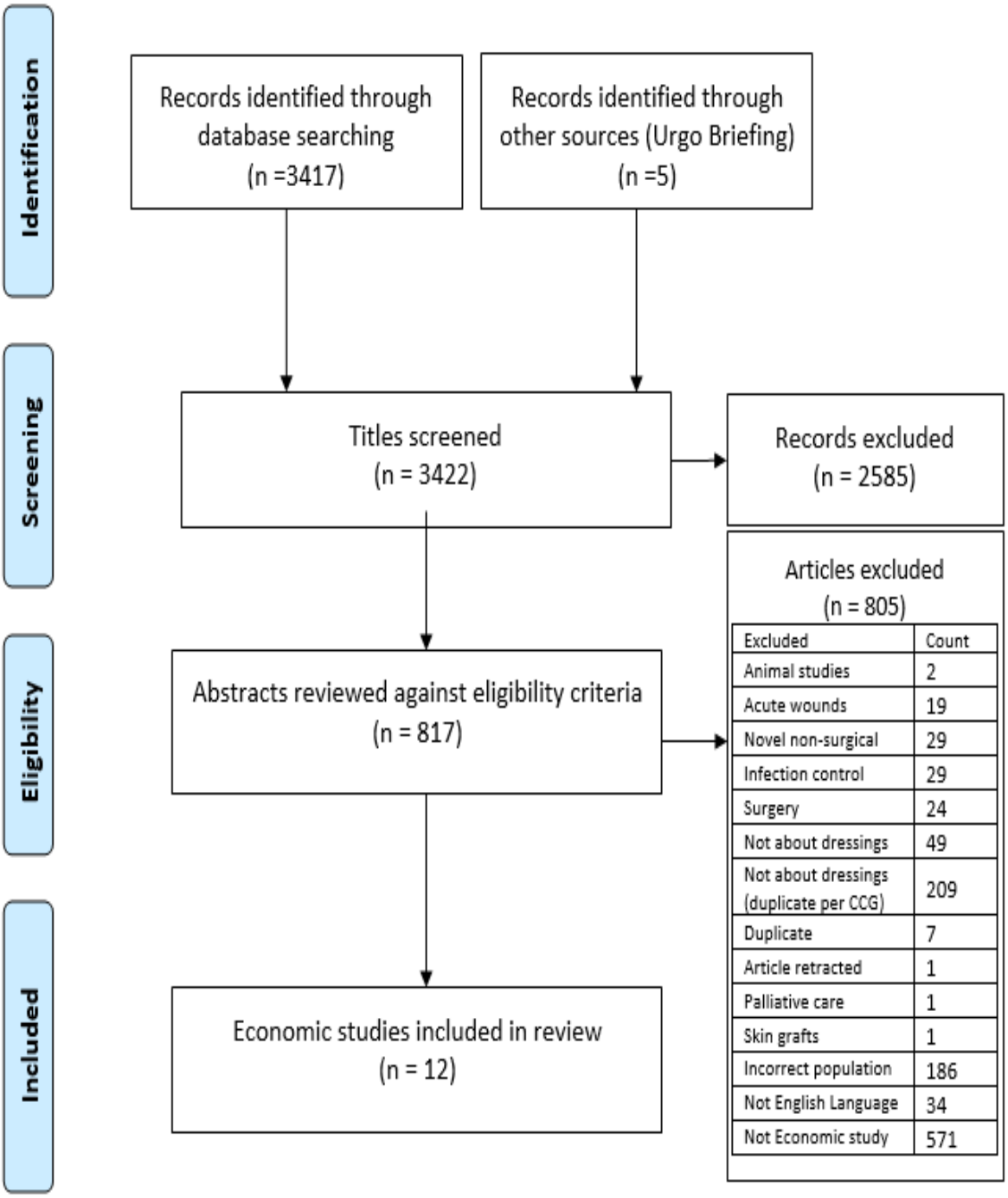
2.3.5 Results

From searching the databases, 3417 results were returned (Table 2.12). Discussion with experts and manufacturers provided 5 further titles. After initial screening of the 3422 titles and abstracts, 2585 were excluded for being not relevant to the research questions. The remaining 817 texts were judged against the inclusion and exclusion criteria in Table 2.2. Of these, 805 titles were excluded, with 12 being included as per the PRISMA flow chart in Figure 2.3.

Table 2.12. Economic SLR article sources

Search tool	Count
Science Direct	2479
NICE Evidence search	805
Medline (PubMed)	78
CRD (University of York)	47
Cochrane	8
Discussion with experts and manufacturers	5
Total exported to EndNote:	3422

The design of the included studies can be found in Table 2.13 and the endpoints, documented resource use and results are shown in Table 2.14, with a record of 'n/a' if the study did not report these items.



Excluded	Count
Animal studies	2
Acute wounds	19
Novel non-surgical	29
Infection control	29
Surgery	24
Not about dressings	49
Not about dressings (duplicate per CCG)	209
Duplicate	7
Article retracted	1
Palliative care	1
Skin grafts	1
Incorrect population	186
Not English Language	34
Not Economic study	571

Figure 2.3. Economic SLR PRISMA reporting diagram

Table 2.13. Economic SLR design of included studies

Study	Wound	Type	Intervention	Comparator	Setting	Perspective
Apelqvist & Ragnarson-Tennvall, 1996	DFU	CMA	Cadexomer iodine	Standard care	Sweden	Societal
Persson et al., 2000	DFU	CEA	Becaplermin gel	Good wound care	Sweden	Health system
Schonfeld et al., 2000	LU	CEA	Graftskin	Compression	USA	Payer
O'Brien et al., 2003	LU	CEA	Compression	Standard care	Ireland	Health board
Guest et al., 2005	LU	CEA	Carboxymethylcellulose	Gauze dressing	USA/ Germany	Payer
Guest et al., 2009	LU	CUA	Amelogenin	Compression	UK	Health system
Guest et al., 2012	LU	CEA	Skin protectant	Standard care	UK	Health system
Craig et al., 2013	DFU	CCA	Soft castings	Standard care	UK	Health system
Ashby et al., 2014	LU	CEA	Compression hosiery	Compression	UK	Health system
Jemec et al., 2014	LU	CEA	Silver dressing	Standard care	UK	Health system
Augustin et al., 2016	LU	CUA	Sucrose octasulfate	Standard care	Germany	Payer
Nherera et al., 2016	LU	CUA	Cadexomer iodine	Standard care	USA	Payer

Abbreviations: CCA: cost-consequence analysis, CEA: cost-effectiveness analysis, CMA: cost-minimisation analysis, CUA: cost-utility analysis, DFU: diabetic foot ulcer, LU: leg ulcer, UK: United Kingdom, USA: United States of America

Table 2.14. Economic SLR endpoints, resource use and results of included studies

Study	Time horizon	Health states	Efficacy source	Efficacy	Utility	Resource use	Results
Apelqvist & Ragnarson-Tennvall, 1996	12 weeks	n/a	Economic analysis with trial.	WAR > 50% from baseline	n/a	Material, drug, staff, and transportation	Mean weekly cost saving of SEK 518
Persson et al., 2000	1 year	Unaffected/ Infected/ Gangrene/ Healed/ Amputation/ Deceased	Pooled analysis. (Smiell et al., 1999)	Healing rate. Amputation rate	n/a	Interventions, inpatient/ outpatient, amputation costs	When amputated Becaplermin saves $370.
Schonfeld et al., 2000	1 year	Unhealed/ Healed Recurrent/ No therapy	Single study. (Falanga et al., 1998)	Probability of healing	n/a	Interventions, inpatient/outpatient, tests, adverse events	Average monthly cost 10% lower
O'Brien et al., 2003	12 weeks	n/a	Economic analysis with trial.	Time to healing	n/a	Dressings, nurse time, GP/hospital.	Median reduction: €24/ leg healed
Guest et al., 2005	18 weeks	n/a	Synthesis of 8 studies.	Probability of healing	n/a	US- Medicare Germany- Local sources.	USA saving $1491.20/patient. Germany saving €633.69 /patient.
Guest et al., 2009	1 year	Healed/ Improved/ Unchanged/ Worsened/ Recurrence/ Dead	Single study. (Vowden et al., 2007)	Change in wound area	Ulcer 0.64. Improved 0.73. Healed 1.00. (Clegg & Guest, 2007)	Nurse visits, dressings, and prescriptions.	10% reduction in 12-month cost, considered dominant.

Study	Time horizon	Health states	Efficacy source	Efficacy	Utility	Resource use	Results
Guest et al., 2012	6 months	Not reported.	The Health Improvement Network Database study	% healed and QALYs at 6 months.	Ulcer 0.64. Improved 0.73. Healed 1.00. (Clegg & Guest, 2007)	Staff time and visits. Dressings & bandages. Change frequency.	May facilitate healing of larger wounds without increasing costs.
Craig et al., 2013	1 year	n/a	Economic analysis of audit	Healing, improving or deteriorating.	n/a	Material cost, staff time, orthotic boot.	10% cost-saving for prevention & 6% for treatment
Ashby et al., 2014	3 years	n/a	Clinical trial.	Time to healing	Values not reported	Compression, ulcer-related consultations	£300 saving. Dominant
Jemec et al., 2014	4 weeks	n/a	Meta-analysis. (Leaper et al., 2013)	RWAR ≥40% at 4 weeks	n/a	Dressings, primary/secondary care and tests.	£141.57 saving due to faster wound closure.
Augustin et al., 2016	8 weeks	n/a	Single study. (Meaume et al., 2012)	RWAR ≥40% at 8 weeks	n/a	Dressings, primary/secondary care, side effects.	€486 saving per patient.
Nherera et al., 2016	1 year	Healed. Unhealed. Infected. Dead	Meta-analysis. (O'Meara et al., 2014)	Probability of healing.	Unhealed 0.73. Infected 0.64. Healed 1. Recurrence 0.64.	Hospitalization, drugs, outpatient and homecare	$643 saving per patient. Dominant treatment

Population

The studies predominantly examined LU, with nine studies focusing on these patients (Schonfeld et al., 2000; O'Brien et al., 2003; Guest et al., 2005; Guest et al., 2009; Guest et al., 2012; Ashby et al., 2014; Jemec et al., 2014; Augustin et al., 2016; Nherera et al., 2016). The dominance of the LU studies in this review is reflective of these wounds being the most common of the chronic wounds. Only three of the studies looked at DFU, including the two oldest included studies (Apelqvist & Ragnarson-Tennvall, 1996; Persson et al., 2000; Craig et al., 2013). In the 12 studies, 14 interventions were used. Standard (or good) care was used 8 times.

Settings and perspectives

Five studies were carried out in the UK (Guest et al., 2009; Guest et al., 2012; Craig et al., 2013; Ashby et al., 2014; Jemec et al., 2014), four in the US (Schonfeld et al., 2000; Guest et al., 2005; Nherera et al., 2016), two in Germany (Guest et al., 2005; Augustin et al., 2016), two in Sweden (Apelqvist & Ragnarson-Tennvall, 1996; Persson et al., 2000) and one in Ireland (O'Brien et al., 2003). One study covered both the US and Germany (Guest et al., 2005). All studies were from the Healthcare provider or payer perspective; except for Apelqvist & Ragnarson-Tennvall (1996) which took a societal perspective.

Study types

Included were seven cost-effectiveness analyses (Persson et al., 2000; Schonfeld et al., 2000; O'Brien et al., 2003; Guest et al., 2005; Guest et al., 2012; Ashby et al., 2014; Jemec et al., 2014), three cost-utility analyses (Guest et al., 2009; Augustin et al., 2016; Nherera et al., 2016), one cost-consequence analysis (Craig et al., 2013) and one cost-minimisation analysis (Apelqvist & Ragnarson-Tennvall, 1996).

Results of included studies

The results of economic analyses are presented in Table 2.14, with standard care being used as a comparator or combination therapy treatment in eight instances. Positive economic outcomes in favour of the study intervention were recorded in all studies. All the interventions measured by the included economic analyses were either dominant, cost saving, cost-effective, or resulted in savings to the healthcare system when measured against their comparators; even the interventions that had a higher acquisition cost. Faster healing, or a

higher rate of healing was the driver behind the cost savings on most of the studies; this is because the less time a patient has an ulcer, the less time they are consuming costly healthcare resources.

Standard care

Due to the nature of treating chronic wounds, standard care such as offloading, compression, debridement, dressings and infection control are used, alongside treatment by multidisciplinary teams including practice nurses, podiatrists, vascular surgeons, tissue viability nurses, and health care assistants. A range of methods of achieve offloading, compression, debridement, dressing and infection control were used in the studies, depending on the stipulation of the study design. Use of the different techniques to achieve wound healing was as clinically required; determined by clinician judgement upon inspection of the wound.

Of the five studies set in the UK, standard care was used in 3 cases (Guest et al., 2012; Craig et al., 2013; Jemec et al., 2014). Guest et al., (2012) reported that the 6-monthly National Health Service (NHS) cost of managing a LU was approximately £2200 in all three groups, with little difference between the interventions. Craig et al., (2013) reported an annual cost for DFU outpatient and inpatients at £3330 and £4488 respectively. Jemec et al., (2014) measured the cost of a LU being £1468.14 for a period of 16.7 weeks until healing.

Resource use

Many of the studies measured the direct costs and excluded indirect costs; with only one taking a societal perspective, this model was published in 1996, before the conception of NICE and other Health Technology Assessment (HTA) bodies; so, the exclusion of perceived non-relevant costs may not have seemed appropriate (Apelqvist & Ragnarson-Tennvall, 1996). Persson et al., (2000) found that 83% of costs are accounted for by topical treatments and inpatient care and practice nurse visits accounted for up to 58% of costs reported by Guest et al., (2012). Staff costs such as nursing time, affected by number of dressing changes, was found to be an important parameter (Guest et al., 2005; O'Brien et al., 2013).

Data sources

Four studies were economic analyses carried out concurrent to a clinical trial, (Apelqvist & Ragnarson-Tennvall, 1996; O'Brien et al., 2003; Craig et al., 2013; Jemec et al., 2014) and a

further three were subsequent analyses based on prior clinical trials (Schonfeld et al., 2000; Guest et al., 2009; Augustin et al., 2016). Three studies were based on published pooled studies or meta-analyses (Persson et al., 2000; Ashby et al., 2014; Nherera et al., 2016). The studies that used meta-anyses or a synthesis of peer-reviewed and published data are arguably more generalisable as the effectiveness data is based on more than one source. Further to this, one study synthesised eight studies to obtain effectiveness data, but this was not published (Guest et al., 2005) and a further study used real-world data to power the model; which can also be viewed as more generalisable as due to the heterogeneity of real-world data and the fact that is has been taken from routine practice (Guest et al., 2012).

Clinical endpoints

Wound healing or closure was the endpoint in most of the studies; measured in time to healing, probability of healing or healing rate. Those that did not use full healing looked at wound area reduction (Apelqvist & Ragnarson-Tennvall, 1996; Guest et al., 2009; Jemec et al., 2014; Augustin et al., 2016). In one study, recurrence had a probability of 0.10 regardless of intervention (Guest et al., 2005) and in another, (Schonfeld et al., 2000) recurrence varied by treatment arm, with Graftskin having an increase of 2.85 months ulcer-free in a 12-month follow-up than use of Unna's boot alone.

Health states

Studies used varied and different health states. All models included unhealed ulcers and healed ulcers, with different studies specifying sub-categories of these. Infected and complicated ulcers were included in two studies (Persson et al., 2000; Nherera et al., 2016). One study also differentiated between improved, unchanged and worsened ulcers (Guest et al., 2009), and two had a separate health state for recurrent ulcers (Schonfeld et al., 2000; Guest et al., 2009). When included, amputation was treated as a health state (Persson et al., 2000).

Critical appraisal- CHEERS checklist

The methodological quality of the studies that were included in this review was assessed by use of the widely endorsed CHEERS statement (Husereau et al., 2013). The CHEERS statement measures the transparency and completeness of the reporting of methods and findings in economic evaluations using modelling. Table 2.15 shows the review of the included studies using the checklist. The most thoroughly reported study included here was (Persson et al.,

2000), whilst Ashby et al., (2014) reported on the least items. No study reported on all items in the CHEERS checklist, demonstrating that there is further information that could guide conclusions or any subsequent decision making based on these studies.

Table 2.15. Economic SLR CHEERS checklist

Criteria	(Apelqvist & Ragnarson-Tennvall, 1996)	(Persson et al., 2000)	(Schonfeld et al., 2000)	(O'Brien et al., 2003)	(Guest et al., 2005)	(Guest et al., 2009)	(Guest et al., 2012)	(Craig et al., 2013)	(Ashby et al., 2014)	(Jemec et al., 2014)	(Augustin et al., 2016)	(Nherera et al., 2016)
Title	1	1	1	1	1	1	1	1	1	1	1	1
Abstract	1	1	1	1	1	1	1	1	1	1	1	1
Introduction	1	1	1	1	1	1	1	1	1	1	1	1
Methods												
Target population	1	1	1	1	1	1	1	1	1	1	1	1
Setting and location	1	1	1	1	1	1	1	1	1	1	1	1
Study perspective	1	1	1	1	1	1	1	1	0	1	1	1
Comparators	1	1	1	1	1	1	1	1	1	1	1	1
Time horizon	1	1	1	1	1	1	1	1	1	1	1	1
Discount rate	0	1	0	0	0	0	0	0	0	0	0	0
Effectiveness measure	1	1	1	1	1	1	1	1	1	1	1	1
Estimating resources and costs	1	1	1	1	1	1	1	1	1	1	1	1
Choice of model	0	1	1	0	1	1	1	0	0	1	1	1
Assumptions	0	1	1	0	1	1	1	0	0	1	1	1
Result												
Study parameters	0	0	0	0	0	0	0	0	0	0	0	0
Incremental costs and outcomes	1	1	1	1	1	1	1	1	1	1	0	1
Characterizing uncertainty	0	0	0	0	0	0	0	0	0	0	0	0
Characterizing heterogeneity	0	0	0	0	0	0	0	0	0	0	0	0
Discussion												
Findings, limitations, generalizability, current knowledge	1	1	1	1	1	1	1	1	1	1	1	1
Total	12	15	14	12	14	14	14	12	11	14	13	14

2.3.6 Discussion

This review synthesises evidence suggesting that topical interventions can offer cost-effective solutions for treating chronic wounds compared with standard care alone. The objectives of study 1b were:

- To establish a definition of standard care
- To document economic evaluations of topical interventions for chronic wounds
- To establish if more expensive wound care products be cost-effective

The economic impact of new topical interventions for chronic wounds has been shown to be negligible when the new intervention is coupled with an improvement in healing outcomes. The key drivers of cost are the resource-intensive approach to treating wounds that require a multidisciplinary team and often multiple clinician appointments per week. Improving time to healing is important to redistribute these resources elsewhere; patients with a healed wound no longer require intensive treatment. This review has shown that, according to the included studies, more expensive wound care products can be cost-effective as long as they improve healing outcomes. This review has failed to provide a definition of standard care, given the multiple different treatment protocols prescribed across the different studies.

This review shows that more expensive interventions in all instances are cost-effective when compared to standard care; likely a result of decreased healing times, faster onset of healing and reduced healthcare system costs for a patient with a long-lasting wound. Costs relevant to the NHS are of the most interest to this research, as it is UK treatment guidelines that are of interest. In the UK, for DFU patients, an annual cost of £3909 was measured in one study when finding the mean of inpatient and outpatient costs (Craig et al., 2013). For LU, annual costs of £4400-£4571.45 can be extrapolated from the included studies (Guest et al., 2012; Jemec et al., 2014). These results indicate that wounds are expensive to treat, approximately £4000 per year per patient.

The strengths of this review are that it uses recognized reporting guidelines, PRISMA and the CHEERS statement for reporting economic studies, and the broad inclusion criteria allowed for a range of interventions to be included, providing greater information regarding the disease area. The broad inclusion criteria may also be considered a limitation, as the studies were not suitable for meta-analysis due to heterogeneity, however a broad synthesis was preferred as

wound care studies are not often homogenous even when investigating the same intervention; as shown in the clinical SLR presented earlier in this chapter. Another limitation of this study was the inclusion criteria spanned a long time; which means that costs between the studies are difficult to compare like for like. However, to mitigate this, this SLR did not aim to make explicit comparisons between the results of the included analyses but was looking for patterns and trends with regards to topical wound care interventions for DFU and LU. This review only included studies in the English language due to the capabilities of the research team; so, it is possible that relevant literature in other languages may have been excluded. Further research into chronic wounds by a multi-lingual study team would be necessary to confirm these results outside of English-language only publications.

In an external environment of budget cuts and financial pressure on the healthcare systems, cost-effective solutions to health care problems are desirable. This study has shown that cost-effective interventions are not necessarily those with the lowest acquisition cost, the use of which may not lead to the best possible healing outcomes for patients. Longer term costs should also be factored in, regarding the ongoing costs of treating a chronic wound and the risk of recurrence.

Current NICE guidance does not prescribe a specific dressing or intervention nor indicate clearly when different dressings or interventions are required (NICE, 2018). The lack of direction coupled with an abundance of products available leads to a vast number of interventions being used for treating chronic wounds. The variance of treatment methods is evidenced in this study, presenting eight instances of standard care, which included a vast array of different protocols. Without a specific definition of standard care, a meta-analysis will likely continue to be impossible to perform for wound care.

2.3.7 Conclusions

Currently, a clinician is directed to use “the least costly” dressing, an instruction demonstrated by this review that is unlikely to result in cost-effective treatment pathways. With a mandated treatment pathway, it is likely that there could be improvements in improving patient outcomes. Improving outcomes for patients is ultimately the most effective way to alleviate strain on the healthcare system; if the uncertainty surrounding evidence supporting new treatments can be balanced with robust economic modelling. Future research to investigate

the economic impact of full wound closure, recurrence and treatment of complicated wounds would aid in achieving efficient resource allocation. To ensure that economic analyses are reliable, they need to be based on high-quality clinical evidence.

2.4 Critical review and lessons learned

The two SLRs presented in this chapter had different study aims and objectives that were intended to serve the needs of the PhD thesis. The clinical SLR had a focussed approach, only examining the PMM interventions that are of interest to this thesis. The economic SLR had broader search terms due to the fact that PMM interventions only account for a small share of the market and there is only one published economic evaluation that would have been available to analyse (Augustin et al., 2016). This broad approach required numerous titles and abstracts to be screened against the inclusion and exclusion criteria; assessing over 3000 titles was a time consuming activity.

The focus of the clinical SLR was on the sucrose octasulfate dressing and ORC matrix intervention; which were the only two registered PMM interventions on the BNF website prior to applying the inclusion and exclusion criteria. Since this time, the BNF list of PMM dressings has been updated, to include more interventions; however 2 of these are not currently on formulary in the UK (BNF, 2019). A targeted search of online databases for the 2 additional products, Cadesorb ointment (Marketed in the UK by Smith & Nephew Healthcare Ltd) and Catrix dressing sachets (Marketed in the UK by Cranage Healthcare Ltd) did not reveal any new RCT, observational trial, or economic model on patients with DFU or LU to include in this review.

The economic SLR sought to understand if interventions that have higher acquisition costs can be cost-effective, and also to understand and define standard care with regards to DFU and LU. The study was able to determine that cost-effectiveness is not driven by the acquisition cost of a device, but rather its efficacy with regards to improving healing outcomes for a patient. The more certain a decision maker can be with regards to the clinical evidence supporting an intervention, the more likely they are to realise the economic benefits that can be offered through faster healing and fewer adverse events.

A strength of these systematic reviews is that they been performed according to guidelines from ISPOR and PRISMA, which means that the results can be interpreted as reliable and

generalisable as the methods used to carry out the research meet recognised international standards. In addition to this, multiple researchers were involved in the data selection and extraction process; a further strength as it helps to limit unconscious bias that an individual could bring if working in isolation.

A limitation of both reviews is that due to the included studies being heterogeneous, meta-analysis of the results was not undertaken. These systematic reviews also have limitations given the inclusion of only English language studies, so relevant literature in other languages may have not been captured by the search. Chronic wounds are not only an issue in English-speaking countries and follow-up research focussing on the rest of the world would help to confirm these results.

2.4.1 Implications

This chapter has presented two SLRs on different topics, both relating to chronic wounds as per the primary aim, to investigate both clinical and cost-effectiveness. The two reviews together provide more insights than would have been found should only one have been performed. In this case, coverage was given not only to the intervention of interest but also to the wider economic impact of wound care and related management strategies.

The economic SLR presented in this chapter is the first SLR that explicitly explores the divergence in standard care for patients with chronic wounds. The lack of standardized standard-care has been an issue in earlier research; Cochrane SLRs of wound dressings have found in depth meta-analysis difficult to perform (Dumville et al., 2013; Dumville et al., 2013; Wu et al., 2015; Westby et al., 2016) due to heterogeneity. The economic SLR presented in this thesis, looks further at the standard care arm and identified multiple protocols that made a meta-analysis impossible. Further to this, a review of the economic outcomes provides evidence that interventions with a higher acquisition cost can be cost-effective, and even cost dominant in some circumstances. When comparing the evidence produced here with NICE Guideline 19 (NICE, 2016) instructing clinicians to use the dressing with the lowest acquisition cost; there is an obvious disconnect. Because of this research, policy makers should be aware of the findings that the lowest cost dressings are not necessarily the best; and consider this when making recommendations on dressing types to use.

The clinical SLR presented in this chapter is the first to investigate PMM interventions in both DFU and LU patients. Addressing the wound aetiologies separately, but together, is important as DFU and LU are distinct types of wound but can be treated similarly by HCPs. Finding a dressing that improves outcomes for patients with both DFU and LU would simplify treatment; clinicians would be able to treat DFU and LU patients with the same dressing and not be disadvantaging one group. Using the same dressing for both patient groups would also streamline NHS procurement processes; as one dressing could be used in place of many others.

The clinical SLR is the first to include the large scale real-world observational study of patients using the sucrose octasulfate dressing; and the double blinded RCT of the same dressing in patients with DFU (Edmonds et al., 2018; Munter et al., 2018). The clinical SLR, included a head to head study of two different PMM interventions, the sucrose octasulfate and ORC which showed the sucrose octasulfate to be superior when considering WAR. The clinical SLR also included studies comparing sucrose octasulfate and ORC to a neutral dressing, and whilst the sucrose octasulfate dressing found a significant benefit, the ORC failed to reach significance. Therefore, this research can assert with confidence that PMM dressings offer benefits to patients, and particularly the sucrose octasulfate dressing.

2.5 Chapter summary

The two SLRs presented in this study complement one another as part of the wider portfolio of work on PMM dressings. They have shown that list price is not an indicator of cost-effectiveness and should not be used as the only parameter to judge wound care dressings. They have also shown a divergence in treatment practice; standard care was not standard enough to enable a meta-analysis in either SLR. Finally, they have shown that PMM dressings can offer improved healing outcomes for patients; and thus are a good candidate for further study into cost and QoL outcomes.

The reviews indicate that more thorough investigation into standard care for patients with a DFU or LU is required, and that modelling, and utility scores need to be updated to be relevant to the UK. The next chapter in this thesis is a Delphi method expert panel, which seeks input from a wide range of key stakeholders in the management of DFU and LU.

2.6 Dissemination

The results of these studies have been presented at The International Society of Pharmacoeconomics and Outcomes Research (ISPOR) conference in the United States, Baltimore 2018. The abstracts and posters are available in Appendix D.

Chapter 3 Delphi methodology expert panel to gain consensus on the use of dressings in the management of chronic wounds

3.1 Introduction

Expert opinion can both explain and inform best practice by providing enhanced understanding of current treatments and factors affecting outcomes that may not be evident in desk or clinical research. Opinion is unfortunately often subject to low levels of evidence; yet there are methodologies to counter this; one being the Delphi methodology, with core principles of anonymity and iteration. This study uses a Delphi methodology to achieve the objective of consensus on best practice and ideal treatments or treatment pathways. The methodology is modified to accommodate the use of electronic review, and to include a literature review of studies found using a systematic search as the first part of the study (see Figure 3.1) of the study. Issues pertaining to patient experience and resource use considerations are also addressed by the panel.

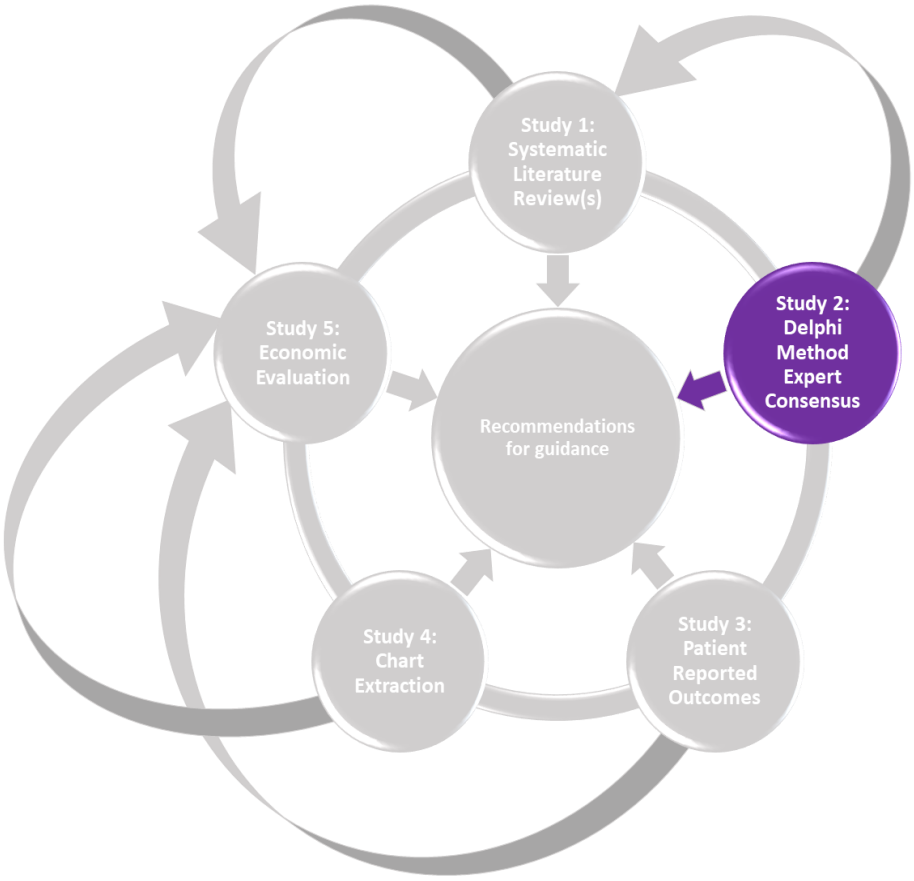


Figure 3.1. Delphi methodology expert panel within the PhD framework

This chapter presents study 2 of the thesis, which is a Delphi study investigating areas of uncertainty present in literature surrounding dressings for chronic wounds; determined by the literature review undertaken as the first part of the study and the second part of the study sought to seek consensus from a range of experts on these issues to gain clarity and a direction for study.

3.2 Background

With large patient populations presenting with chronic wounds there are many treatments available including a variety of dressing types. There are varying levels of evidence to support these interventions, but the quality of the trials is often dubious, and SLRs from organisations such as Cochrane struggled to find strong evidence towards certain treatments versus others (Westby et al., 2016).

Therefore, there is a large amount of uncertainty with regards to dressings in wound management. Uncertainty can present in many ways, including:

1. An inconclusive SLR(s),
2. A subject being deemed as not having enough robust evidence judged against risk of bias and level of evidence tools.
3. Opposing results published on the same subject, often by competitor products.

National Institute for Health and Care Excellence (NICE) guidance for treating diabetic foot ulcers (DFU) is not specific on the type of dressing (NICE, 2016). The vague instruction to use the dressing with the lowest acquisition cost can be attributed to the large number of available dressings, and the current lack of robust evidence to support a single type above all others in improving wound outcomes. Uncertainty is present not only in the NICE guidelines for treatment of DFU but also in the Scottish Intercollegiate Guidelines Network (SIGN) guidance for treating leg ulcers (LU), endorsed by NICE (SIGN, 2010). The lack of specific guidance on which dressings to use on which patients leads to inconsistencies across formularies and regions in the United Kingdom (UK). It is this prevailing climate of uncertainty which demonstrated the need to seek expert advice.

According to the Grades of Recommendation Assessment, Development and Evaluation (GRADE) system, expert opinion is not regarded as robust as other methods such as

randomised controlled trials (RCTs), or database studies (Guyatt et al., 2008). Expert opinion sought via a regular expert panel can be subject to uncontrolled bias; from intentional bias of malicious intent to unintentional biases or dominance of any individual. The risk of bias, left unchecked without an apparent method of control, leads to low levels of evidence classifications. It is speculated by the author of this thesis that a low level of evidence ranking can lead to the undervaluation of the breadth and depth of knowledge available through consultation with experts and thus a rich source of knowledge is underutilised. Enhancements to the methods of eliciting and reporting expert opinions with a focus on improving levels of scrutiny and transparency, would enable meaningful and robust consensus outcomes that could be subject to more favourable levels of evidence rankings than unstructured expert panels.

The Delphi methodology aims to arrive at an expert consensus using an iterative process. The method consists of a group of experts anonymously replying to questions; then receiving the group feedback, after which this process repeats itself (RAND Corporation, 2019). The Delphi methodology was developed in the 1950s with the goal of obtaining the most reliable consensus from a group of experts. The methodology involved the repeated individual questioning of the experts, avoiding direct confrontation of the experts with one another as introduced by Dalkey & Helmer in 1963. This practice encourages individuals to reflect on their own opinions and knowledge in the context of the feedback from others outside of their usual sphere of activity, leading to final consensus statements truly representative of a wide range of individuals and disciplines.

Despite the limitation of the Delphi methodology having a low ranking according to the GRADE system; The International Society of Pharmacoeconomic and Outcomes Research (ISPOR), a leading organisation in the field of Health Economic research, has recognised the Delphi methodology as the preferred approach in a guidance document (Mullins et al., 2014). It is hoped that this endorsement should lead to a greater uptake of the Delphi methodology as a process to obtain expert advice; and is the rationale for using the methodology in this research. Having a structured, methodological approach to a meeting with an expert panel provides a repeatable paradigm that can be carried out with other experts to produce comparable opinions.

When compiling evidence to support a new intervention or practice, the Delphi methodology is a useful tool to test assumptions, validate data and understand drivers, without the expense associated with a clinical trial. Innovations are seldom developed in isolation, and the input of a variety of clinical, economic, and policy experts are vital. Bodies such as NICE seek expert opinion for Health Technology Appraisals (HTA) by submission of an evidence dossier, and it is critical to shaping the understanding of a technology.

Pharmaceutical and medical device companies often hold advisory boards, a popular method of eliciting expert opinion, regulated by the Code of Conduct for the Pharmaceutical Industry as enforced by the Prescriptions Medicines Code of Practice Authority (PMCPA) (PMCPA, 2019). Advisory boards are useful for guiding strategy or asking medical questions, which cannot be answered through a literature search. Advisory boards are under intense scrutiny due to several trespasses of the PMCPA code of conduct by companies in the recent past (PMCPA, 2015; 2015; 2018; 2018)

The Delphi methodology can provide more transparency and scientific rigour than a traditional Advisory Board when there is a need to seek guidance from experts to validate assumptions and compare results of published literature with clinical expertise. Table 3.1 shows a comparison of advisory boards (expert panel) and the Delphi methodology.

Table 3.1. Comparison of Delphi methodology and traditional expert panels

The modified Delphi Methodology vs a traditional Expert Panel	
Delphi Methodology	**Expert Panel**
The methodology is structured to place equal weight on the opinion of all panel members.	Unstructured expert panels or advisory boards can be led by dominant or more senior individual.
Iterative; multiple rounds of voting encourages individuals to reflect on their own opinions and knowledge in the context of feedback from others.	Usually a single meeting, individuals are encouraged to put forward their own opinions and not necessarily reach a consensus.
Participants are anonymous when they feed back their opinions.	Participants are not anonymous to one another.
Transparent methodology, the workbook is the basis for all discussions.	Unstructured method without controls on biases. Can allow for more freedom of discussion.

3.3 Study aims

The aim of study 2 was:

- To identify uncertainty regarding the use of dressings in the management of DFU and LU and gain consensus

The objectives of study 2 were:

- To perform a literature review on a broad topic to create evidence-based statements
- To test the evidence-based statements with a multidisciplinary group using the Delphi methodology to generate a consensus.

3.4 Methods

This section discusses the methodology that was used in this study. First the design is presented, and the six stages of the study are discussed in turn. The stages are literature review, statement generation, anonymous voting and feedback, the face-to-face meeting and the consensus development. This study was conceived in April 2017, with the expert panel meeting held in early June 2017. Prior to the consensus meeting, a systematic literature search was carried out to source articles for thematic analysis and the generation of evidence-based statements to put to the panel. This review was the first to be carried out for this PhD thesis, acted as an exploratory review to inform the SLRs carried out on the topics of clinical and cost-effectiveness in study one, presented in chapter 2.

3.4.1 Study design

The study was designed in two parts; first, a literature review to generate evidence-based statements followed by the expert consensus process carried out in accordance to the Delphi methodology. The literature search presented in this chapter was carried out in line with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines (Moher et al., 2009). Quotations were extracted from the included titles that highlighted areas of uncertainty identified using the criteria set out in section 3.2. This review generated a set of statements included in a workbook sent to participants. The workbook also contained details of the methodology and search strategy with bibliographic details of all titles for transparency and to enable participants to review the evidence independently.

Following the literature search and statement generation, the Delphi methodology was used to validate the statements. The Delphi methodology was modified to include electronic review and voting, followed by a face-to-face meeting. Experts received the electronic workbooks to record agreement or dissent with the list of statements. After each round of voting, all responses were compiled, and anonymised responses were circulated to the group.

The face-to-face meeting agenda was to review the statements already confirmed or rejected, and to discuss and try reach consensus on any outstanding statements. The process is demonstrated in the schematic in Figure 3.2.

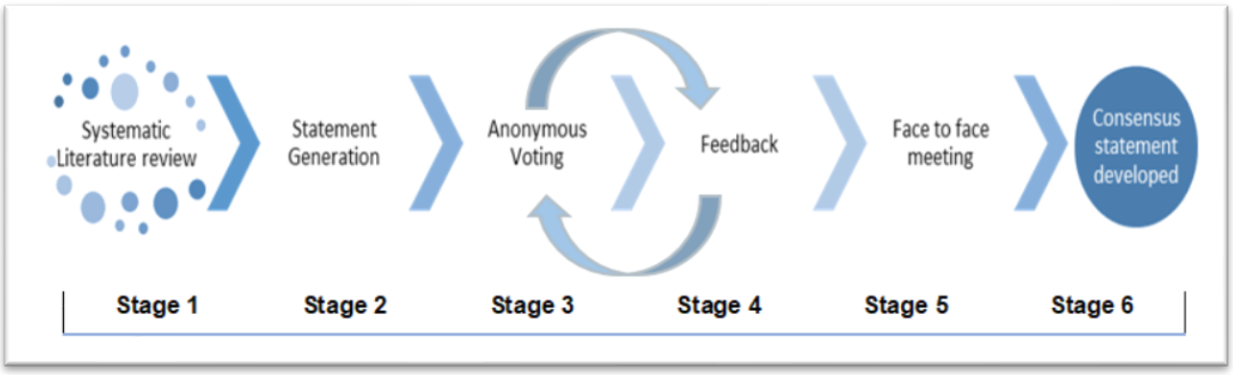


Figure 3.2. Process flow of Delphi study methodology

3.4.2 Stage 1: Literature review using systematic search methods

A set of search terms were identified in line with the Population, Intervention, Comparator, Outcome (PICO) framework to identify areas of uncertainty in wound management. The PICO framework is recommended by the Cochrane Handbook of Systematic Reviews (Higgins & Green, 2011). The search terms were used to obtain literature relating to DFU, and LU and their management, treatment, or care using a dressing. Further terms were used to identify economic outcomes, efficacy outcomes, and quality of life (QoL) outcomes, see Appendix B for a full list of search terms. There were no specific comparators searched for, because 'dressings' is a large category that would include a variety of different interventions.

Five electronic databases were searched using these search terms. Databases were chosen because of their broad coverage; Centre for Reviews and Dissemination (CRD) from University of York was included because of the search for economic data, in addition to all the trials and

review articles returned by ScienceDirect. The NICE Evidence search was used as well as the Cochrane database of systematic reviews.

Abstracts were exported to EndNote and AB undertook initial screening of titles and abstracts to discard duplicate articles, irrelevant titles, foreign language, and any letters, editorials or other discourse pieces. An Excel database was created to store bibliographic information and links to the full text of titles not discarded at initial screening stage. The titles exported to the Excel database were reviewed against the inclusion and exclusion criteria shown in Table 3.2.

Table 3.2. Delphi literature review inclusion and exclusion criteria

Inclusion criteria		
Population	Diabetic foot ulcer, leg ulcer, or a study of mixed wounds	
Interventions	Dressings	
Outcomes	Wound healing, wound area reduction, healing 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	English language	
Search dates	After 1987	
Exclusion criteria		
Population	Paediatrics (<18), acute wounds	
Interventions	Surgical, novel non-surgical, infection control measures, debridement, bioengineered skin substitutes or offloading	
Outcomes	Not meeting inclusion criteria	
Study design	In vitro studies, review or discussion articles	
Language	Non-English language	
Search dates	Before 1987	

An adult population was selected as chronic wounds in children are considered unlikely and potentially treated using different protocols. Acute wounds such as burns, trauma or surgery were excluded due to the different presentations of these wounds. Dressings were the intervention of interest, given the lack of robust guidance relating to this significant part of treatment. Non-English language articles were excluded due to the language ability of the review team. The time parameter was only to include the last 30 years to limit articles to practices and interventions that are still in use, and not to consider outdated advice.

Articles were judged as having 'met', 'maybe met', or 'not met' the inclusion and exclusion criteria. The included texts were critically appraised by ranking against the GRADE evidence classification system (Guyatt et al., 2008). Due to time restrictions involved with this project a more in-depth critical review was not possible. The results of this first systematic search were used to inform the development of more specific SLR protocols executed in chapter 2 of this thesis to look at clinical and economic outcomes for patients with chronic wounds. The SLRs presented in chapter 2 were appraised using more in-depth methods as prescribed by guidelines from ISPOR and NICE (Drummond & Jefferson, 1996; Husereau et al., 2013).

3.4.3 Stage 2: Statement generation using thematic analysis

Thematic analysis is the process of identifying patterns or themes within data (Maguire & Delahunt, 2017). This study has used the six steps set out by Braun and Clarke (2006).

The first step required becoming familiar with the data by reading included study articles and extracting quotations regarding uncertainty, as defined in section 3.2. After this, initial codes were assigned deductively using 4 pre-defined categories (clinical effectiveness, economics and cost, QoL, and epidemiology). Within these categories themes were developed using open coding, meaning that the categories were not pre-determined and were refined throughout the process.

Themes were reviewed to ensure they were separate and distinct and source documentation consulted to ensure that references still supported the theme. The statements were then written by AB using the themes from each category. The source materials were then re-checked to ensure the data supported the statement. Some semantic refinement was made to a few statements and for each statement and the source documents and quotations were made available to the participants to ensure transparency. Finally, the statements were

reviewed by the Manchester Met supervisory team and the workbook was produced and sent to participants (Appendix B.3)

3.4.4 Stage 3 and 4: Delphi methodology

To inform the Delphi approach that this study has used earlier examples were sought; however, despite being noted as a useful and flexible approach by Hasson et al., (2008) very limited examples were found in the field of wound care research. In a previous example of a Delphi panel in wound care, the statements tested are the researchers own hypotheses, or ideas that are to be tested among an expert population (Mokkink et al., 2010). This study wanted to improve credibility by developing a set of evidence-based statements generated from a systematic search of the literature to submit to the panel. This was carried out prior to the statement generation, and full search details were made available to participants.

Participants were asked "Do you agree with this statement?" with yes or no being the only response options. It was considered to mandate the ranking of a statement on a scale on 0-9, ranging from "do not agree at all" to "totally agree", which arguably provides a more in-depth view of the opinions of the panel. However, after discussion with the supervisory team, this study opted for a binary approach due to the ambitious objective of creating a unanimous consensus document endorsed by all participants. A wider range of answers could lead to an increased sense of uncertainty about a statement but would be beneficial in highlighting the perceived importance of the statements in relation to one another.

The methodology followed consisted of two iterations of expert review and voting, using the workbook provided by Manchester Met. The rating column had a drop-down option restricting to yes or no only and a message encouraging participants to offer useful feedback that would be conducive to finding a consensus. In offering the participants the option to rephrase the statement, this method allows for modification due to semantics.

This study used a methodology that allowed the amendment of statements until a unanimous consensus, or a consensus above an 80% threshold, was reached attempts to prevent the inclusion of any weakly supported statements. Using previous wound care Delphi methodology studies as a guide, 80% consensus is considered a relatively high threshold (Mokkink et al., 2010). Any statement that fell in between 80% 'yes' and 80% 'no' was amended using the comments made by the participants and resubmitted to them in the following round. As part

of this process, each reference for every statement was given a Level of Evidence (LoE) ranking using an adapted version of the SIGN classification (Harbour et al., 2011).

A face-to-face meeting was carried out to discuss the consensus, implications for clinical practice and area of future research.

Panel members

The study was designed with the aim of arriving at consensus on a range of pre-defined statements using a multidisciplinary panel, representative of experts with diverse areas of expertise. McKenna (1994) stated that 'experts' referred to a 'panel of informed individuals, and so this formed the basis of panel selection. The selection criteria of the panel members stated that they had to be actively involved in patient care for chronic wounds of any aetiology. Individuals were identified by Urgo Medical Ltd and their credentials checked by the lead researcher (AB). It has been argued that to define one group as representative of all expert opinion is problematic; given that an individual's willingness to participate will be driven by their interest in the research question (Strauss & Zeigler 1975). To mitigate this issue, this study sought to include participants with varied backgrounds, to be as representative of the whole wound care community as possible.

The panel members were deliberately chosen to not be homogenous, in the hope that encouraging consensus amongst a varied group would generate important insights. The value of this heterogeneity is fully exploited by the Delphi principle of anonymity; which serves to empower members of the group who may otherwise feel unable to voice their opinion face-to-face with their peers and superiors.

The clinical practitioners on the panel represented Nursing, (Vascular Nurse Specialist, Nurse Consultant Tissue Viability, Lead Tissue Viability Nurse, Senior Lecturer in Nursing), Tissue viability speciality (Clinical lead, Tissue Viability, Head of Tissue Viability Services), Podiatry (Clinical Lead Podiatrist, Hospital Podiatrist, Advanced Podiatrist), Surgery (Consultant Vascular Surgeon), and Diabetology (Consultant Diabetologist).

DFUs and LUs are most often seen by Nurses, including Tissue Viability Specialists who make decisions regarding treatment strategies, including dressings and topical treatments during weekly or bi-weekly appointments, they are also often responsible for communicating the

treatment plan to a patient. Their front-line exposure to chronic wounds gives knowledge and insight into the patient experience and the practical application of the treatment.

Podiatrists are health care professionals who have been trained to prevent, diagnose, treat and rehabilitate abnormal conditions of the feet and lower limbs. They also prevent and correct deformity, keep people mobile and active, relieve pain and treat infections. They can give advice to patients on how to look after their feet and what type of shoes to wear (NHS, 2018).

Vascular Surgeons can be involved in the treatment pathway for wounds requiring surgery, especially in surgery to treat and prevent the underlying cause of LUs, the venous insufficiency.

Diabetologists are experts in the treatment of diabetes, and subsequently are exposed to patients suffering from DFUs. Due to the nature of a consultant's position, these health care providers may only see patients periodically and although they advise on optimal treatment plans, they are not routinely involved with the practical day-to-day implementation of this plan.

Optimising treatment pathways for patients and improving wound outcomes are the responsibility of a diverse team of healthcare professionals. This methodology offers the opportunity for these disciplines to take advantage of their individual unique insights and collectively use their knowledge to offer advice on best practice.

The geographical spread of the panel covered the North, South, East and West of England, representing 9 National Health Service (NHS) Trusts. Many of the clinicians on the panel were working at teaching or university hospitals.

The panel members included professionals at varied stages of their careers and at different levels of seniority. Panel representation is available in Appendix B. The diversity of roles held along the treatment pathway by the participants was hoped to enable a robust discussion which offered a platform to a multitude of opinions.

In addition to the wound care clinicians on the panel, there was also a range of technical specialists invited to review the evidence presented to support the statements generated from the SLR. Three Professors in Health Economic and Outcomes research or Health Policy and academic representation were consulted in order provide an academic standpoint on the presented the evidence. A third-party facilitator was also present at the meeting to help the

running of the day, as directed by the Panel Chairperson, who sought to ensure a fair but flexible application of the methodology. The author of this thesis (AB) led the sessions on the methodology used to produce the statements, workbook and amendment of the statements throughout the process.

3.4.5 Stage 5: Face-to-face meeting

A face-to-face meeting was arranged for the panel members to come together to discuss the process, results and their knowledge and experience. Hosting a face-to-face meeting did not undermine the principle of anonymity for the Delphi process; given that the workbooks had already been completed individually by each participant; and they had already seen the comments made on earlier revisions. The agenda consisted of a thorough review of the statements and comments made (including on statements that had reached consensus) and a session to discuss the final consensus document; its presentation and any supporting documentation. The clinical experts were also asked to discuss:

1. Platforms for dissemination.
2. How a consensus document could lead to awareness, and a change in clinical practice.
3. How to determine the impact of this consensus statement.
4. Areas of future research interest.

3.4.6 Stage 6: Consensus generation

Using the Statements that reached consensus, a consensus statement was constructed; grouping the statements into categories and where necessary providing additional contextual and supporting information. After the face-to-face meeting, the terminology used was agreed and defined and these definitions accompany the consensus statement. The statement was submitted to the entire panel for their review and final approval and was then published in the Journal of Wound Care (Russell et al., 2018).

3.4.7 Ethics considerations

In this study, Urgo UK Ltd sponsored the funding of the panel, providing travel, subsistence and payment for a day's work for the members of the panel. The transfer of value creates an inevitable risk of bias towards the favouring of Urgo products due to their involvement. As a part of this agreement, the action of matrix metalloproteinases (MMPs) was one of the four

final themes of this study, however the systematic, iterative, and independent qualities of the methodology, work to protect from the risk of bias.

The PhD researcher (AB) and the Manchester Met study team handled the methodology and execution of both the SLR and statement generation, independently of Urgo input. The 'arms-length' agreement extends across all studies to protect the academic rigour of the study and was respected by both parties. The study was granted ethics approval by the Manchester Metropolitan Faculty Ethics committee (Ethics Reference: 1486).

The development of the methodology was undertaken by the Manchester Met study team. All communications regarding the structure, content and format of the meeting was the responsibility of Manchester Met. Urgo contact with the participants was limited to logistical arrangements for the final face-to-face meeting, held at a modest location convenient for many of the delegates.

The workbook used in the study was designed to present a broad evidence base. The agenda for the final face-to-face meeting consisted of an overview of responses so far and a further discussion with representation from the faculty of Health, Psychology and Social Care.

3.5 Results

This section discusses the results of this study with each of the six stages addressed in turn. The stages are: SLR, statement generation, anonymous voting and feedback, the face-to-face meeting and the final consensus development.

3.5.1 Stage 1: Systematic literature review

The search of the electronic databases retrieved 3417 titles as shown in Table 3.3. Titles were screened; leaving 817 abstracts to be reviewed against the inclusion and exclusion criteria.

Table 3.3. Delphi literature review search results from each database

Search tool	Count
Science Direct	2479
NICE Evidence search	805
Medline (PubMed)	78

CRD (University of York)	47
Cochrane	8
Total exported to EndNote:	3417

After application of the inclusion and exclusion criteria by two researchers, 295 texts remained, of which 240 were available in English (Figure 3.3). These articles were read by AB and where relevant, quotations extracted in the four stipulated categories to inform the development of the statements.

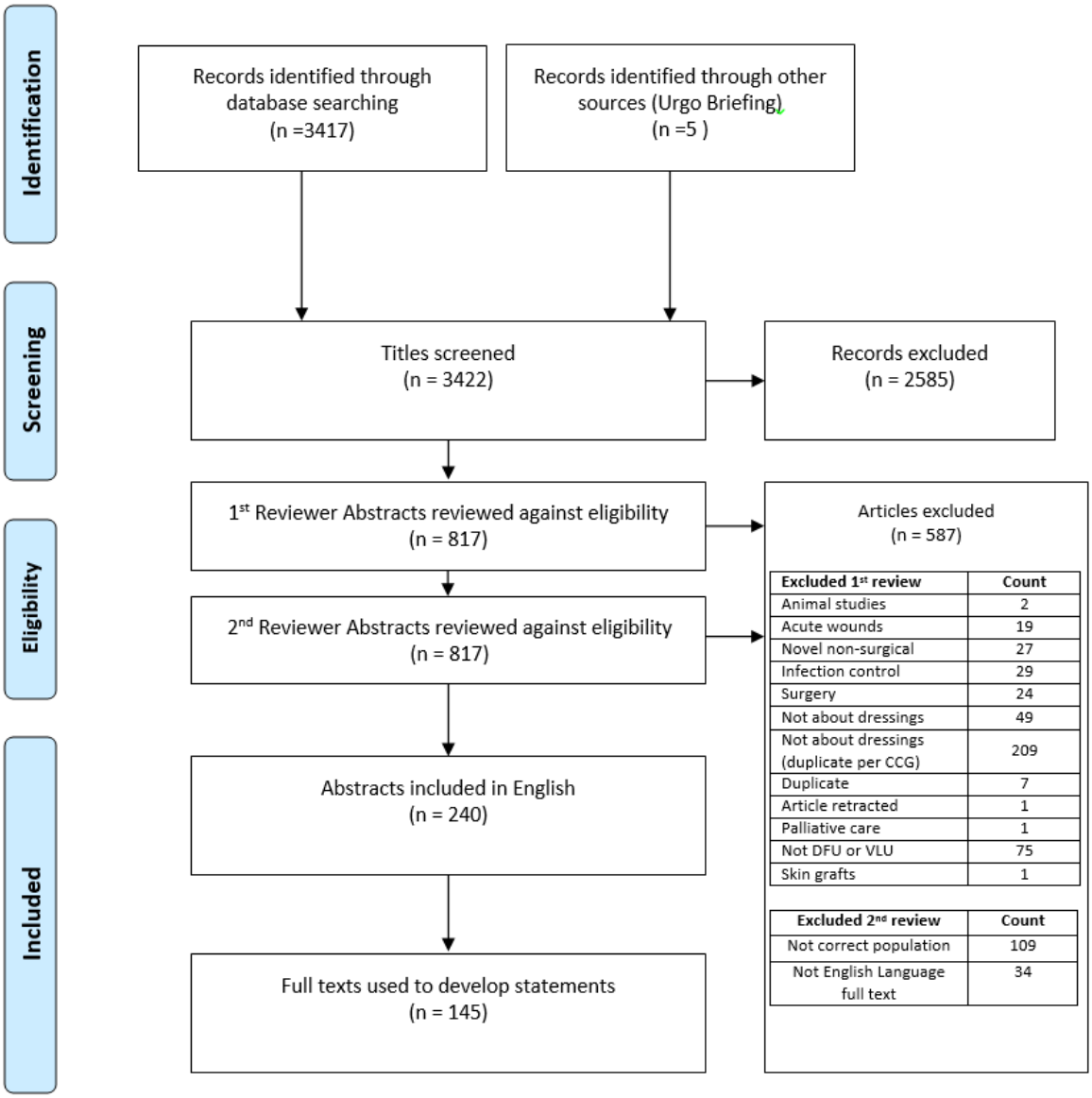


Figure 3.3. Delphi literature review PRISMA flow diagram

3.5.2 Stage 2: Statement generation

From the texts included in the literature review, 311 quotations were extracted from 145 texts. These statements were given sub-categories and were placed into logical groups shown in Table 3.4. An initial list of 48 statements was developed, addressing the topics shown in Table 3.5.

Table 3.4. Thematic analysis of statements

Clinical Effectiveness	Quality of life	Epidemiology	Economics & Cost
– Antimicrobial – Compliance – Compression compliance – Dressings – Early intervention – Failed Healing – Guidelines – Healing indicator – Protease – Ultrasound	– Broad impact – Caregivers – Chronic illness – Compression compliance – Dressings – Improvement – Odour – Pain – Physical – Psychological – Treatment focus	– Chance of healing – Chronic condition – Diagnosis – Follow up – Patient characteristics – Prevalence – Protease – Wound environment	– Cost – Cost-effectiveness – Cost of illness – Early treatment – Healing time – Resource Use

Table 3.5. Statements and categories

Clinical effectiveness (n=10)	Quality of life (n=11)	Epidemiology (n=16)	Economics and cost (n=11)
– Compression (n=3) – Guidelines (n=2) – Protease (n=2) – Dressings (n=1) – Early intervention (n=1)	– Dressings (n=2) – Healing (n=2) – Broad impact (n=1) – Caregivers (n=1) – Chronicity (n=1) – Compression (n=1)	– Protease (n=6) – Wound environment (n=6) – Healing (n=2) – Characteristics (n=2)	– Cost-effectiveness (n=4) – Cost of illness (n=3) – Resource use (n=3) – Early intervention (n=1)

– Failed healing (n=1)	– Pain (n=1) – Psychological (n=1) – Treatment focus (n=1)	– Chronicity (n=1) – Diagnosis (n=1) – Follow up (n=1) – Prevalence (n=1)	

The final list of statements was included in the workbook that was sent to participants for their review and assessment of the evidence in the first iteration of voting. The final workbook consisted of 6 sheets and can be found in Appendix B:

1. Cover sheet: For participants to record their name, affiliation and job title.
2. Introduction: An overview of the workbook and the process
3. Instructions: An overview of the tasks needed to be completed by the participant.
4. Voting sheet: For the participants to record their responses.
5. References: Full listing of quotations, with bibliographic information and level of evidence rankings.
6. Search methodology: An overview of the search strategy and results of the SLR.

The workbook was developed by the researcher (AB). Critical discussions then took place with the study team at Manchester Met to pilot and refine the workbook. Once finalised the workbook was sent to Urgo Medical Ltd for user acceptance testing. The hyperlinks to the full texts were all checked by a second reviewer and after final sign off by all parties, was emailed to participants.

3.5.3 Stage 3: Delphi panel iteration 1: Anonymous voting

The modified process that was used for this study included two rounds of anonymous email voting followed by a face-to-face meeting. The threshold for consensus was 80%, and participants had the option of voting yes or no against the statements, thereby confirming or rejecting the statements respectively.

The initial feedback from the participants was good, regarding the functionality of the workbook and their understanding of their role. Ten participants returned the workbook within the stipulated period to allow for feedback to be compiled. The comments received on each of the statements are detailed in Appendix B.

Iteration 1 of the workbook resulted in 38 statements confirmed according to the methodology, and 9 statements amended and resubmitted to the next round. Zero statements were rejected. There was zero incidence of a participant voting no on a question and not leaving a comment.

3.5.4 Stage 4: Delphi panel iteration 2: Anonymous voting

Results were sent to participants along with the second workbook with amended statements. The 9 statements that did not reach the consensus threshold were amended considering the comments received, either omitting words, adding clarification or by deferring to the wording suggested by the experts. The 9 amended statements were the basis of workbook 2 used in iteration 2. Participants could see comments that were made on the statements by their peers, and the consensus levels reached per statement. By providing feedback in this way, it was hoped that participants would understand the amendments made to the statements.

Iteration 2 followed the same process as iteration 1; with participants receiving the workbook via email. Due to the number of statements confirmed and removed, workbook 2 was much smaller and far quicker to complete. The amended statements were in the voting sheet of workbook 2, as shown in Appendix B.

The same 10 participants returned the workbook before the deadline, and their responses were included in the work that was carried forward to the meeting. The contents of the workbooks were used to develop and inform the agenda for the face-to-face meeting, where all 10 participants, plus one late entry, would be present. Statements and their comments can be seen in Appendix B.

Iteration 2 resulted in the confirmation of 5 statements, leaving 4 statements to be amended and discussed at the face-to-face meeting; along with an overview of all the confirmed statements. Zero statements were rejected and wherever a participant replied no, a comment was always made.

3.4.5 Stage 5: Face-to-face meeting

A final face-to-face meeting was the culmination of this Delphi process, 19 people attended the final meeting. These consisted of:

- 11 Clinical experts.

- 4 representatives from Manchester Met (IO, FF, GY, AB)
- 1 Chairperson; Professor of Health Economics (ND)
- 1 facilitator (RS)
- 2 Urgo representatives (RN, LG)

The representatives of the study from Urgo did not participate in the discussions and were only in the room to observe, with RN leaving after the morning session. There were no presentations from Urgo team members at any point in the meeting.

The day was split into two parts, with the morning session to provide an opportunity to discuss the confirmed statements from both voting iterations. Using the Delphi methodology, a total of 31 comments were ignored because the statement had reached 80% consensus. Many of the comments made resonated with the panel and there was lively debate over semantics, with vocabulary, grammar and definitions being discussed by the panel. With the inclusion of a definitions section relating to certain terminologies, the panel managed to reach a unanimous consensus for all statements making up the consensus statement; to be constructed from the statements in the second half of the day.

Following earlier preparatory work grouping the statements, AB updated the statements and created an outline to share with the group after lunch. The four groups used to categorise the statements were:

1. The role of matrix metalloproteinases (MMPs)
2. QoL for patients with LU/DFU/PU
3. Time to healing and NHS burden
4. Early intervention and economic impact

Forty-one statements were arranged in 9 paragraphs to the participants, with 4 regarding the role of MMPS (18 statements used), 3 regarding QoL for patients (11 statements used), 1 for time to healing and NHS burden (8 statements used), and 1 for early intervention and economic impact (4 statements used).

The last session of the day was to discuss the purpose of making the consensus statement and dissemination opportunities. The panel produced listings of potential platforms for dissemination, not only for awareness by also a change in clinical practice. The panel also

produced a list of measures to understand the impact of the consensus and areas of future research interest. These responses can all be seen in Appendix B.

The members of the panel all signed off on the output of the day and deemed it a truly representative consensus.

3.5.6 Stage 6: Consensus development

The consensus statement was developed using the statements confirmed at the face-to-face meeting. The statements were left exactly as they had been agreed, no changes to the text were allowed. Building the consensus statement required adding some additional explanatory text, which was often based on the definitions also provided at the end of the statement.

The thorough semantic appraisal at the meeting allowed for the statement to be representative of many views. The consensus statement was drafted and circulated to the panel for review, which was overwhelmingly positive and after minor amendments produced the final consensus statement appearing below.

3.6 Consensus statement

There is a need for consensus in areas of uncertainty. Uncertainty can be identified by contradictory information in the literature, a lack of robust evidence or systematic reviews that prove inconclusive. Recent reports and guidelines on wound management are not specific and do not make recommendations on treatment options. The Cochrane Review "Protease-modulating matrix treatments for healing venous leg ulcers" identifies the need for further research into these dressings.

Contents of this consensus statement:

1. The role of matrix metalloproteinases (MMPs)
2. Quality of life for patients with DFU, LU and PU
3. Time to healing and NHS burden
4. Early intervention and economic impact
5. Summary of findings
6. Definitions

The statements that were voted on are identified below with bold text (sections 3.6.1 – 3.6.4). Underlined words or phrases must be interpreted according to their definition, listed in Table 3.6 at the end of the consensus statement (section 3.6.6).

3.6.1 The role of MMPs in chronic wounds:

Wounds are deemed chronic when they do not follow a normal healing pattern and can be perpetuated by having an underlying aetiology (Levine, 1995; Schuren et al., 2005; Demidova-Rice et al., 2012; Flegg et al., 2015; Frykberg and Banks, 2015; Kelichi et al., 2015). A normal healing pattern contains four phases of healing categorised according to the activity of their cellular components: haemostasis phase, inflammatory phase, proliferative phase, and maturation (or remodelling) phase. Wounds with underlying aetiologies include diabetic foot ulcers (DFUs), leg ulcers, (LUs) and pressure ulcers (PUs).

Matrix metalloproteinases (MMPs) are a part of healthy healing, expressed at the inflammatory phase of early wound healing (Crovetti et al., 2004; Brougton et al., 2006; Moffat et al., 2014; Olczyk et al., 2014; Heublein et al., 2015). MMPs are enzymes that are responsible for degradation of the extracellular matrix and play a pivotal role in regulation of cell proliferation, migration, differentiation, and death. **When a wound moves to the proliferative phase of healing, the level of MMPs fall** (Trengove et al., 1999). If the wound does not advance to the proliferative phase of healing in an expected time, it can be considered chronic. **These chronic wounds have been shown to have up to 30 times the level of MMPs than an acute wound** (Trengrove et al., 1999; Eming et al., 2007; Medical Advisory Secretariat, 2009; Zelen et al., 2015; Ahmad, 2016; Westby et al., 2016)

Wounds such as DFU, LU and PU are shown to have raised levels of MMPs from first presentation to a wound care specialist (Beidler et al., 2008; Rayment et al., 2008; Menghini et al., 2013; Heublein et al., 2015; Lazaro et al., 2016). **With raised levels of MMPs, the wound is stuck in the inflammation phase, leading to the destruction of new tissues** (Wysocki et al., 1993; Snyder, 2005; Schmutz et al., 2008; Ravari et al., 2011) thus **preventing progression to the next stage of healing** (Ravari et al., 2011; Heublein et al., 2015; PrescQIPP, 2015).

Persistently elevated levels of MMP are predictive of non-healing (Wysocki et al., 1993; Schuren et al., 2005; Snyder, 2005; NICE, 2016; Westby et al., 2016) and specifically, **of the 24 known MMPs, MMP-9 has been shown to be detrimental to healing, killing growth factors**

(Trengrove et al., 1999; Campbell and Parish, 2010; Moffat et al., 2014; Heublein et al., 2015; Kelechi et al., 2015). Interventions that modulate the wound environment may enhance healing (Trengrove et al., 1999; Schuren et al., 2005; Meaume et al., 2012; Humbert et al., 2014; Moffat et al., 2014; Heublein et al., 2015; Alavi et al., 2016), because evidence suggests removing excess MMPs from wounds improves healing (Meaume et al., 2012; Grier et al., 2013; Humbert et al., 2014; PrescQIPP, 2015; Westby et al., 2016). A specific MMP-9 inhibitor is potentially more effective in stimulating healing (Rayment et al., 2008; Campbell and Parish, 2010; Heublein et al., 2015). In addition to modulating the wound environment, the ideal dressing should be cost-effective, acceptable to the patient, easy to change, effectively manage exudate, and also be effective on older and larger wounds (Phillips et al., 1994; Ouahes and Phillips, 1995; O'Donnell and Lau, 2006; Medical Advisory Secretariat, 2009; Australian Wound Management Associated Inc. and the New Zealand Wound Care Society Inc, 2011; O'Donnell and Balk, 2011; Kim and Steinberg, 2012; CADTH Rapid Response Reports, 2013; Kruger et al., 2013; NICE, 2014; Kelechi et al., 2015; PrescQIPP, 2015; Widener, 2015; Wu et al., 2015; Alavi et al., 2016; NICE, 2016).

The lipido-colloid nano-oligosaccharide factor (TLC-NOSF) technology inhibits MMPs and accelerates healing (Schmutz et al., 2008; Meaume et al., 2012; British National Formulary, 2015; Augustin et al., 2016), it has been shown as superior to basic foam dressings in reducing healing time (Meaume et al., 2012; Augustin et al., 2016) and as superior to oxidized regenerated cellulose and collagen, especially in non-responsive, older wounds (Schmutz et al., 2008). Further to this, TLC-NOSF has been shown to reduce levels of MMP-9 in vitro (Bernerd et al., 2008; Coulomb et al., 2008)

3.6.2 Quality of life for patients with DFU, LU and PU

Wounds such as DFU, LU and PU are associated with increased morbidity and mortality (Frykberg, 1998; Nelson et al., 2006; Medical Advisory Secretariat, 2009; Diabetes UK, 2013; Zelen et al., 2015; Mousa et al., 2016). In addition to this increased risk of death and high likelihood of comorbidities, patients with these conditions suffer significantly reduced health related quality of life across dimensions such as pain, physical limitation, social isolation, and anxiety/depression (Krasner, 1998; Purwins et al., 2010; Gorecki et al., 2012; Hogg et al., 2012; Green et al., 2014). The psychological impact of these wounds can be severe, with patients reporting a loss of self, poor self-image, feelings of being a burden and hopelessness for the

future (Phillips et al., 1994; Kinmond et al., 2003; Herber et al., 2007; Gorecki et al., 2012; Green et al., 2014). These wounds can take a long time to heal and have a high likelihood of recurrence, which again detracts from quality of life (Korn et al., 2002; Etufugh and Phillips, 2007; Jones, 2009; Hogg et al., 2012; Green et al., 2014; Wu et al., 2016; NICE 2017). Clinician focus tends to be on the treatment of the wound, which fails to account for the large psychological and social burden experienced by some patients (Dealey, 2001; Green et al., 2014; NICE, 2017; NIHR, 2016).

The pain caused by chronic wounds impacts quality of life (Phillips et al., 1994; Krasner 1998; Herber et al., 2007; Tabolli et al., 2007; Ciliberti et al., 2014, Alavi et al., 2016; Domingues et al., 2016: Mousa et al., 2016). Dressing changes can be a cause of pain: products and techniques to minimise this are recommended (Phillips et al., 1994; Krasner, 1998; Tabolli et al., 2007; Ciliberti et al., 2014; Alavi et al., 2016) Dressing changes and local management of the wound site is considered easy in most cases with the TLC-NOSF dressing (Stevens and Chaloner, 2005; Schmutz et al., 2008), which has also been shown to significantly reduce pain/discomfort and anxiety/depression for a patient (Schmutz et al., 2008; Meaume et al., 2012).

In addition to the health-related quality of life burden, the patient also faces financial costs such as time away from work, early retirement, medications, dressings, and transport costs (Ouahes and Phillips, 1995; Reichardt, 1999; Etufugh and Phillips, 2007; Kelechi et al., 2015). Chronic wounds are a burden to both the patient and to the carer (Tabolli et al., 2007) and this cost is often excluded or underestimated in cost-effectiveness models (Phillips et al., 1994; Ouahes and Phillips, 1995; O'Brien et al., 2003; Tabolli et al., 2007; Jeffcoate et al., 2009; Souliotis et al., 2016).

3.6.3 Time to healing and NHS burden

As well as a quality of life burden to patients, DFU, LU and PU are a significant workload burden for healthcare providers (Ghatnekar et al., 2001; Ohura et al., 2004; Martinez-Sanches et al., 2005; Vikatmaa et al., 2008; Guillen-Sola et al., 2013; Hopkins and Worboys, 2014; Moffat et al., 2014; Ahmad, 2016; Alavi et al., 2016; NHS Rightcare, 2017; NICE, 2017). Home visits are a key driver of the cost to treat chronic wounds (Rudolph, 2001; Short and Bull, 2009; Foglia et al., 2012; Guest et al., 2012; Alavi et al., 2016). Advanced dressings require fewer changes and

therefore fewer visits are more likely to reduce costs, especially when the dressing also reduces healing time (Rudolph, 2001; Short and Bull, 2009; Foglia et al., 2012; Guest et al., 2012; Alavi et al., 2016). Protease inhibitors have been shown to be a cost-effective option (Nisi et al., 2005; Moffat et al., 2014; Augustin et al., 2016). Management plans associated with shorter treatment periods and fewer adverse events are more cost-effective (Franks and Bosanquet, 2004; Ohura et al., 2004; Augustin et al., 2016; Zelen et al., 2015; Souliotis et al., 2016). Ulcers can be slow to heal, with wound size and duration affecting healing (O'Brien et al., 2003; Margolis et al., 2004; O'Meara et al., 2009; Watson et al., 2011; Alavi et al., 2016). The initial wound area reduction at 4 weeks is predictive of healing by 24 weeks (Margolis et al., 2003; Meaume et al., 2012; PrescQIPP, 2015).

3.6.4 Early intervention and economic impact

Early diagnosis and treatment of a DFU, LU or PU can improve quality of life for a patient (Meissner et al., 2007; Kelechi et al., 2015). This early investment in treatment provides a reduction in long-term costs; prolonged futile treatment is more costly (Augustin and Vanscheidt, 2012; Kelechi et al., 2012; Augustin et al., 2016; Raju et al., 2016). There is a need for a long-term view from decision makers, for example, the purchase price of a dressing is not indicative of cost-effectiveness (Schmutz et al., 2008).

Some ulcers are more expensive to manage, these include: chronic wounds, recurrent wounds, and older wounds (Currie et al., 1998; Smith and Ingram, 2010; Dealey et al., 2012; Guidelines and Audit Implementation Network, 2013; Demarre et al., 2015). Older wounds are harder and more expensive to heal so early intervention will reduce the healing time and cost (Smith and Ingram, 2010; Augustin and Vanscheidt, 2012; Hopkins and Worboys, 2014; Augustin et al., 2016; Raju et al., 2016). LU is more prevalent in older populations who may benefit from less invasive treatment options (Ouahes and Phillips, 1995; Rudolph, 2001; Pang et al., 2010; Australian Wound Management Association Inc. and the New Zealand Wound Care Society Inc., 2011). An adjunctive therapy such as a dressing that modulates the microenvironment can promote faster healing in complicated wounds (Reichardt, 1999; Snyder, 2005; Meissner et al., 2007; Meaume et al., 2012; Carter et al., 2014; Ghatneker at al., 2015; Alavi et al., 2016). An adjunctive therapy to standard wound care should be considered in cases where you anticipate wound healing may be compromised (Reichardt, 1999; Snyder, 2005; Meissner et al., 2007; Meaume et al., 2012; Ghatneker at al., 2015; Alavi et al., 2016).

3.6.5 Consensus summary

This consensus process sought to address areas of uncertainty in the management of chronic wounds. The expert consensus panel has agreed that

- Chronic wounds including DFU, LU and PU significantly impair a patient's health and quality of life and this needs to be taken into consideration in patient care with the aim of reducing healing time.
- Inhibiting MMPs plays an important role in wound healing and raised levels of these enzymes have been shown to be present in DFU, LU and PU.
- Early interventions are a more cost-effective option, both in terms of health and quality of life improvement for a patient and in financial savings to the healthcare system

3.6.6 Definitions

Table 3.6. Consensus statement definitions

Term	Definition
Normal healing pattern	A normal healing pattern contains four phases of healing categorised according to the activity of their cellular components. The phases are haemostasis phase, inflammatory phase, proliferative phase, and maturation (or remodelling) phase. Normal healing will move through these phases at a predictable rate.
Aetiology	The cause or origin of a disease or disorder as determined by medical diagnosis.
Matrix metalloproteinases	By regulating the integrity and composition of the extracellular matrix, these enzymes play a pivotal role in the control of signals elicited by matrix molecules that regulate cell proliferation, differentiation, and death.
Acute wound	An injury to the skin that occurs suddenly rather than over time. It heals at a predictable and expected rate according to the normal wound healing process
Basic dressings	A foam dressing with no active agents.
Morbidity	A diseased condition or state.
Mortality	Likelihood of death, or death rate.
Significantly	Having reached statistical significance.
Carer	An unpaid carer; a relative, friend or neighbour.
Healthcare Provider	Any individual, institution, or agency that provides health services.
Advanced dressings	Dressings that regulate wound healing by simple physicochemical means, typically by controlling moisture levels.
Adjunctive therapy	Another treatment used together with the primary treatment. Its purpose is to assist the primary treatment.
Standard wound care	Standard care used to promote wound healing, which can be achieved through off-loading in DFU, compression in LU and/ or repositioning in PU

3.7 Discussion

This section discusses the strengths and limitations of this study, the impact of the core principle of anonymity and the systematic search and literature review that preceded the expert panel. This modified Delphi methodology expert consensus panel was carried out in a short time frame, between April and June 2017. The aims of this study were to identify areas of uncertainty present in literature surrounding dressings for chronic wounds and seek consensus from a broad range of wound care practitioners, academics and policy experts on topics of uncertainty in using wound dressings. This study achieved these aims, the literature search had a broad scope and resulted in the generation of evidence-based statements using thematic analysis to understand the uncertainty present in the literature. The participation of both the clinical and technical experts is invaluable, with decades of experience culminating in a 1200-word document detailing agreed best practices and observations based on clinical practice.

The strengths of this process include the systematic literature search performed to generate the statements, and the transparency of the workbook that allowed participants to access all the quotations from literature that the statements were based on. The iterative approach that is inherent when using the Delphi methodology is another key strength, in this study, two rounds of individual voting was followed by a face-to-face meeting. The iterative nature of the Delphi methodology allows participants to review their own answers in the context of comments from other members of the panel. Iteration is conducive to arriving at a consensus, as the same questions are deliberated multiple times, with new information. This study also made commenting mandatory in case of an answer that disagreed with the statement. This obligation was insisted upon for the process to provide the response that was needed to develop a statement that reflected the thinking of the panel. The mandatory commenting allowed for flexibility; the ability to edit statements in line with comments was useful when crafting the wording of the statements in line with the panel's opinions. The evidence was repeatedly consulted, to check if evidence was available to support a new suggested wording.

The limitations of this process included the protocol consensus threshold, if strictly applied, would have led to 31 comments from experts being overlooked because the statement reached a threshold of 80%. The intricate semantic discussions that took place during the face-to-face meeting addressed these comments. The binary answering option could be considered

a limitation, the choice to not rank the statements was deliberate to facilitate consensus, however in hindsight could have proven advantageous when structuring the statement. The assumption that a consensus would not easily be achieved was incorrect. As with all research of individual opinion, there needs to be understanding of any personal bias that could impact the results.

It is asserted that the low level of evidence limitations of a Delphi panel are best addressed by conducting one as a part of a rage of evidence generation activities, such as SLRs, database studies, clinical trials, and modelling activities. A Delphi panel is an important part of a wider portfolio of work required to assess any new intervention. In terms of qualitative data, the expert panel is only half of the picture, given that the clinicians and health care providers are only one group of stakeholders involved with wound management. The patient experience also needs to be understood to make robust recommendations about treatment.

To ensure that all participants were on an even footing, and to avoid a situation where the majority fall in line with the most senior in the room, the first two rounds of voting were carried out remotely, via the electronic workbook that was sent to the participants. When consulting a varied group of participants from a range of disciplines including nurses, podiatrists, clinicians, surgeons, academics, and health policy experts, there is a risk that the group can become overwhelmed by a particularly senior or vocal member. To minimise this risk and to give all participants an equal voice, the voting was carried out individually and where a statement was disagreed with, a reason explaining why, or a suggestion for how it could be better worded or phrased was mandatory. All participants complied with this rule; which meant that wherever there was dissent, there was explanation.

As part of the process all comments were shared with the group, with the identity of the author redacted. Anonymity allows the opinions of every group member to be considered as equal, with no weighting for seniority or discipline. It also allows the participant to consider their own opinion in the context of others, and at the face-to-face meeting it became apparent that these were really considered, resulting in numerous semantic changes in line with the comments, resulting in statements that represented the views of the entire group. The anonymity contributes significantly to this, because it empowers the participants to be actively involved with no barriers.

The modification of the traditional Delphi methodology to include a literature review as the first stage of the study further increased the robustness of this study. The search strategy for the systematic search was made available to all participants throughout the process, as was the full bibliographic details of all quotations and references used to inform the statements. Being transparent with the methods and sources used to develop the workbook was intended to encourage the participants to familiarise themselves with the evidence base and access the raw data when making conclusions and decisions about the validity of a statement.

Consulting the literature is vital to understand the current published evidence base on a topic, however the reality of a situation can often differ from the clinical trial setting of a paper, or from the guidelines recommended by a governing body. To then test the validity of statements generated from the literature review using a panel of experts allows for a synthesis of both quantitative and qualitative evidence. This synthesis is useful in informing understanding about real-world practice, clinical opinion and expert guidance in areas of uncertainty.

3.8 Chapter summary

This chapter has explored the use of expert advice to gain knowledge and understanding regarding clinical use, treatment pathways and current standards of care. Expert opinion is often subject to low levels of evidence classifications, due to its typically uncontrolled nature, however this can be counterbalanced using a Delphi methodology. The Delphi methodology, and its anonymous, iterative approach protects from many of the risks of a traditional expert panel. A multidisciplinary panel was chosen, and a Delphi methodology expert consensus panel was carried out; resulting in the creation of a consensus document which can claim to be both evidence-based and expert endorsed, with a transparent methodology and results to support those claims.

The next chapter of this thesis explores the patient perspective of chronic wounds, through two real-world evidence studies, one looking at patient reported outcomes and one performing a chart review of patient records.

3.9 Dissemination

This study has been presented as a conference abstract, poster presentation and published as a manuscript in peer reviewed journal available in Appendix D.

Chapter 4 A study of real-world health-related quality of life and treatment switching in people with Diabetic Foot Ulcers and Leg Ulcers

4.1 Introduction

The previous chapter elicited expert opinions from a range of professionals in the field of wound care using the iterative Delphi methodology. Expert opinion can be considered as a lower level evidence compared with clinical trials due to its subjective nature and risk of bias as explored in chapter 3. Despite this, expert opinion helps to shape the treatment landscape for people with chronic wounds. To provide a fuller picture of the narrative surrounding wound management, it is necessary to gather real-world data through medical records and consultation with patients. This chapter therefore presents a real-world assessment of health-related quality of life and treatment switching in patients with diabetic foot ulcers (DFU) and leg ulcers (LU), both from patients directly and from electronic medical records.

Real-world data (RWD) can come in many formats and can be broadly defined as data that is not collected in a clinical trial setting, such as electronic health records or product and disease registries (Makady et al., 2017). Real-world evidence (RWE) is the product of real-world data, once analysis has taken place and insights generated (U.S. Food & Drug Administration, 2019). For this thesis two sources of real-world data were sought; meaning that no intervention was delivered to patients and the studies only collected enough data to satisfy the needs of the studies. The two studies presented in this chapter are study 3, patient reported outcomes and study 4, chart extraction. These studies, and how they are linked to the overall thesis is shown in Figure 4.1.

The patient reported outcomes (PRO) study focussed entirely on patients and the burden of living with and managing a chronic wound. Understanding the impact and burden of chronic wounds, such as DFU and LU, is almost impossible without incorporating the patient voice into data collection. Historically, treatment decisions have been made by health care providers in isolation, or under the directive of clinical guidelines, however patient empowerment is a movement that is growing in the twenty-first century. The European Patients' Forum defines patient empowerment as the patients' ability to express their needs, present their concerns and be involved in decision making (European Patients Foundation, 2015). Empowering

patients helps to highlight what is important when it comes to management and care; from the perspective of the people who are the ultimate customer and consumer of the product.

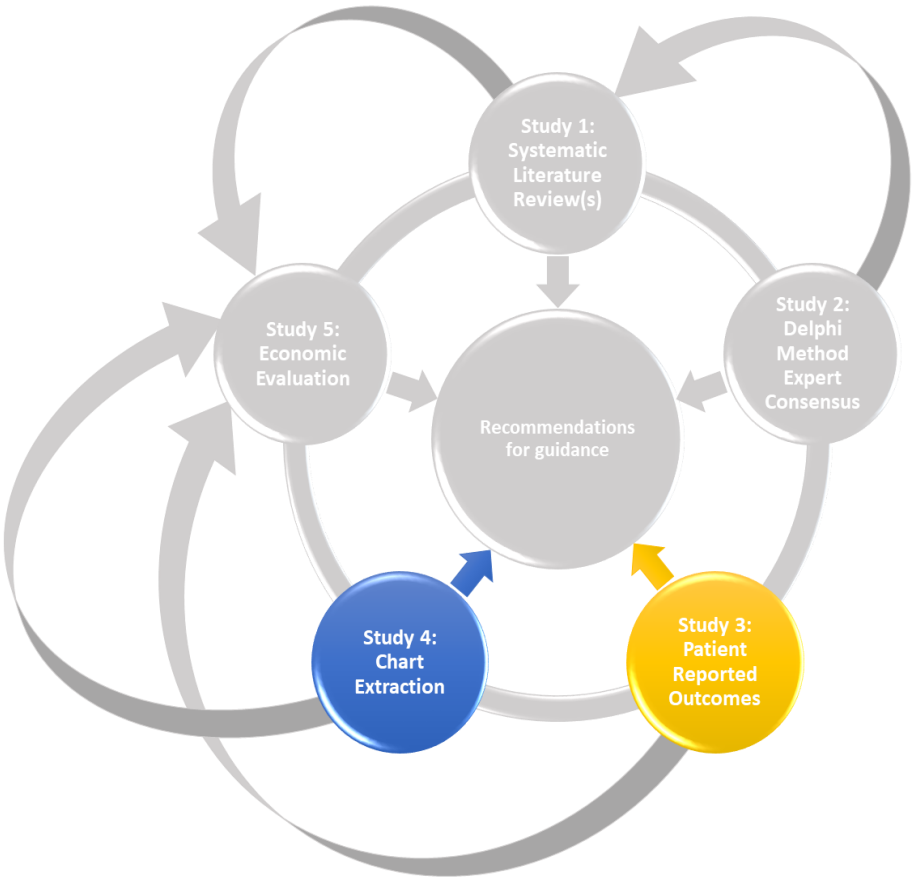


Figure 4.1. Real world studies within the PhD framework

The chart extraction study is a retrospective review of electronic patient records collected from treatment settings in England. This study sought to examine of real-world treatment practices that exist within care pathways, to compare this with treatment practices recommended by clinicians or in clinical guidelines.

4.2 Background

4.2.1 Quality of life and chronic wounds

There is a body of existing literature examining quality of life (QoL) for patients with chronic wounds. A thorough two-part systematic literature review (SLR) analysed both qualitative and quantitative studies of the patient experience for those with a LU (Green and Jester, 2009; Green and Jester, 2010). The qualitative review by Green and Jester (2009) synthesised 8

studies and advocated a holistic treatment approach, highlighting the need to understand that the practitioner is treating the patient, and not just the wound. The quantitative review by Green and Jester (2010) looked at PRO measures (PROMs) from 11 studies and found that patients with wounds suffered deficits in QoL and demonstrated that pain, mobility, and mood were the most significantly impaired when compared to the general population.

The reviews by Green and Jester (2009 and 2010), although thorough, only focussed on patients with LU. Whilst these patients make up a significant portion of all chronic wounds (Guest et al., 2015), other wounds, including DFU are also of interest to the National Institute of Health and Care Excellence (NICE); when scoping a technology for wound care NICE gathers evidence to ensure the inclusion of all patient groups that could possibly benefit from the review of an intervention. The protease-modulating matrix (PMM) technology that is the focus of this research has also been shown to be of benefit to DFU patients (Edmonds et al., 2018) thus findings from this population also need to be investigated to fully understand the benefits offered by this intervention.

Therefore, to address literature relating to DFU patients and the QoL burden they face; this chapter includes a review of the literature in relation to QoL outcomes for all chronic wound patients. Like Green & Jester (2009 and 2010), both qualitative studies assessing patient experiences with chronic wounds and quantitative randomised controlled trials (RCTs) with a health-related QoL PROM as a secondary endpoint were included.

A review of the literature identified 11 qualitative studies and 6 RCTs with endpoints relating to patient QoL. Of the 11 qualitative studies, 5 assessed LU 2 looked at pressure ulcers (PUs), 1 at DFU, and 3 looking at chronic wounds more broadly. Of the 8 RCTs included for data extraction, 4 of the studies assessed LUs and 2 assessed DFUs.

The 11 qualitative articles returned by this search strategy were varied in their design, including using semi-structured interviews of small groups (Kinmond et al., 2003; Van Hecke et al., 2011; Gorecki et al., 2012) and larger online surveys to reach over 1000 people (Gethin et al., 2014). Many of the studies focused on LU, with only one addressing DFU directly (Kinmond et al., 2003) which found that having a DFU led to patients living a restricted life, existing in social isolation, and an idea of ‘loss of self’ and becoming a burden. These psychosocial factors have major implications for the QoL of these individuals but are not unique to DFU. A qualitative

study performed using unstructured interviews of 13 patients with LU in the United Kingdom (UK) also found that patients were concerned by the restrictions they faced; struggled to cope with ulceration and the perceptions of others towards them (Walshe, 1995). This study also highlighted the fact that the significant restrictions on patients' activities such as going out, washing, or walking around were not sufficiently addressed by treatment.

Six quantitative studies of QoL were carried out in an RCT setting (Jeffcoate et al., 2009; Michaels et al., 2009; Watson et al., 2011; Moffatt et al., 2014; Meaume et al., 2017; Edmonds et al., 2018). These trials used a range of PROMs, but predominantly generic tools to assess QoL including EQ-5D/VAS (Jeffcoate et al., 2009; Michaels et al., 2009; Watson et al., 2009; Moffatt et al., 2014; Meaume et al., 2017; Edmonds et al., 2017). Only one of the studies (Jeffcoate et al., 2009) used a disease-specific PROM, the Cardiff Wound Impact Schedule (CWIS), in addition to the generic SF-36 measure. The scoring of the measures demonstrated reduced QoL and utility scores for patients, driven by mobility and psychological scores relating to anxiety and depression.

The review of the current literature demonstrates that whilst there have been studies carried out on patients with DFU and LU to assess their QoL, the PROM data has been collected exclusively in an RCT setting. Arguably the patient's included in these studies are not generalisable to the wider population given the often-strict inclusion and exclusion criteria enforced by clinical study protocols. They are also impacted by the fact that the patient is participating in a clinical trial and is not experiencing standard care that they would experience in the real-world. Another limitation of the more informal studies, such as those carried out in an observational setting is that they often have small numbers of patients and do not use PROMs to collect data, relying on more qualitative methods such as interviews and focus groups. These are extremely important methods that enable a researcher to delve into patient insights, but not the focus for the present study.

4.2.2 Real-world evidence and chronic wounds

In addition to patient insights and understanding the burden of disease; real-world data collection can be useful in determining current treatment patterns, resource use, and patient outcomes (Huang et al., 2018). Data collected in a real-world setting can be compared to data from clinical trials, giving a researcher insight into the impact of the highly regulated

environment and the strict inclusion and exclusion criteria. Real-world data relating to clinical outcomes and resource use can be derived in several ways, from electronic medical records, product and disease registries, clinical audits, data from mobile devices, and, where relevant, insurance and claims data. In the UK there are several large datasets generated from electronic medical records of patients within the National Health Service (NHS), owned by the government Department of Health, managed by NHS Digital (CPRD, 2019; NHS Digital, 2019). There are also privately-owned datasets, including The Health Improvement Network (THIN) database (UCL Institute of Epidemiology and Health Care, 2018).

The THIN database was the data source for a pair of studies published in 2018 on DFU and LU management in the UK (Guest et al., 2018a; Guest et al., 2018b). This database contains data from 11.1 million patients, of which about 3.7 million patient records are active, with a coverage of 6.2% of the UK. However, it is worth bearing in mind that the THIN database is based on the Vision software, which is developed for patient management and not clinical research; meaning that data endpoints sought by researchers may not be available. GP practices are also only one care setting that patients interact with health care professionals and as such, the THIN database only provides a partial view of the patient journey. The study designed for this research sought to understand the full patient journey by including multiple care providers.

The studies by Guest et al., (2018a and 2018b) reported the cost of wound care over 12 months for a DFU and a LU as being £7800 and £7600 respectively. The study on DFU noted that 48% of patients received at least one prescription for a compression system, despite compression being not recommended for use in patients with DFU, and patients who did not receive compression were significantly ($P < 0{\cdot}001$) more likely to heal (Guest et al., 2018b). Conversely, the gold standard of treatment for LU should always include a compression system, whereas their study found that 13% of patients did not receive one. However, these patients did not have a reduced chance of healing but did incur significantly ($P<0.001$) longer time to healing (Guest et al., 2018a). This deviation in standard treatment practice highlights the importance of identifying a clinical and cost-effective treatment strategy that can be clearly communicated to health care providers (HCPs) via continuous medical education to ensure adherence to methods that lead to improved clinical outcomes and QoL for patients.

4.3 Study aims

The aim of study 3 was:

- To document and quantify QoL for DFU and LU patients.

The objectives of study 3 were:

- To use PROMs in an observational treatment setting.
- To inform utility scoring for economic modelling.

The aim of study 4 was:

- To establish treatment pathways, incidence of treatment switching, outcomes and resource use across multiple care settings.

The objectives of study 4 were:

- To collect data from patients using retrospective real-world data
- To use thematic analysis to develop a model to interpret the incidence and cause of treatment switching.

4.4 Methods

This section describes the methods used for both the PRO and the chart extraction studies. First, the design of the studies is described, followed by an overview of the included participants; and an explanation of the tools used in each study. Following this, the analysis plans and data collection methodology for each study is set out and finally ethics considerations addressed. Both studies are examples of real-world evidence generation, the PRO study had a focus on patient QoL, and the chart extraction examined electronic patient records.

4.4.1 Study designs

Study 3, the PRO study, was a prospective, non-comparative, cross-sectional study of validated tools to investigate QoL in patients with DFU and LU.

Study 4, the chart extraction study, was a retrospective, non-comparative review of electronic patient records carried out in multiple treatment settings to investigate incidence of treatment switching in patients with DFU and LU.

4.4.2 Participants

The patients that were included in the PRO study and the chart extraction, were of similar demographic characteristics, subject to very broad inclusion criteria.

For Study 3, the PRO study, the patients were included if they had either a DFU or LU. There was no requirement for the size of the wound, nor for wound duration. No exclusion criteria were set regarding comorbidities or any requirements for overall health status. Patients with a closed wound were eligible to partake in the study if they were still attending the DFU/LU clinic; to understand the ongoing burden of ulceration, given the chronicity of the disease.

For study 4, the chart extraction study, patients were included if they had a DFU or LU and a record in the selected centres, with a minimum of two appointments to facilitate the analysis of treatment patterns. Again, there were no exclusion criteria relating to comorbidities or requirements for health status.

The stipulations for patients were intentionally kept broad for these two studies, to align with the ethos of real-world evidence; to provide a contrast with RCTs. RCTs operate using a strict protocol and all deviations are carefully managed to minimise any bias or confounding factors that could influence the results. RCTs are devised to ensure that the effect measured is related to the investigative product and not due to any other factor and they sit atop the hierarchy of evidence classifications due to their methodological robustness (Guyatt et al., 2008). Trials can be designed to isolate treatment effect and can perhaps use endpoints not routinely measured in practice, or surrogate or proxy endpoints that do not have much meaning to patients. In contrast to this, these studies investigate a sample of patients that exist outside of the trial setting. These patients not only have the disease of interest, in this case DFU or LU, but also have a range of comorbidities, and are likely to be of worse health than a population in a clinical trial.

The patients recruited into the two real-world evidence studies described in this chapter are intended to be a representative sample of the patients found in routine clinical practice. For the PRO study (study 3), patients were recruited consecutively at clinics, after providing written consent to participate. The patient sample in the chart extraction was selected by the nurse who carried out the data extraction with no influence from the researcher.

Patients in the chart extraction study provided written consent prior to data collection. Patients who were recruited into the PRO had to complete the study questionnaire pack, which was designed with patient accessibility in mind, the pages were printed single side with a minimum font size of 16 point. Patients could be helped by a carer, relative, or health care professional if they struggled to read or understand the questions.

The target level of recruitment for each study was set at 100 patients, with a desired ratio of DFU and LU patients at 1:1. This figure was reached based on calculations using a sample size calculator, which indicated that a sample of 96 patients would be able to give a confidence level of 95% with a confidence interval of ±10 (Creative Research Systems, 2018).

4.4.3 Study tools

Study 3: Demographic sheet

Study 3, the PRO study, made use of validated PROMS as tools to collect data on patients' QoL and wellbeing. These tools are often used as companion measures in a clinical trial, to provide secondary outcomes on patient QoL. With multiple measures from individual patients, clinical trial statisticians are then able to present a longitudinal dataset for each patient, allowing for analysis of QoL over time, and to measure the impact of the investigative product. In this cross-sectional study, there was only one interaction with any recruited patient and no follow up period. With just one measure from each patient, there is no way to follow patients and their progress over time.

To counter this, a demographic questionnaire was developed. This demographic sheet was designed to collect data about patients to contextualise their answers to the validated PROMs. The demographic sheet was 3 pages in length, at font size 16, designed to not burden patients with excessive forms. The questionnaire contained questions regarding: sex, age, wound type, size and duration, single/multiple wounds, wound recurrence and the number of visits to different health care practitioners (HCPs).

Patients were asked about the size of their wound at two time-points; at the beginning of treatment and on the day of completing the questionnaires. They were asked to compare the size of their wound to the $8cm^2$ image in the pack and answer if their wound was smaller, or the same size or bigger at the start of treatment. For the present day, they were also given an option to check if their wound had now closed.

The demographic sheet asked for details regarding visits to different HCPs and use of different wound care dressings; compression with the aspiration of understanding patient resource use. There was also a question regarding the use of companion diagnostics such as a doppler ultrasonography which is used in patients with a LU to map and understand venous insufficiency in the lower limbs (Galeandro et al., 2012). These details were collected with the intent of creating a matrix of patient demographics versus QoL.

The demographic sheet sought to identify and provide evidence for some theorised factors that can negatively impact QoL for patients with a DFU and LU. Vice versa, it was hoped that some level of understanding could be sought about the demographics and resource use of patients with very poor QoL scores; to see if patients with severely suppressed QoL consumed the most healthcare resources and reported multiple wounds and many different treatment options.

The demographic sheet was piloted on a sample of 10 patients and was well received by patients. However, details of treatment plans including visits to HCPs and use of companion diagnostics was not always reliably recorded. After discussion with the supervisory team at Manchester Met it was decided to retain these fields but due to missing and inconsistent data recording, it was acknowledged that a quantitative analysis of these fields would be unlikely.

Study 3: Validated PROMs

Validated PROMs are instruments that are integral to comparative research to understand patient experience and insights. The International Society for Quality of Life Research (ISOQOL) have recommended minimum standards for PROMs used in research and include the following requirements for the PROM to be acceptable: documentation of the conceptual and measurement model; evidence for reliability, validity; interpretability of scores; quality translation, and acceptable patient and investigator burden (Reeve et al., 2013).

There are both generic PROMs and disease-specific PROMs; which are among the hundreds of validated tools available for research. Disease specific measures can measure dimensions of interest to patients suffering with a certain disease, in this case DFU and LU. Examples of disease specific questionnaires that have been validated for measuring QoL for patients with chronic wounds include the Charing Cross Venous Ulcer Questionnaire (CXVUQ), Diabetic Foot Ulcer Scale (DFS), and Cardiff Wound Impact Schedule (CWIS). A systematic review of PROMs

in patients with DFU found that there was no 'gold-standard' PROM that was superior to all others for assessing QoL (Hogg et al., 2012).

The study described in this thesis included patients with both DFU and LU; different to other QoL studies of patients with chronic wounds. Despite Jull et al., (2010) showing the CXVUQ as more sensitive, this measure is only intended for use in patients with LU, and not DFU. As a result, this PROM was excluded from this study and CWIS was chosen for this study as it could be used for both aetiologies of interest.

CWIS is a disease specific tool that was developed over three stages, informed by patients at each step; a focus group, a pilot group and a 3 month follow up process all determined the final form (Price and Harding, 2004). Analysis during development showed no significant differences between responses across the wound types; which makes CWIS suitable for this study, which includes both DFU and LU. CWIS is a longer tool, at 7 pages when included in the final study pack. The tool asks patients about various issues, on the domains of well-being, physical symptoms and daily living, and social life. It also has a slight repetitive guise that could be misleading. In Sweden, during the translation and validation process for CWIS, patients commented that the tool was too extensive, with too many questions (Fagerdahl et al., 2014).

In addition to including the disease specific CWIS, this study was also intended to capture utility scores for the economic modelling performed in chapter 5. Utility scores are a numerical valuation of a given health state. Usually, values are given between 0 and 1; where a value of 1 represents perfect health and 0 indicates death. Some value sets include values below 0; which indicate that the health state is considered worse than death (York Health Economics Consortium, 2016).

Using generic PROMs provide results that can be used to calculate quality adjusted life years (QALYs) for patients in designated health states. EuroQol 5-dimension (EQ-5D) is the most commonly used utility instrument, and therefore comparisons to other diseases using a like-for-like scale can be achieved, which is likely why the EQ-5D is preferred and recommended by NICE (NICE, 2013). It is possible to map other generic tools to EQ-5D using statistical methods, however as with all data manipulation there is the risk of loss of meaning as the data is transformed. As this study was designed to be mindful of the requirements and preferences of NICE, it was decided to use EQ-5D.

EQ-5D is measured across 5 domains: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. These can either be measured using a 3-point or 5-point scale using the EQ-5D-3L and EQ-5D-5L, respectively. The EQ-5D-5L system was first made available in 2011 and has now been translated into upwards of 150 languages (Herdman et al., 2011). A study comparing the use of EQ-5D-3L and EQ-5D-5L concluded that the 5L had increased sensitivity and precision; and that past use of EQ-5D-3L may have led to an overestimation of quality adjusted life years in economic evaluations (Janssen et al., 2018).

NICE has issued a position statement on the use of EQ-5D-3L and the adoption of EQ-5D-5L (NICE, 2018). The position statement states that NICE does not currently recommend the use of the 5L value set due to the lack of data, and some concerns raised by a quality assurance group (Hernández-Alava et al., 2018). The advice is not to cease using the EQ-5D-5L tool, which has been shown to have greater precision; but in the manner of reporting. The preferred method is to use a methodology that maps the EQ-5D-5L responses to the valuation set for the EQ-5D-3L, a nonparametric model that was more simple than other proposed methodologies (van Hout et al., 2012).

In addition to EQ-5D, which reports a utility score, this study explored the use of the Self-Assessment of Treatment, version 2 (SAT-II). This PROM measures the patients experience with pain and focuses on the treatment impact upon their pain (van Nooten et al., 2017). This measure was considered of interest after a review of literature found that pain was a dimension repeatedly reported by patients as important to them and had a high prevalence across the studies included. Pain is assessed by EQ-5D, but after consideration it was decided to use SAT-II in the pilot testing, to interrogate important issues that impact QoL for patients. The patient burden was considered low as SAT-II consisted of only 3 questions spread over 2 pages.

The final PRO study pack consisted of a participant information sheet and written consent form, the demographic information sheet, and the three validated PROMs, SAT-II, EQ-5D-5L and CWIS. The pack was 19 pages long and only available in hard copy, which was deemed appropriate as the use of pen and paper tools has been proven to be equivalent to electronic tools in an extensive meta-analysis of 65 studies (Gwaltney et al., 2008).

Study 4: iPad tool

Study 4, the chart extraction study did not use any pre-existing validated measures and the data capture tool was custom created especially for this study. The tool was designed by a joint project between Manchester Met and Urgo Medical Ltd as part of a pilot before commencement of this PhD. The development of the software and user interface as an iPad application was carried out by a data analyst at Urgo Medical Ltd. The iPads were loaned to each centre for the period of data capture, and once this was complete the iPads were then returned to Urgo Medical Ltd where the data analyst uploaded the data into a specially made database in Microsoft Excel.

The development of the application was designed in collaboration with Nurse practitioners who were familiar with the databases used by health care professionals in clinics. The iPad application was designed to mimic the layout and information collected by these systems, used every day by clinicians, to reduce the workload burden of the individual performing the data capture.

The iPad tool created a record for each visit by a patient; with no identifying information included. Patients were assigned a wound number which increased consecutively with each visit; creating a longitudinal data set for each patient. The data headings shown in Table 4.1 are those that were included as fields on the iPad application for data extraction. These fields were used to extrapolate further inferences, which were calculated by the database and are listed in the data analysis plan (see section 4.4.5).

Table 4.1. Data fields included in iPad extraction tool

CR-WoundNo	RecordID	Sex	Wound number	Date of final visit
Initial visit date	Date wound closed	Wound type	Wound Severity	Visit Date
Why was plan changed	Primary dressing	Secondary dressing	Bandage/Hosiery	Frequency of dressing change
Appointment duration in minutes	Care setting	Treatment given by	Infection/No infection	

The iPad application was piloted and initially used on just one centre for 10 patients to receive feedback and to understand how the tool could be improved for use in other centres. The feedback received was entirely to do with the user interface, such as the positioning of fields and links on the screen, and there were no comments regarding the data sought. These issues were fixed and refined by the data analyst at Urgo Medical Ltd and the tool was rolled out for use in the study.

It is important to note that the iPad tool did not make fields mandatory to complete a record. This decision was made due to practitioner advice during development; nurses advised that many records in electronic medical records were incomplete and this would make data collection more difficult if a cohort of complete records needed to be found. The risk of receiving partial data was offset with the need to be pragmatic when collecting the data.

4.4.4 Data collection

The data collection for study 3, the PRO study, and study 4, the chart extraction differed in their approach, but both were rigorous methods of data collection. The PRO study was prospectively administered at centres across the UK. For the chart extraction study, data collection was managed through Urgo Medical Ltd using nurses at each centre to extract data into the iPad tool provided, discussed earlier in this chapter. In addition, the local governance and approval flows for each of the centres was followed to ensure compliance with the highest ethics standards (see section 4.4.6 ethics).

Study 3: PRO study

This study was carried out in person, at clinics, there were no electronic records completed and the packs were presented only in paper format. Due to this, there was no way for the researchers to mandate that fields be completed consistently across patients, and no way to ensure that fields were completed at all. The risk of missing data was considered when developing the questionnaire pack, but the use of electronic devices would have been impractical; multiple patients would often be completing the study packs concurrently, and the number of devices that would be necessary would have been more than allowed by budgetary constraints.

For the PRO study, centres were not paid for their participation, and nor were patients reimbursed for their time. Included centres could request access to their own dataset to

understand their own results relevant to their clinical setting and were able to access this data free of charge. The patients would have no access to their data after it had been submitted; due to the logistical difficulties that this would entail; needing to identify records and return them was out of the scope of this study and not required under the Data Protection Act 1998.

To drive patient recruitment, given the short time window for data collection in this study; the PRO study questionnaire pack was also included in materials used as part of patient education days left with centres for patients to complete when a member of the Urgo Medical Ltd team interacted with a centre. Some patients required assistance when filling in the PRO study pack, and this was provided by either a carer who accompanied them, or the health care professional supervising the completion; or, rarely, a member of the Urgo Medical Ltd team who was trained by the Manchester Met researcher (AB) in how to assist with queries. AB was not present during data collection due to the restraints of the ethics approval granted by the university not authorising direct access to patients. Having members of the Urgo Medical team collecting data was potentially a cause for concern, however after study team discussions it was decided to not be an issue as this was not a product specific exercise, and there was no risk of promotion to patients. In addition to this; the code of practice that is enforced upon the pharmaceutical industry is not mandated for medical device companies; due to the additional educational programmes they run given that a lot of products, including dressings, are used by patients or carers without health care professional input.

Study 4: Chart extraction study

The patient data was recorded either for the study period, until wound closure, or the patient left treatment for another reason; whichever was the soonest. Data regarding which treatments were given, products used, patient and wound status, and all free-text notes were captured by this study. For the chart extraction study, centres were paid the equivalent of the salary of a band 5 nurse, for 2 weeks per 20 records extracted to recompense the centre for the time cost of having the nurse complete the data extraction and was not an incentive payment. All payments were approved and paid by Urgo Medical Ltd as part of their role in this partnership. The data that was extracted was then sent to Urgo Medical Ltd for upload into a database, but all analysis was completed by the primary researcher (AB) as part of the agreed arms-length relationship between the parties. The chart extraction study did not involve asking

patients to fill in any details; which is why a nurse at the centre was given the role of data extraction.

Due to the nature of the study; there were additional local governance procedures to follow in each of the centres after initial ethics approval had been granted by the Manchester Met. The fact that there was a transfer of value between Urgo Medical Ltd and the centres involved posed a risk of bias, but after careful consideration; it was decided that this was balanced by the thorough and rigorous data analysis plan.

4.4.5 Data analysis

Descriptive analysis of the data is presented for both studies, with subgroup analysis performed for the PRO study and thematic analysis of the reasons for treatment switching included in the chart extraction. No inferential analyses were carried out for either study due to the cross-sectional nature of the data and small sample size, especially when considering subgroup analysis.

Study 3: PRO study

Study 3, the PRO study was designed to give insight into the patient experience of living with and managing a chronic wound to address the objectives set out in section 4.3. Together, the demographic sheet and the validated PROMs can be used to paint a picture of different patient archetypes. One of the key pieces of information that were collected by the demographic questionnaire was the duration of the wound, which fell into one of the following categories: 0-6 months, 7-12 months or 13 months and longer. Wound duration is important to patients, because of the understandable long-term impact of having a chronic wound; but is also important to clinicians because of the known correlation between wound duration and a lowered likelihood of healing (Bosanquet and Harding, 2014).

In addition to wound duration, the size of the wound is deemed important when considering treatment; many clinical trials have a wound size stipulation, which implies a preference for a certain size of wound to facilitate healing. Larger wounds, by their nature, have more skin to recover and thus, even at the same healing rate, would take longer until fully closed. As time to healing is often a primary endpoint in clinical trials, it is potentially important to manufacturers and study sponsors to exclude wounds that could reduce the impact of their results when included in any future meta-analysis.

Using a matrix of duration vs size, a severity matrix was developed to classify wounds as either mild, moderate or severe. The matrix can be seen in Table 4.2. DFU and LU patients would each be stratified in accordance with their severity rating as per the matrix to perform subgroup analysis on the outcomes of the PROMs to explore the differences between patients with wounds of varying duration and size.

Table 4.2. Wound severity matrix

13 months +	Severe	Severe
7-12 months	Moderate	Severe
0-6 months	Mild	Moderate
	Smaller than $8cm^2$	Larger than $8cm^2$

Using a matrix of duration vs size was decided upon because of these characteristics being prevalent in the literature (Frykberg and Banks, 2015). Not only have these factors been analysed as determinants of healing, but they are also often included in the patient baseline attributes in clinical trial reports. Due to the cross-sectional nature of the PRO study, it was deemed appropriate to attempt to generalise results in a context familiar to clinicians and researchers by including an overt reference to size and duration of wounds. The additional benefit of these two measurements is that they are easy to ascertain and are non-invasive for a patient.

The validated PROMs have been scored according to their own methodologies; with CWIS being represented as a score out of 100, over three domains; well-being, physical functioning and social life, with the lower the number, the worse the score. The instructions for scoring CWIS are not publicly available, but as part of the licence for CWIS the scoring tool was sent to the researcher to interpret the results.

EQ-5D-5L results have been interpreted using the so called 'crosswalk methodology' which transformed the results using the EQ-5D-3L valuation set (van Hout et al., 2012). The EQ-5D

scores are reported as an index value; which can be termed a utility score. The EQ-5D tool also asks patients to score their own health on a visual analogue scale (VAS) of 0-100; which give an insight into a patient's own opinion of their quality of life; compared to the utility score that is transformed using a value set produced by a broader population.

SAT-II has only been reported in literature as a longitudinal tool, and as such the clinically meaningful differences identified in the scoring tool are for comparing one patient's own records over time (van Nooten et al., 2017). This PROM presented a challenge to interpret, and it was decided to apply the clinically meaningful differences between patient groups of interest. Patient subgroups of interest included patients with wounds that were mild/moderate or severe, stratified by wound aetiology. EQ-5D index scores are also reported for subgroups relating to patient demographics such as age, sex, wound recurrence and, in the case of DFU, amputation history.

Study 4: Chart extraction study

The chart extraction study, study 4, collected many data points, as shown in Table 4.1. From these data fields, other data points could be calculated in the database, to aid analysis. A list of fields that were generated by the database from the data that was collected using the iPad tool is shown in Table 4.3.

For the chart extraction study, the research aims presented in section 4.3 were to investigate incidence of treatment switching and the rationale behind these switches. The incidence of treatment switching, was the primary endpoint. Every appointment was coded in accordance with whether a switch had occurred or not. Table 4.4 shows the codes used.

A treatment switch was defined as only a change of primary dressing; a change of the secondary dressing and bandage/compression system was not considered to be a treatment switch for the purposes of this study. After discussion with wound care experts, a secondary dressing was deemed to not be influential in wound healing and thus not of interest to this study. Secondary dressings are intended to mainly provide extra cushioning for a patient, or to hold the primary dressing in place when a non-adhesive product is used.

Reasons for treatment switching, if provided, were also recorded. Thematic analysis was used to analyse the records to identify patterns or persistent themes (Braun et al., 2015). Categories

and sub-categories were assigned where appropriate; and the categories were not pre-defined, as per the thematic analysis methodology.

Table 4.3. Database fields for chart extraction

Data field	Description
Count	How many appointments the patient had attended
Wound closed at end	Was the wound closed at the last recorded visit
Infection ended	When the last infection had ended
Changes to infection cure	Number of dressing changes before infection resolved.
Cured infection	Date that infection was cured
Infection occurrences	How many times a single patient had had an infection
Infection day 1	When the infection was first reported
Infection duration	How long the infection lasted
Treatment number	Was the treatment first line, second line, third line etc.
RunTot_Treatment Number	Running total of treatments received by a patient
DaysToClose	How many days did the wound take to close
Days Dressing Used	How many days a dressing was used for
No weeks on treatment	How many weeks the patient had been on all treatments.

Table 4.4. Coding of treatment switching

Code	Meaning
0	No potential for switch- either a first assessment or a final visit due to wound closure
1	No switch; the same primary dressing used as at previous visit
2	Treatment switch; primary dressing different to previous visit

Secondary endpoints include descriptive analysis of patient treatments and outcomes, including the number of visits made by patients to each healthcare provider, split by aetiology. Further to this, a healing outcome of the proportion of DFUs and LUs healed at 20 weeks is presented. This endpoint has been selected to compare, non-statistically, with prospective

randomised clinical trials to highlight if there is a discrepancy in real-world healing rates. Subgroup analysis comparing the centres' switching rates and healing outcomes has also been performed using non-inferential descriptive statistics.

4.4.6 Ethics considerations

Both studies presented in this chapter; study 3, the PRO study, and study 4, the chart extraction; were granted ethics approval by the Manchester Metropolitan Faculty Ethics committee (Reference: 1486). This ethics approval process was rigorous and included needing to submit all patient facing documentation through the process. The PRO study pack, and chart extraction letter to patients requesting consent for inclusion were both included in the approval; which was sought for all studies in this thesis.

The Data Protection Act 1998 (DPA), was adhered to when carrying out this study, as it preceded the implementation of General Data Protection Regulation (GDPR) implemented on the 25th May 2018. Despite this; the research presented here had adhered to the 7 principles of GDPR, which are: lawfulness, fairness and transparency; purpose limitation; data minimisation; accuracy; storage limitation; integrity and confidentiality (security) and accountability.

NHS approval was not required for either of these studies as their designs; questionnaire and retrospective medical chart studies fall under the category of unnecessary consent, as defined by Manchester Met (Manchester Metropolitan University, 2019). Despite this; consent was sought from patients for the PRO study; and all centres that participated in the chart extraction completed their own local governance and approval processes for research.

Patients could ask any questions before they provided consent and were able to withdraw this consent at any time. To withdraw consent, a patient would have to be identified before their data was destroyed. Patients could only be identified by using their consent form, which was signed by them and coded with their patient reference number. All data uploads into databases only included this patient reference number, made up of a centre code and a sequential number, to track numbers of patients from each centre. The consent forms were separated from the rest of the study questionnaire packs and have been kept stored in separate locked files, accessible only by the main researcher (AB).

Due to the nature of the PRO study being administered via a questionnaire; this study has gone over and above the usual standard by gaining signed written consent. For a questionnaire study; this is not usually required due to the implied consent granted by the patient filling out the questionnaire. This study also wanted to gain explicit consent, as the patients included could be considered vulnerable due to their age and impaired health status.

Anonymity was central to the chart extraction study, with the data being extracted from medical records being anonymous, and the lead researcher (AB) having no way of identifying patients. Should consent be withdrawn, the study centres hold the key to identifying the patients; however, they do not have a copy of the data as this was stored on the iPad tool, which was returned to Urgo Medical Ltd, who also cannot identify the patients.

Due to the nature of the data including medical details, and this considered as sensitive private data, considerations are made when using disaggregated data, or subgroups, to ensure that no groups of less than 5 patients are analysed. Small number suppression was applied not only for sample size considerations, but also in case any person can be identified by their wound characteristics or other data provided (Office for National Statistics , 2006).

The scientific principles of transparency, data integrity and ethical behaviour are upheld in these studies; through attitude and integrity of the research team, both at Manchester Met, and at Urgo Medical Ltd, who understood the importance of the arms-length agreement in protecting patients and the results of the study.

4.5 Results

This section first describes the results of study 3, the PRO study, then followed by the results of study 4, the chart extraction study. First the characteristics of the patients included in each study is presented, followed by insights into QoL, using the validated PROMs for the PRO study, and a descriptive analysis of incidence of treatment switching and thematic analysis of the reasons for switching for the chart extraction study. Attention is paid to the subgroups of interest; across wound aetiologies, wound severity and health states including open, closed and amputated wounds.

4.5.1 PRO study

A total of 94 patients were included in the PRO study; of these, 42 had a DFU and 51 had a LU; 1 patient did not complete this field and was excluded from the analysis as it was impossible to determine their wound aetiology, which was the basis for stratifying the cohort.

DFU participants

For the DFU patients (n = 42), the mean age was 64.05 years (±11.24) with a range of 45-85 years. The group was predominantly male, with 29 individuals (69%) versus only 13 females (31%). In this cohort, the mean number of previous wounds was 2.15 (±2.54). Of the 42 patients, 36 answered regarding a prior amputation, and of those that answered, it was an even split (50%/50%) between patients with a prior amputation and those without. The question specified that the amputation had to be because of their wound, and not for an unrelated incident.

When using the wound severity matrix of size versus duration this could be calculated for 41 patients, only 1 with missing data. Of these; 17 patients (41.5%) had a severity of mild of moderate, and another 17 (41.5%) reported wounds that fit the severe category. Of the 41 patients, 7 (17.1%) reported on closed wounds.

There was also a near even spit between new and recurrent wounds in this patient subgroup, with 21 (51.2%) new wounds and 20 (48.8%) recurrent wounds. Again, one patient was missing from this analysis. When analysing data regarding single or multiple wounds, the group was not so evenly divided, with 27 (67.5%) single wounds and 13 (32.5%) multiple wounds; two patients did not answer this question on the demographic sheet. Table 4.5 shows the breakdown of patient characteristics for those in the DFU group.

LU participants

For the LU patients (n = 51), the mean age of patients was 71.12 years (±11.83) with a range of 48-93 years. The group was nearly evenly split with regards to gender, with 25 (49%) males and 26 (51%) females. In this cohort, the mean number of previous wounds was 4.4 (±14.54). For this question, one patient had answered that they had 100's of previous wounds; which was inputted at 100 despite this perhaps being an exaggeration. This may have contributed to the large standard deviation on this item. Patients with LU were not expected to answer the question regarding amputation, as it specified as being only for patients who had identified

that they had a DFU, however 6 LU patients did answer this question, but all responded that they had not had an amputation because of their wound.

When using the wound severity matrix of size versus duration this could be calculated for 50 patients, only 1 with missing data. Of these; 16 patients (32%) had a severity of mild/moderate, and 19 (38%) reported wounds that fit the severe category. Of the 50 patients, 15 (30%) reported that they had a closed wound on the day they filled in the PRO questionnaire pack.

Patients with a new wound made up 54% of the sample, with 27 people reporting that the wound in question was on a new wound site; and a recurrence made up the other 46% of the group, with 23 people nothing that the study wound was one that had previously been closed and had reopened. Again, one patient was missing from this analysis. When asking about single or multiple wounds, the group was not at all evenly divided, with only 15 (29.4%) single wounds and 36 (70.6%) multiple wounds; all patients answered this question on the demographic sheet. Table 4.6 shows the breakdown of patient characteristics for those in the LU group.

Table 4.5. DFU participant characteristics

	Mean (n =)	Standard Deviation
Patient age	64.05	11.24
Previous wounds	2.15	2.54
Sex	(n =)	%
Male	29	69.0
Female	13	31.0
Total	42	100.0
Prior amputation	(n =)	%
Yes	18	42.9
No	18	42.9
Missing	6	14.3
Total	42	100.0
Wound severity	(n =)	%
Mild	9	21.4
Moderate	8	19.0
Severe	17	40.5
Closed	7	16.7
Missing	1	2.4
Total	42	100.0
Wound type	(n =)	%
New wound	21	50.0
Recurrent wound	20	47.6
Missing	1	2.4
Total	42	100.0
Number of wounds	(n =)	%
Single	27	64.3
Multiple	13	31.0
Missing	2	4.8
Total	42	100.0

Table 4.6. LU participant characteristics

	Mean (n =)	Standard Deviation
Patient age	71.12	11.83
Previous wounds	4.40	14.54
Sex	(n =)	%
Male	25	49.0
Female	26	51.0
Total	51	100.0
Wound severity	(n =)	%
Mild	11	21.6
Moderate	5	9.8
Severe	19	37.3
Closed	15	29.4
Missing	1	2.0
Total	51	100.0
Wound type	(n =)	%
New wound	27	52.9
Recurrent wound	23	45.1
Missing	1	2.0
Total	51	100.0
Number of wounds	(n =)	%
Single	15	29.4
Multiple	36	70.6
Total	51	100.0

PROM results

After including the SAT-II in the pilot study of the first 10 patients, it was decided not to include this outcome measure in the main study, since both EQ-5D-5L and CWIS had questions regarding pain, and further research into the scoring methodology of SAT-II highlighted difficulties. The patient group size here was not large enough to power a study reliant on the minimum clinically important difference between subgroups instead of over time. The SAT-II

had only been reported longitudinally and it was deemed out of the scope of this thesis to validate its use in a cross-sectional study prior to reporting the results. Due to this, the following section only reports on the EQ-5D-5L and CWIS validated tools; this is not thought to undermine the robustness of this study, given that both a generic and a disease specific tool were still used to report QoL.

The research undertaken and presented in the background and methods section of this chapter asserts that EQ-5D is the most relevant for economic modelling and reports that CWIS can accurately represent QoL for patients with both DFU and LU. Even though the study included both DFU and LU patients, and was designed to accommodate both in the design, the reporting of results presents the wound aetiologies separately. This is because ultimately, they are different diseases, driven by different underlying causes and if they were combined in an aggregated analysis then some key issues important to each patient group may be less clear, or lost entirely.

EQ-5D

Table 4.7 shows the results of the analysis using EQ-5D for both DFU and LU patients. For both patient groups, the index score calculated using the crosswalk methodology to map to the EQ-5D-3L value set is shown and the result of the VAS is also presented (van Hout et al., 2012). The VAS asks the participant to record their self-rated health on a 20-cm vertical, visual analogue scale with one end labelled 'the best health you can imagine' and the other labelled as 'the worst health you can imagine' (van Reenen & Janssen, 2015).

Table 4.7. EQ-5D index scores and VAS results for DFU and LU patients

EQ-5D-5L scores DFU	(n =)	Mean	Std. Deviation
	40	0.55	0.28
Visual analogue scale	41	59.88	20.39
EQ-5D-5L scores LU	(n =)	Mean	Std. Deviation
Index score	51	0.64	0.30
Visual analogue scale	51	63.63	21.34

For the DFU group, two patients' responses did not enable the calculation to an index score, and one patient did not mark a response on the VAS. In the LU group, all patients completed the PROM and were included in the analysis.

In the DFU group, the mean index score (SD) was 0.55 (±0.28), with some respondents obtaining the maximum score of 1.00, the lowest reported index score was 0.04. For LU patients, the index score was higher, with a mean score of 0.64 (±0.30). Patients also reported index scores of 1.00, the maximum score. However, the lowest result in this group was -0.20; a score of less than 0 indicates a health state that is deemed worse than death.

The mean VAS score for DFU patients was 59.88 (±20.39), with a range of 17-95. The LU patients again scored marginally better on this measure, with a mean VAS score of 63.63 (±21.34) and range of 15-99.

CWIS

CWIS is scored on a 0-100 scale, with a higher score representing better QoL outcomes. The tool produces a score in three categories: well-being, physical functioning and everyday living, and social life. Table 4.8 presents the results for the CWIS tool as reported by the DFU and LU patients in this study.

Table 4.8. CWIS results for DFU and LU patients

CWIS Scores DFU	(n =)	Mean	Std. Deviation
Well-being	34	51.15	22.93
Physical symptoms & daily living	36	71.16	25.73
Social life	40	81.57	21.28
CWIS Scores LU	(n =)	Mean	Std. Deviation
Well-being	49	49.71	25.02
Physical symptoms & daily living	44	75.07	21.98
Social life	47	83.34	20.95

More patients did not complete all the fields of the CWIS tool when compared to EQ-5D. For DFU patients, out of total possible 42 patients, 34 patients were included in the analysis for well-being, 36 for physical symptoms and daily living and 40 for social life. When considering LU patients, the full cohort was 51 patients and 49 completed the well-being section and were included in the analysis, 44 for the physical symptoms and daily living section and 47 for social life.

For DFU patients, the mean scores (SD) for well-being, physical activities and daily living, and social life were 51.15 (±22.93), 71.16 (±25.73) and 81.57 (±21.28) respectively. Each category saw patients that scored the maximum available 100 points, indicating a fully positive score, and the minimum social life score was 17, wellbeing score was 7 and for physical symptoms and daily living there was a patient who scored 0 points.

For LU patients, the mean scores for well-being, physical activities and daily living, and social life were 49.71 (±25.02), 75.07 (±21.98) and 83.34 (±20.95) respectively. Each category saw patients that scored the maximum available 100 points, indicating a fully positive score, and the minimum social life score was 8, wellbeing score was 4 and for physical symptoms and daily living 13; for the LU subgroup, no patients scored 0 points.

Subgroup analysis

When using the severity matrix of duration versus size, the proportion of wounds that fit each category in each of the two groups is shown in Figure 4.2. 32% of LUs were classified as mild/moderate vs 38% severe and 41.5% of DFUs mild/moderate and 41.5% severe. More LUs were reported as closed compared to DFUs, 30% and 17% respectively, potentially due to the ongoing maintenance and compression needed by LU patients to prevent a recurrence. The number of reported closed wounds was more than was expected, and the results for closed wounds have not been presented here; as they were deemed unlikely to be generalisable, given that the patients were still receiving treatment and the wound had likely only just healed.

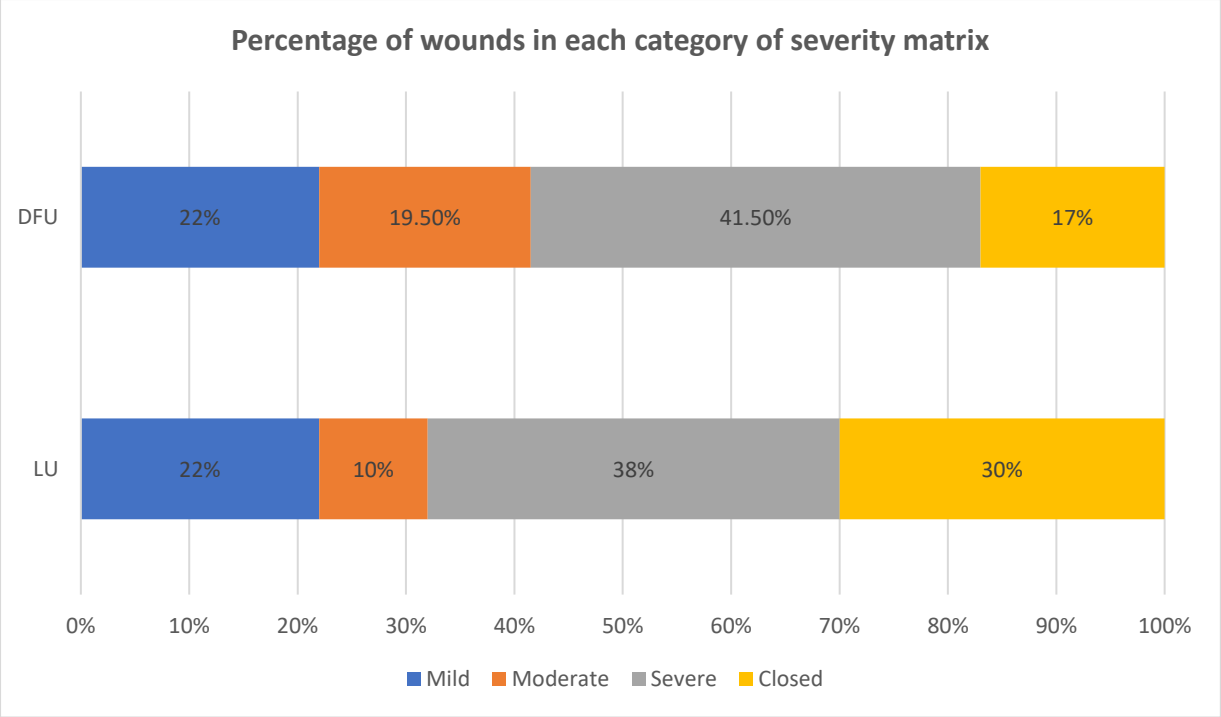


Figure 4.2. Wounds stratified according to severity

EQ-5D subgroup analysis

Table 4.9 presents the DFU results for the subgroups of mild, moderate, and severe wounds for the EQ-5D index score and the VAS result. The mean with 95% confidence interval, and standard deviation are presented for each group.

For the index scores, the mean results for mild, moderate and severe wounds were 0.80, 0.55 and 0.47, respectively; following the expected pattern that QoL decreases as a wound becomes more severe. The VAS for these subgroups follows a different pattern, with mean results for mild, moderate and severe reading out at 61.11, 65.50 and 61.15.

Table 4.9. EQ-5D results for DFU severity subgroups

DFU Subgroups EQ-5D			
Index score	Mild	Mean	0.80 (CI: 0.69 - 0.91)
		Std. Deviation	0.14
	Moderate	Mean	0.55 (CI: 0.33 - 0.78)
		Std. Deviation	0.22
	Severe	Mean	0.47 (CI: 0.32 - 0.62)
		Std. Deviation	0.25
Visual analogue scale	Mild	Mean	61.11 (CI: 48.25 - 73.97)
		Std. Deviation	16.73
	Moderate	Mean	65.50 (CI: 47.16 - 83.84)
		Std. Deviation	17.48
	Severe	Mean	61.15 (CI: 48.09 - 74.22)
		Std. Deviation	21.62

Table 4.10 presents the LU results for the subgroups of mild, moderate, severe, and closed wound for the EQ-5D index score and the VAS result. The mean with 95% confidence interval, and standard deviation are presented for each group.

For the index scores, the mean results for mild, moderate and severe wounds were 0.83, 0.73 and 0.56, respectively. As seen in the DFU subgroups, the scores follow the expected pattern that QoL decreases as a wound becomes more severe. The VAS for the subgroup of LU is again non-concordant with the index score results, with mean results for mild, moderate and severe reading out at 62.50, 65.00 and 61.06.

Table 4.10. EQ-5D results for LU severity subgroups

LU Subgroups EQ-5D			
Index score	Mild	Mean	0.83 (CI: 0.72 - 0.94)
		Std. Deviation	0.16
	Moderate	Mean	0.73 (CI: 0.38 - 1.07)
		Std. Deviation	0.14
	Severe	Mean	0.56 (CI: 0.41 - 0.72)
		Std. Deviation	0.30
Visual analogue scale	Mild	Mean	62.50 (CI: 49.97 - 75.03)
		Std. Deviation	17.52
	Moderate	Mean	65.00 (CI: 20.22 - 109.78)
		Std. Deviation	18.03
	Severe	Mean	61.06 (CI: 48.90 - 73.22)
		Std. Deviation	23.64

The mean EQ-5D index and VAS scores and 95% confidence intervals for DFU and LU when stratified by sex, age, recurrence and amputation history for DFU are reported in Table 4.11.

Table 4.11. EQ-5D results for DFU and LU demographic subgroups

		DFU		LU	
Category	Subgroup	Index	VAS	Index	VAS
Age	< 65	0.54 (0.41, 0.68)	61.05 (52.26, 69.84)	0.57 (0.42, 0.72)	62.00 (52.37, 71.63)
	≥65	0.54 (0.41, 0.66)	58.75 (49.26, 68.24)	0.68 (0.58, 0.79)	63.56 (55.45, 71.68)
Sex	Male	0.60 (0.50, 0.69)	60.46 (53.11, 67.82)	0.65 (0.51, 0.79)	64.35 (54.42, 74.28)
	Female	0.45 (0.27, 0.63)	58.62 (46.51, 70.72)	0.66 (0.55, 0.77)	62.04 (53.98, 70.09)
Recurrence	New	0.61 (0.47, 0.75)	60.00 (51.01, 68.99)	0.67 (0.59, 0.76)	62.96 (54.72, 71.19)
	Recurrent	0.48 (0.38, 0.59)	59.00 (49.79, 68.21)	0.63 (0.47, 0.79)	61.62 (52.06, 71.18)
Number of sites	Single	0.59 (0.48, 0.70)	62.62 (55.02, 70.21)	0.80 (0.71, 0.89)	73.57 (61.20, 85.94)
	Multiple	0.47 (0.30, 0.63)	53.62 (41.80, 65.43)	0.59 (0.48, 0.70)	58.44 (51.82, 65.06)
Amputation history	Yes	0.61 (0.46, 0.75)	57.65 (46.85, 68.45)	Amputation history not collected for LU patients	
	No	0.52 (0.38, 0.66)	62.89 (54.12, 71.66)		

The mean EQ-5D index scores for all patients representing each wound aetiology from this study is shown in context with EQ-5D scores reported in the literature for other chronic diseases in Figure 4.3 (Peters et al., 2014). This comparison is not a statistical meta-analysis; however it is one of the advantages of using EQ-5D; as comparisons can be made between disease areas; and the trend highlighted here shows that DFU and LU score poorly when compared to other diseases.

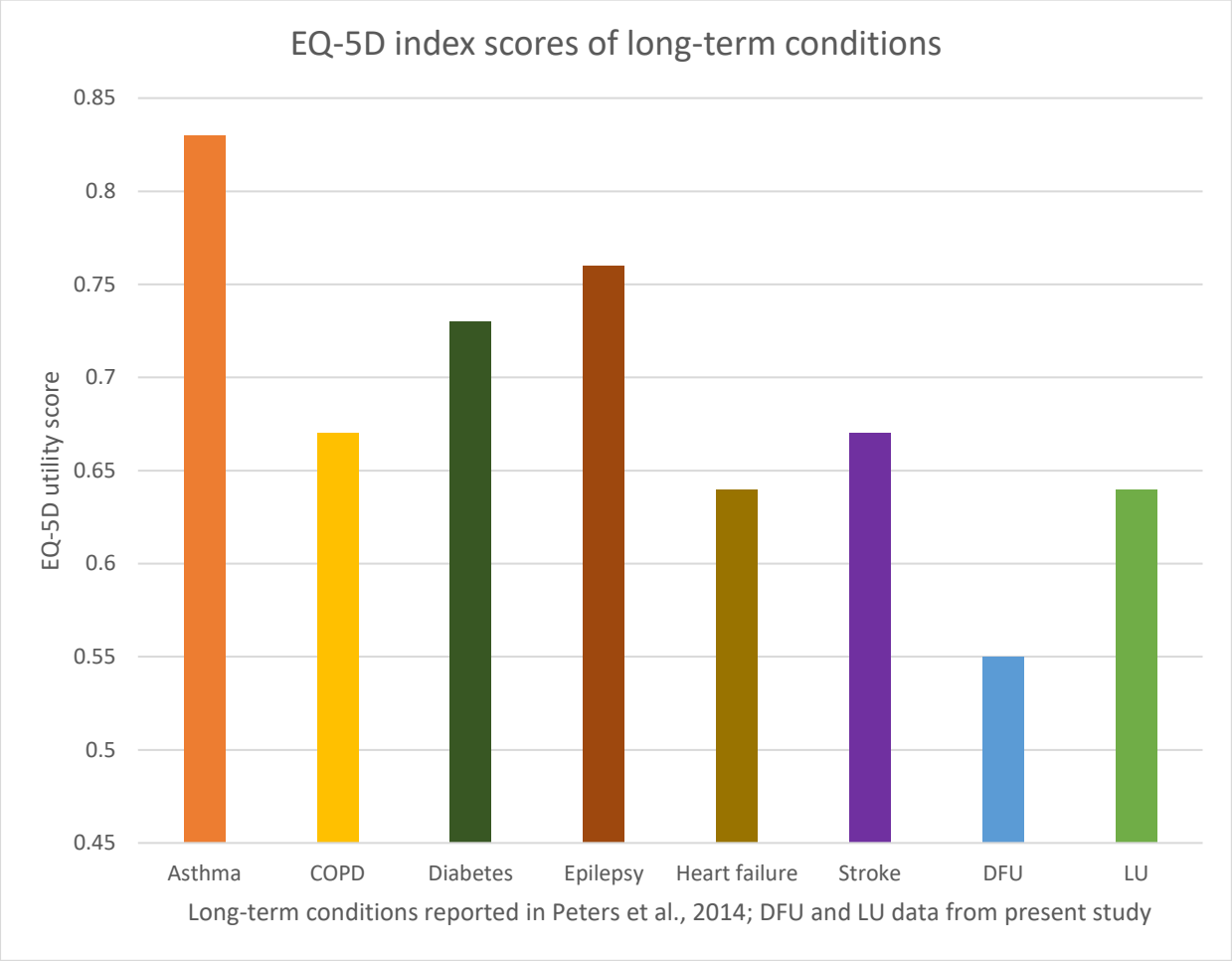


Figure 4.3. EQ-5D utility scores of DFU and LU compared with other long-term conditions

CWIS

Table 4.12 below presents the DFU results for the subgroups of mild, moderate and severe wounds for the three endpoints reported by the CWIS tool. The mean with 95% confidence interval, and standard deviation, are presented for each group.

Table 4.12. CWIS results for DFU severity subgroups

DFU Subgroups CWIS			
Well-being	Mild	Mean	54.34 (CI: 43.55 - 65.13)
		Std. Deviation	14.037
	Moderate	Mean	60.12 (CI: 32.65 - 87.59)
		Std. Deviation	26.177
	Severe	Mean	43.41 (CI 29.27 - 57.54)
		Std. Deviation	23.390
Physical symptoms and daily living	Mild	Mean	85.89 (CI 78.99 - 92.79)
		Std. Deviation	8.981
	Moderate	Mean	74.13 (CI: 48.11 - 100.16)
		Std. Deviation	24.802
	Severe	Mean	63.38 (CI: 47.42 - 79.35)
		Std. Deviation	26.424
Social life	Mild	Mean	93.97 (CI: 88.64 - 99.29)
		Std. Deviation	6.931
	Moderate	Mean	79.85 (CI:61.57 - 98.13)
		Std. Deviation	17.419
	Severe	Mean	79.18 (CI: 65.82 - 92.54)
		Std. Deviation	22.106

For CWIS well-being scores; mild, moderate and severe DFUs had mean scores of 54.34, 60.12, and 43.41 respectively. For the physical symptoms and daily living; mild, moderate, and severe wounds had mean scores of 85.89, 74.13, and 63.38 respectively. Finally, for the social life domain, mild, moderate, and severe wounds had mean scores of 93.97, 79.85, and 79.18, respectively.

Table 4.13 presents the LU results for the subgroups of mild, moderate and severe wounds for the three endpoints reported by the CWIS tool. The mean, median, standard deviation and 95% confidence interval for the mean are presented for each group.

Table 4.13. CWIS results for LU subgroups

LU subgroups CWIS			
Well-being	Mild	Mean	64.28 (CI: 44.64 - 83.92)
		Std. Deviation	27.454
	Moderate	Mean	47.60 (CI: 42.44 - 52.76)
		Std. Deviation	2.078
	Severe	Mean	40.54 (CI: 26.23 - 54.85)
		Std. Deviation	27.836
Physical symptoms and daily living	Mild	Mean	85.41 (CI: 78.75 - 92.07)
		Std. Deviation	9.309
	Moderate	Mean	73.27 (CI: 38.11 - 108.43)
		Std. Deviation	14.154
	Severe	Mean	68.75 (CI: 56.46 - 81.03)
		Std. Deviation	23.892
Social life	Mild	Mean	95.21 (CI: 90.56 - 99.86)
		Std. Deviation	6.504
	Moderate	Mean	87.50 (CI: 61.66 - 113.34)
		Std. Deviation	10.400
	Severe	Mean	83.82 (CI: 75.59 - 92.06)
		Std. Deviation	16.012

For CWIS well-being scores; mild, moderate and severe LUs had mean scores of 64.28, 47.60, and 40.54 respectively. For the physical symptoms and daily living; mild, moderate and severe wounds had mean scores of 85.41, 73.27, and 68.75 respectively. For the social life domain mild, moderate and severe wounds had mean scores of 95.21, 87.50, and 83.82 respectively.

4.5.2 Chart extraction

Patient characteristics

The chart extraction included 107 patients; of these patients, 36 patients had a DFU and 71 had a LU. In total, 1050 visits were recorded, with a mean of 9.81 visits per patient, for DFU patients the mean number of visits was 7.14 and for LU the patients saw their care provider on average 11.16 times.

From the 1050 visits, there were 208 recorded infections across both wound aetiologies, with 50 occurrences of infection across 257 DFU visits resulting in an incidence rate of 19.46%. From the 793 LU visits there were 158 infections recorded; an incidence rate of 18.37%.

Healing outcomes

Healing outcomes could be measured for the patients in the chart extraction. To compare the outcomes of patients in the real-world with clinical trial endpoints, it was important to measure similar endpoints. An endpoint of the proportion of wounds that had healed at 20 weeks was considered in line with a recent RCT of DFUs (Edmonds et al., 2018). For DFU wounds, 9 wounds out of 36 (25%) had healed by 20 weeks with a mean time to healing of 69 days. For LU wounds, 20 out of 71 (28%) wounds had healed at 20 weeks, with a mean time to healing of 70 days.

Patient distribution

The distribution of patient across the healthcare providers included in this study is shown in Figure 4.4. Most patients in this sample were seen by Practice Nurses (n =42); followed by Podiatrists (n =18) and Tissue Viability Nurses (n =17). Of these practitioners, Tissue Viability Nurses are overwhelmingly intended to support patients with LU; however, Podiatrists; who reported a similar number of patients in this sample, are included on the treatment pathway for DFU patients and not for LU patients.

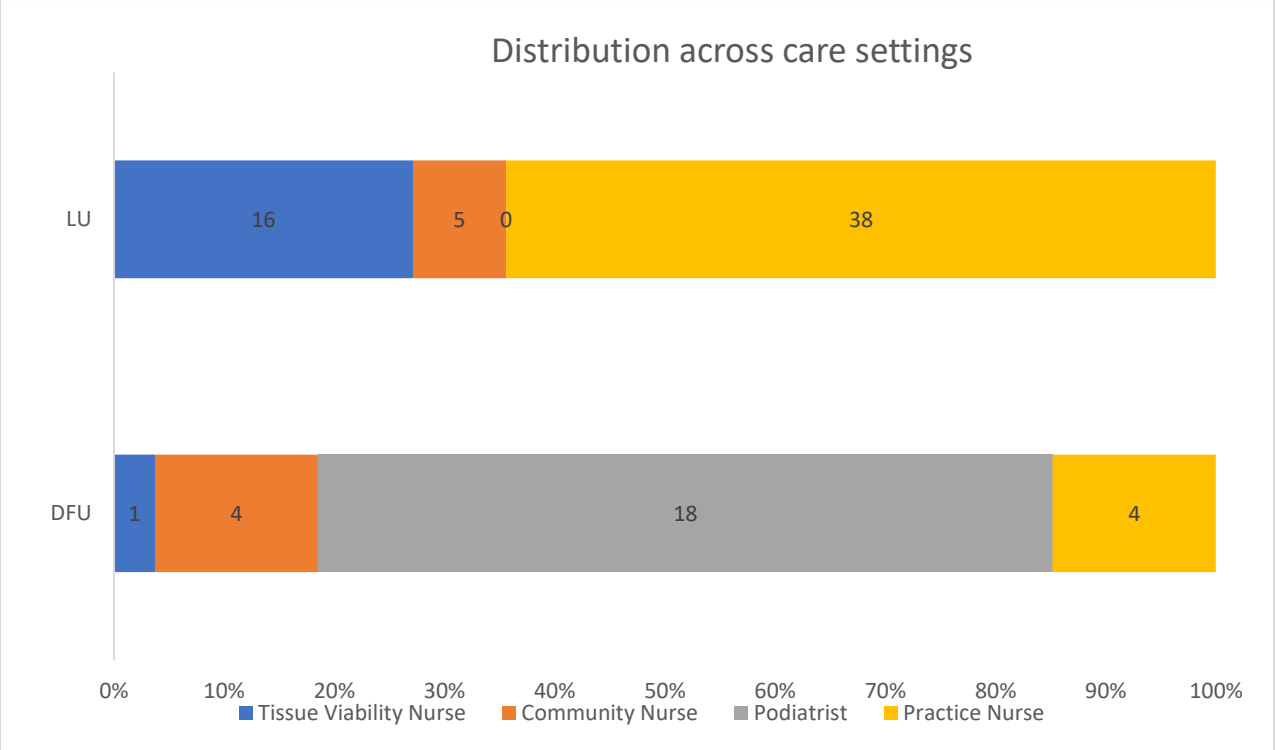


Figure 4.4. Distribution of patients across care settings

Treatment switching

To analyse the incidence of treatment switches, it was first necessary to identify visits that were eligible for having a treatment change. Wounds that were seen for a first assessment (n=27) or were recorded as healed (n=42) at the visit were excluded from the treatment switching analysis as these visits could not feasibly result in a switch as they represented either the commencement or cessation of treatment. After excluding these visits from the full number of 1050, this leaves 981 visits (93.43%) which could have had a potential switch.

Of the visits eligible for a treatment switch, there was no change to the primary dressing at 199 (21%) appointments; meaning that most visits resulted in a treatment switch, with 782 (79%) incidences of a switch. Thematic analysis was used to categorise the reasons given for treatment switching, with four major categories emerging. These were clinical reasons for switching, reasons arising from patient preferences, reasons that were external to both the clinician and patient, and incidences where no reason was given for the switch.

Secondary to these categories, sub-categories were assigned to further understand the reasons that drove changes to treatment. For clinical reasons, sub-categories included a change in the wound environment, including it becoming dry, producing much exudate,

becoming very sloughy or requiring debridement. Other clinical reasons were the presentation of an infection, deterioration or impaired wound healing, improvement of the wound, dressing related adverse events, or other miscellaneous reasons that were too disparate to categorise.

External reasons fitted into two categories; the advice of other health care professionals was being heeded, or issues related to continuity of stock where a treatment switch was necessary as the health care provider could not find the same dressing to replace the one being removed. Patient preference reasons were divided into the following categories, intolerance to the current prescribed dressing, pain from their wound or current dressing, finding it difficult to self-care with the wound prescribed, or lifestyle reasons- for example wanting a waterproof dressing to allow them go swimming on holiday. Where no reason was provided, this was split into two categories, where there were notes provided but these did not explain the treatment switch, or where the notes section was left blank. Figure 4.5 shows the flow of patients through the treatment switching pathway, please note that due to rounding some columns may not equal exactly 100%.

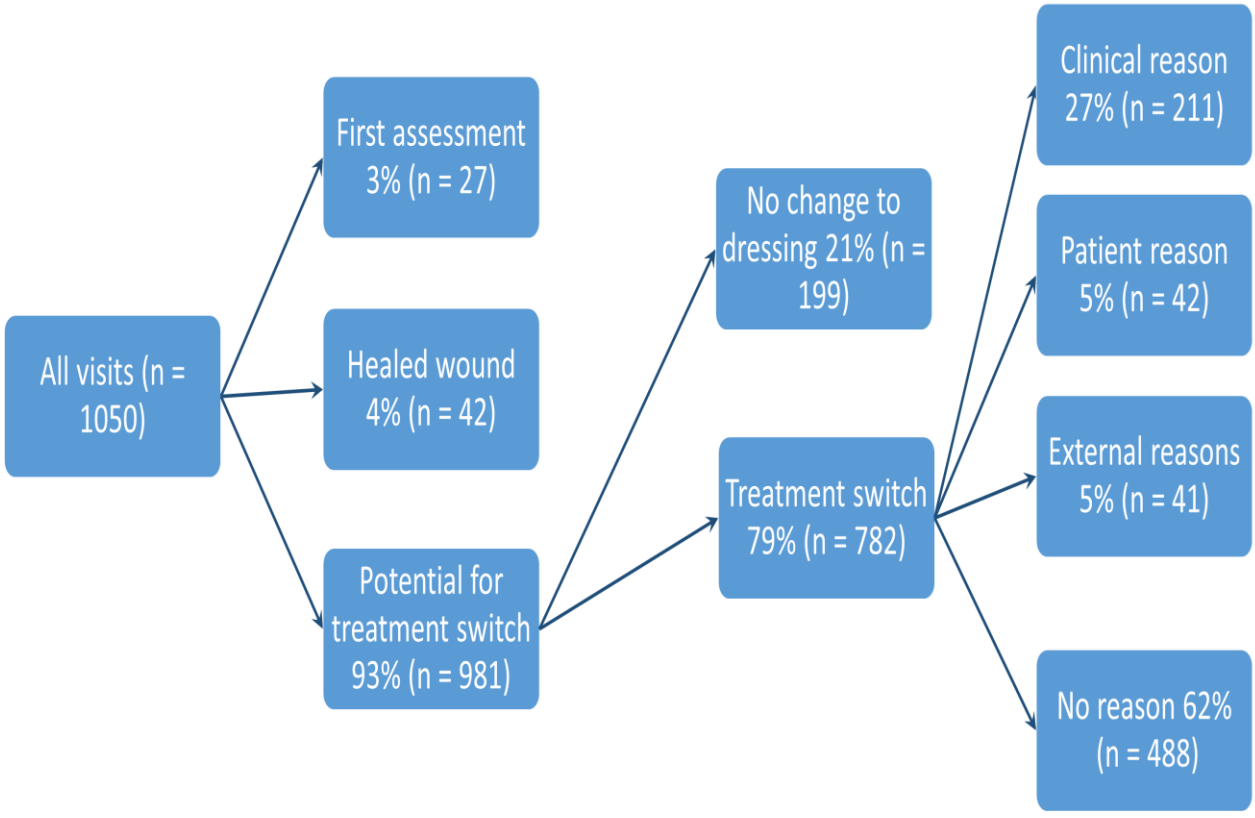


Figure 4.5. Treatment switching pathways

Table 4.14 lists the sub-categories generated through thematic analysis, also showing the number and proportion of patients that these constitute.

Table 4.14. Categories of treatment switching and their prevalence

Switching category	Sub-categories	(n=)	Proportion of main category	Proportion of all switches
Clinical (n = 211)	Wound environment	74	35%	9.46%
	Infection	40	19%	5.12%
	Deterioration/impaired healing	37	18%	4.73%
	Wound improvement	35	17%	4.48%
	Dressing related	12	6%	1.53%
	Other	13	6%	1.66%
Patient (n = 42)	Lifestyle	15	36%	1.92%
	Pain	10	24%	1.28%
	Self-care	4	10%	0.51%
	Tolerance	13	31%	1.66%
External (n = 41)	Other HCPs	27	66%	3.45%
	Stock availability	14	34%	1.79%
None (n = 488)	Notes, but no reason	94	19%	12.02%
	Notes left blank	394	81%	50.38%

Just over half of all visits did not have a treatment note in the record; these cannot be judged to truly be switches made with no reason. If these records are excluded from analysis, then the switches with no reason are the largest cohort, representing 24.23% of all switches with notes available. The smallest category of those with notes available is patient self-care (1.03%), where the patient had opted to treat themselves outside of the healthcare system. The full division of the subcategories, for records that had reasons listed are shown in Figure 4.6, please note that due to rounding figures may not equal 100%.

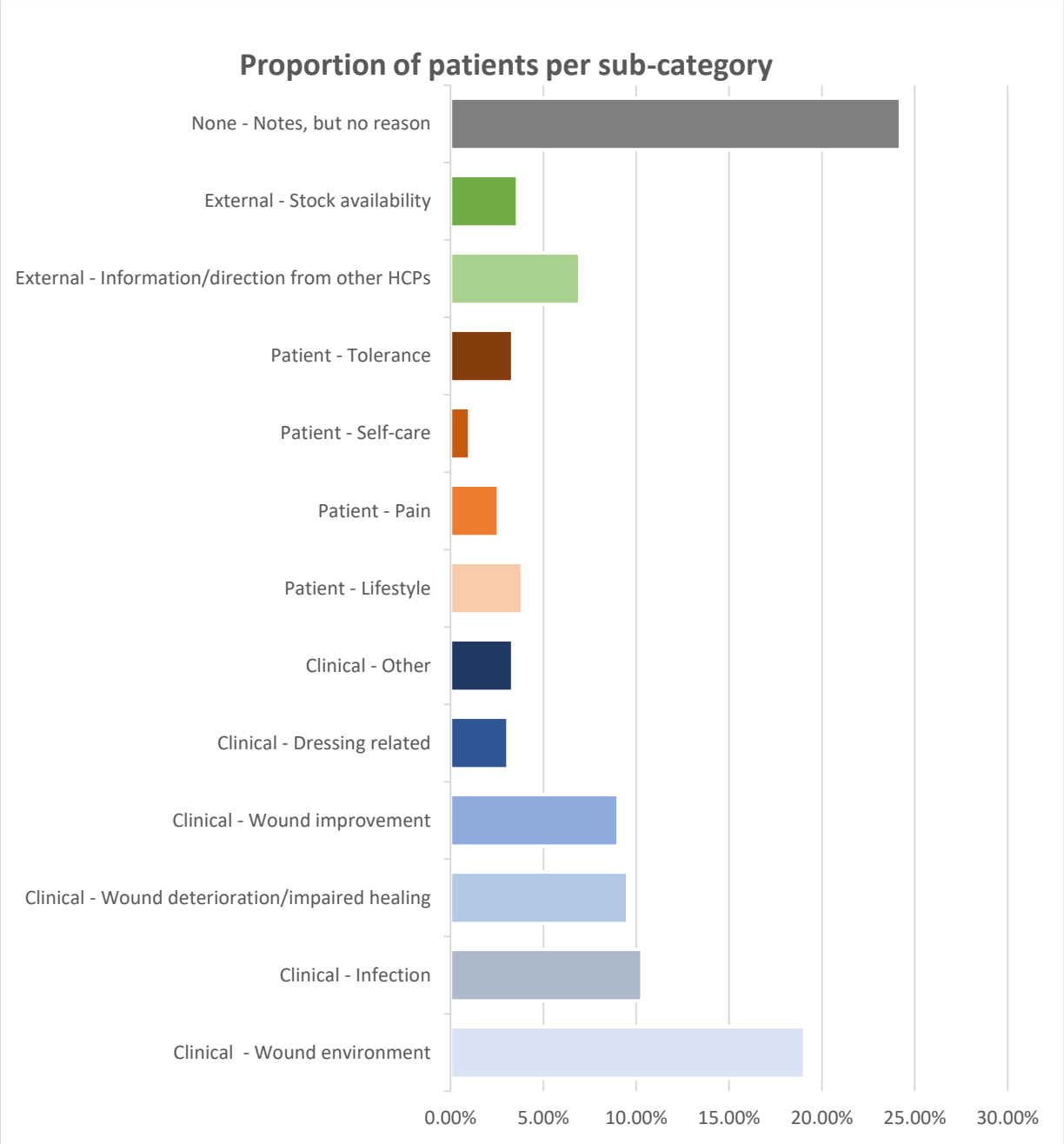


Figure 4.6. Proportion of patients in each sub-category of switching.

Subgroup analysis

Further subgroup analysis was focussed on the individual treatment centres that participated in the study. The rationale behind this stratification was that each centre may have an individual approach to switching, and recording switches, and to understand the divergence in care provided for DFU and LU. The centres are anonymised in this analysis as the purpose is not to reprimand any centre for their recording habits. The number of visits and wounds at each centre is shown in Table 4.15.

Table 4.15. Wound records at each treatment centre

Centre	Wounds (n)	Records (n)	Mean visits per wound
A	14	91	6.5
B	42	427	10.2
C	10	82	8.2
D	25	312	12.5
E	16	138	8.6

Comparisons between the healing rates, measured as the proportion of wounds healed at 20 weeks, at the centres and the incidence of treatment switches are shown in Figure 4.7. Centre A had a low switch rate and high healing rates for DFU and LU; Centre B conversely had a high switching with a low unexplained rate; and achieved average LU healing compared with the group. Centre C had a high switch rate with very high unexplained rate and a very low healing rate for DFU. Centre D had a moderate switch rate and showed high DFU healing and average LU healing rate; and Centre E had a moderate switch rate with low numbers of unexplained switches and recorded a medium-high healing rate for LU.

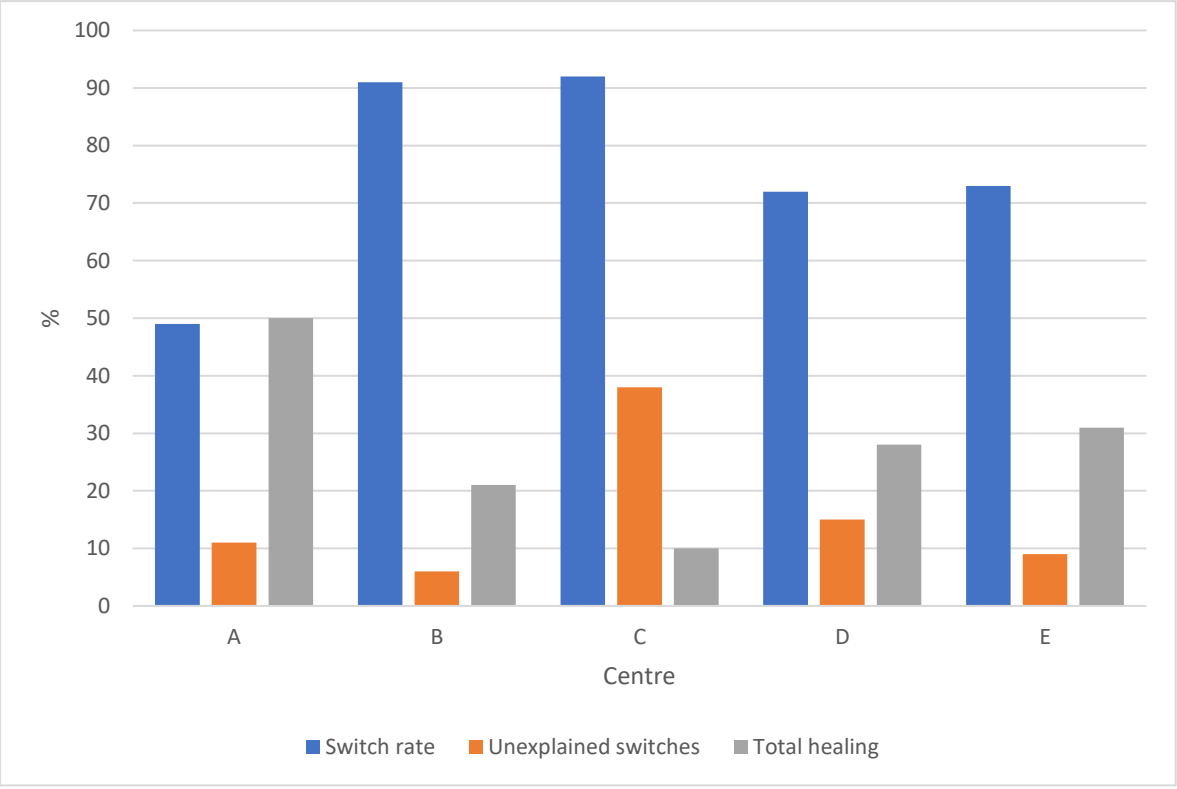


Figure 4.7. Treatment switching, and wounds healed at 20 weeks by centre

4.6 Discussion

This section discusses the results presented by each study, compare the different wound aetiologies and subgroups and look for areas of interest in the results where a level of significance has been reached, or not, and discuss reasons for this. This section also looks at the results of each study in context of the wider body of work presented in this thesis and look to external sources to compare these results with contemporary data. Each study is discussed in turn, given the fact that they have been carried out independently.

4.6.1 PRO study

The PRO study included results from 94 patients in total; however, one record was unavailable for analysis given that the patient had not answered if they had a DFU or LU and this was essential for stratifying and analysing the data. In terms of patient characteristics, there were some key differences between the DFU and LU groups. The DFU patients were younger, with a mean age of 64.05 vs the LU patients' mean age of 71.12. This was an expected result, as often LU patients can be older, given the fact that these ulcers are frequently related to vascular inefficiency, a consequence of aging, compared to DFU patients, who have ulcers caused by their diabetes; which is not necessarily a disease caused by age. This result also aligns with the outcome of clinical SLR presented in chapter 2; which found that DFU patients were younger, and that LU patients were more likely to be female.

The ratio of males to females in the cohorts was different across the groups with the LU patients having a near even split of the sexes, whereas the DFU group included more males. Typically, when comparing to clinical studies LU wounds are perhaps more common in females, which is not represented here. When considering DFU patients, it is interesting to note that, of those who answered, 50% of the group had been through a previous amputation relating to their DFU.

Contrary to expectation, given the high likelihood of recurrence for patients with a LU (Clarke-Moloney et al., 2014), there were higher numbers of new wound sites reported by LU patients, with 27 new wounds vs 23 recurrences. Contrary to this, the DFU group had a more even split with 21 new wounds vs 20 recurrences. When also considering the numbers of single versus multiple wounds, the two wound aetiologies differ majorly; the majority of DFU patients, 67.5%, were presenting with just a single wound, whereas for LU patients 70.6% of the group

reported having more than one wound concurrently at the time of completing the demographic questionnaire. This difference could be attributed to the different wound processes; with a DFU forming often as the result of irritation or abrasion from outside, and a LU being formed by a breakdown of the vascular system inside the legs.

Using the EQ-5D tool, DFU patients had a lower mean index score when compared to patients with a LU, 0.55 vs 0.64 respectively; implying that patients with a DFU have a worse QoL than patients with a LU. When considering the VAS, the DFU patients also rated their health as worse, with a mean of 59.88 versus a mean of 63.63 for LU patients. The results presented here indicate a worse QoL than found in the sucrose octasulfate RCT; that reported utility scores of 0.63-0.69. This may be influenced by the RCT setting; where patients may have renewed optimism and hope for their wound healing (Edmonds et al., 2018). Additionally, patients who are recruited into clinical trials are subject to rigorous entry criteria; which often exclude patients with comorbidities. The cross-sectional real-world data presented here is arguably more representative of the general population; as patients were recruited sequentially, with no specific conditions other than having a DFU or LU.

When analysing the CWIS results, it is apparent that less of the respondents completed all pages of the tool. This could be because this tool is much longer than the generic EQ-5D, however this is often the case for disease specific tools, as they have more areas related to the disease of interest. The CWIS uses a methodology where it asks patients to first state if they had experienced a certain phenomenon, and then how stressful this experience was. Where a patient did not read the explanatory text at the top of the page, they often left the second page blank as it appeared to be a duplicate of the previous page. Confusion could be mitigated in future with clearer explanation, or clinician guidance when administering the tool.

Both patient groups, DFU and LU responded similarly to the CWIS tool; with the well-being element the lowest scored, followed by the physical symptoms and daily living, and then social life being the least impacted. The well-being element was also scored the lowest when CWIS was used in an earlier RCT (Jeffcoate et al., 2009). It is heartening that despite the suppressed well-being of the patients, they still reported generally good social lives; and, the fact that within each domain at least one patient scored 100, a fully positive score.

When analysing the subgroups of mild, moderate, severe and closed wounds it has been noted that a pattern emerges from the EQ-5D index scores. The severe wounds score the lowest, indicating worse QoL, followed by moderate wounds and then mild wounds. For LU, the same is true, with severe wounds shown to be worse than mild wounds. These results imply that there is a patient benefit associated with healing a wound before it can be deemed severe, according to a matrix of duration versus size.

The VAS scores from EQ-5D do not follow this same pattern; which can be construed that patients do not consider their QoL as impaired compared to the general population sample used to create the value set. Mild and severe DFUs scored nearly the same (61.11 and 61.15 respectively) and moderate LUs scored the best using this ranking.

When considering CWIS, the severe wounds scored worse across well-being, physical symptoms and daily living, and social-life for both DFU and LU. For the well-being score, which was the most affected of all the domains when considering the whole sample, severe DFUs scored 43.41/100 and severe LUs 40.54/100.

The anomaly in this study comes when considering the closed wounds subgroups, which in addition to being reported in higher numbers than expected, also reported much poorer QoL outcomes than expected. When using EQ-5D, closed wounds scored index scores of only 0.01 higher than a severe wound for both DFU and LU wounds. This implies that a closed wound is worse than having either a mild or moderate wound and is only fractionally better than a severe wound.

It was considered that the ongoing treatment for LU patients might explain both the larger sample size and the suppressed QoL scores. A theory could be that a patient is focussed on their wound closing and being 'healed' that when they realise, they must continue to wear compression systems, and even potentially attend clinics, they are disheartened and report lower QoL scores; however further research would be needed to validate this speculation. Given that all responses were collected from treatment centres, the patients with a closed wound are logically still attending appointments, which implies the wound is only just closed or they have a further complication. These scores provide an interesting insight into the patient experience and could be the basis for further research into long term QoL outcomes for patients with closed wounds, the impact of any recurrences and ongoing management.

4.6.2 Chart extraction

In total, there were 107 wounds included in the chart extraction; of these, many more were LU, (n=71) but enough DFUs were included to allow for analysis (n=36). When considering patient characteristics, this study has separated the wound aetiologies, but for analysing the incidence of treatment switching all results have been aggregated. This was decided due to the drive to understand the incidence and reasons for switching across centres- as there is no specific guidance or directive for either DFU or LU which could be examined here.

Patients with a LU had more appointments recorded on average, with a mean number of visits at 11.16, 56% higher than the number of visits recorded for DFU patients. This could be due to the need to maintain compression and higher levels of exudate present in these wounds compared to DFUs which tend to be smaller.

The LU sample measured here was predominantly collected from practice nurses, a non-specialist care provider often based at a local GP. This is most likely representative of the treatment received by most LU patients, with some having community nurse visits at home, and some being seen by a specialist tissue viability nurse if their wound continues to be problematic. The DFU patients in the sample collected for this study were mainly treated by a podiatrist; which is a specialist service. Further research, using a larger sample, could test if this is representative of all DFU patients, given the small numbers of DFU patients (n=36) included here.

When considering healing outcomes, this study recorded the proportion of wounds that had healed by 20 weeks of treatment. This endpoint was selected to compare with an RCT of DFU wounds; which has the same endpoint (Edmonds et al., 2018). Using endpoints from real-world data is also important as it is widely recognized that the performance of medical interventions in real life does not exactly mirror the performance measured in RCT.

For LU patients included in this sample, 20/71 (28%) of wounds had healed at 20 weeks; which can be compared unfavourably to results in prospective trials reporting healing rates of between 84%-93.3% (Turner and Ovens, 2017; Towler et al., 2018). This demonstrates the vast difference in healing rates observed in a trial setting versus the real-world, known as the evidence-efficacy gap (Nordon et al., 2016). Similar, but not as divergent is the comparison for DFU patients. In the chart extraction, 9/36 (25%) of the wounds healed within 20 weeks, which

is comparable to the control arm in an RCT which used a neutral dressing and standard care and achieved 30% healing by 20 weeks (Edmonds et al., 2018). However, when looking at the active arm in the RCT, 48% of patients using the sucrose octasulfate dressing had healed within 20 weeks. However, no guidance currently exists mandating use, so treatment switching remains prevalent in standard care.

The incidence of treatment switching was measured at 79% of eligible visits. This means nearly 4 in 5 visits by a patient result in a new dressing. Most manufacturers recommend that their dressing be used for a period of weeks before it is changed, given that dressings can be impregnated with an active ingredient which may take time to work. It is also interesting to note that the 20-week healing rate is demonstrably lower in the chart extraction than in the RCTs included in the clinical SLR presented in chapter 2. An implication here is that using the same dressing, any dressing, for the time stipulated in the study protocol may improve wound healing rates, but this needs to be explored further.

The relationship between treatment switching and healing outcomes has been explored across the centres included in this study. The centre with the lowest incidence of treatment switching, Centre A, recorded the highest proportion of patients healed at 20 weeks in this sample; and had the fewest number of visits per wound. Conversely; the centre that reported the highest number of treatment switches, Centre C, with nearly 40% unexplained switches, also reported the lowest healing rate at 20 weeks. This implies a relationship between unexplained, and potentially unnecessary, switches and healing outcomes, however a limitation of this study was that this is not an inferential statistical analysis and is only indicative of a trend. It is recommended that future research investigates this correlation further; however it may present ethical difficulties to investigate in a prospective RCT and so a larger-scale real-world study of a retrospective dataset might be better suited.

When carrying out the thematic analysis, it became apparent that many of the notes had been left blank; with no reason given to explain the treatment switch. After discussion with the supervisory team about how to categorise these records, it was agreed that they could not be assumed to be switches with no reason; as they may have had a valid reason, but this was not captured for one of many reasons (no time, lack of staff training, under resourcing, and so on). Despite excluding all the records that had blanks, those that did not explaining the switch, were

still the largest sub-category included with nearly ¼ of all records not providing a reason for the treatment switch.

Given that so many records were left blank, and thus excluded from analysis; further research could explore this topic using more in-depth qualitative methods to understand if the treatment notes are a full record; or if the absence of a switching rationale may be a due to other external factors.

It is important for clinicians and decision makers to be aware of real-world evidence that is collected from patients, as this can be used to give additional insights into factors that are important that could have previously been overlooked. An example of this is the suppressed QoL reported by patients with closed wounds. This could be due to a variety of reasons but given that this study did not anticipate this result, no additional data can be provided. This result should highlight that when treating a patient with a LU, as important as it is to heal a wound, it is also important to treat a patient holistically to ensure their overall health status is not impacted.

The large uncertainty present in the management of chronic wounds is not to be underestimated; this chart extraction shows that patient outcomes do not match those seen in clinical trials, and in the case of LU- are wildly different in the number of healed wounds. This issue requires addressing to improve the QoL of patients and drive down costs for the healthcare system. Clear and mandated guidance delivered via robust medical education campaigns could help to empower health care professionals into choosing interventions that could reduce healing time for patients; which is key to reducing the burden of DFU and LU.

4.7 Chapter summary

This chapter has provided an insight into the patient experience in a real-world setting. The PRO study has highlighted the substantial burden on QoL for patients with DFU and LU whilst the chart extraction has shown how real-world healing rates compare with those collected in a clinical trial setting.

The objectives of study 3 were to establish QoL issues and utility scoring for patients with DFU and LU and this study has highlighted that well-being is the dimension most impacted rather

than their physical functioning or social life as measured by the wound specific PROM CWIS. The use of a generic PROM, EQ-5D has enabled a quantification of the QoL burden felt by DFU and LU patients, which has been shown to be worse than several other chronic conditions. Both aetiologies of wound are much more burdensome for a patient across all recorded outcomes when they become severe. A wound becomes severe as it gets bigger, or as time passes without healing. This measurement is easy to apply and non-intrusive for a patient and given the differences in the EQ-5D index score measured between mild and severe wounds; this matrix is precise enough to highlight patients who experience worse QoL than others.

The objectives of study 4, the chart extraction was to understand and investigate the incidence of and reasons behind treatment switching of a primary dressing. This study highlighted the widespread prevalence of treatment switching, with nearly 80% of visits resulting in a change of treatment. When analysing the reasons behind switches; 50% of records did not have any note explaining the switch; and after excluding these, records with notes but no reason for the switch were the largest identified sub-category. This researcher asserts that the prevalence of switching, and perhaps switching without clinical reasoning could be responsible for the reduced healing outcomes seen in patients in the real-world compared to a clinical trial setting; given that within a clinical trial the standard care given is truly standardised; which cannot be said for the sample examined in this chart extraction.

The next chapter presents the economic evaluation of the PMM dressing; using multiple methods of cost-modelling and leveraging data that has been produced by the earlier studies in this thesis.

4.8 Dissemination

The results of these studies have been presented at conference, at The International Society of Pharmacoeconomics and Outcomes Research (ISPOR) in the United States, Baltimore 2018 and at the ISPOR conference in Europe, Barcelona, 2018. The abstracts and posters are available in Appendix D.

Chapter 5 Economic evaluation of a protease modulating matrix dressing versus a neutral dressing for treating DFU and LU.

5.1 Introduction

The economic modelling that is presented in this chapter is the culmination of the work presented so far in this thesis. The systematic reviews (study 1) presented in Chapter 2 explored the clinical effectiveness of different protease-modulating matrix dressings (PMM), economic outcomes associated with topical wound care interventions, and the variance associated with 'standard care' for diabetic foot ulcers (DFU) and leg ulcers (LU). The Delphi methodology expert panel (study 2) discussed in Chapter 3 highlighted the views of clinicians, that there is a need for interventions that offer better solutions for patients, they also supported the use of PMM dressings in addition to standard care to improve wound healing outcomes. Patients themselves were consulted in chapter 4, via the patient reported outcomes (PRO) study (study 3), which elicited patient experiences via the use of validated tools. Chapter 4 also investigated treatment switching via the chart extraction study (study 4); which examined multiple sites and care settings in the United Kingdom (UK).

Economic models are frequently based on the results of a clinical trial; however as shown by the comparison of outcomes of the patients included in the chart extraction (study 4), outcomes that are seen in the real-world are often very different. This thesis has repeatedly noted that the guidance associated with the use of dressings for chronic wounds such as DFU and LU is sparse, with limited advice on the clinical benefits offered by dressings and a focus on cost-minimisation.

This chapter presents the economic evaluation (study 5) and the economic models used to evaluate the clinical and cost outcomes associated with using a sucrose octasulfate dressing; an example of a PMM dressing. The schematic of the five studies can be seen in Figure 5.1, with this study highlighted in green.

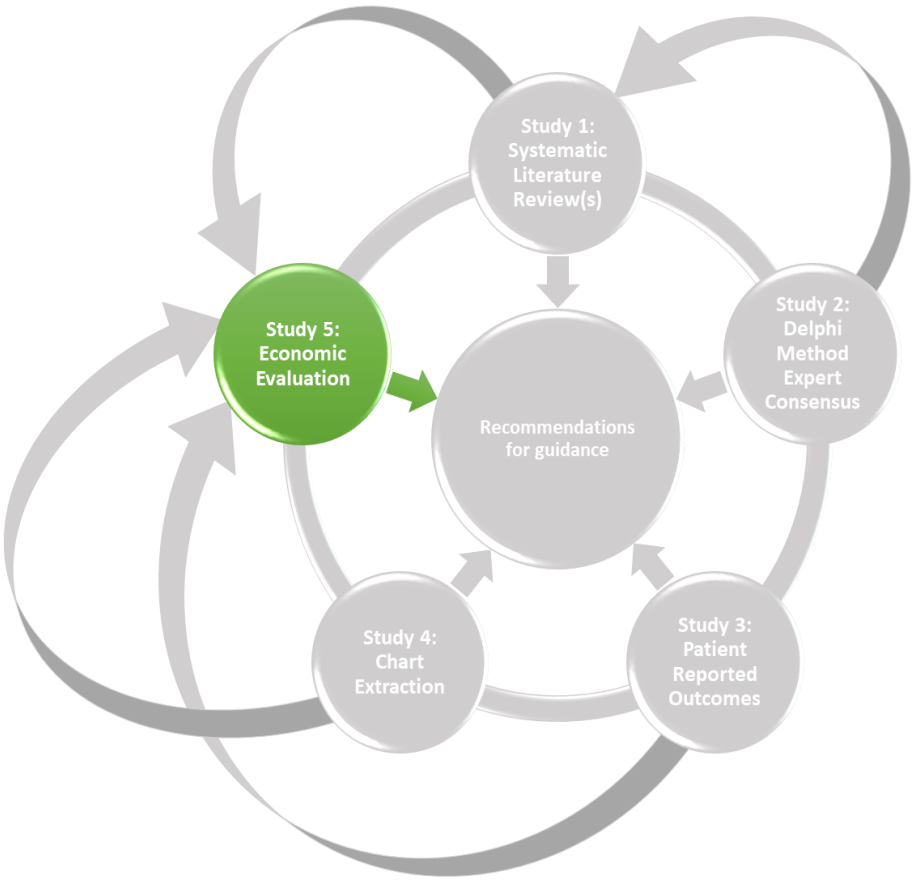


Figure 5.1. Economic evaluation within the PhD framework

This chapter begins with a literature review of economic models examining the PMM dressing with proven clinical benefit to patients (sucrose octasulfate). Then an explanation of the methods used is provided, and the results presented followed by discussion and conclusions.

The rationale for undertaking further cost analysis in relation to the use of PMM dressings, particularly the sucrose octasulfate dressing is discussed in the following section. A full cost-utility analysis relevant to the UK is possible given the data collected in this PhD thesis. Utility scores calculated from EQ-5D in the PRO study, study 3, are used to value health states used by cost-utility modelling.

5.2 Background

5.2.1 Existing economic evaluations of PMM dressings

Economic modelling in the field of wound care is abundant, as demonstrated by the results of the economic systematic literature review (SLR) presented in chapter 2. Economic modelling

allows the assessment of an intervention to society, considering the benefits offered and the costs incurred. Where budgets are finite, as in the United Kingdom (UK) National Health Service (NHS), economic modelling can help to guide decision making regarding the distribution of resources; towards a scenario where maximal health gains are achieved from a set budget. The research in chapter 2 examined the clinical and economic benefits of PMM dressings, and found that the sucrose octasulfate dressing, offered significant improvement ($p < 0.05$) in clinical and patient outcomes in patients with DFU or LU, in terms of wound area reduction or time to wound closure for patients (Meaume et al., 2012; Munter et al., 2017;Edmonds et al., 2018).

To explore the economic modelling already undertaken, specifically related to this dressing formulation, a scoping literature search using a systematic approach was undertaken to understand the economic benefits that could be gained by use of the sucrose octasulfate dressing. Additionally, this review included consultation with the manufacturer, given that sometimes economic models are commissioned but not published. Consultation with the manufacturer allowed the addition of unpublished economic analyses to inform this literature review.

The search strategy used is included in Appendix C. Four studies were identified (see Table 5.1). All four studies were included; resulting in four economic modelling studies that examined the use of the sucrose octasulfate dressing.

Table 5.1. Summary of studies in economic review of sucrose octasulfate dressing

Study name	Augustin et al., 2016	Maunoury et al., 2012	Maunoury et al., 2017 (Unpublished)	Maunoury et al., 2017 (Unpublished)
Location	Germany	France	France	France
Summary	Decision tree Model using Challenge study results.	Markov Model using Challenge study results.	Markov Model using Explorer study results.	Markov Model using Challenge and Reality study results.
Wound	LU	LU	DFU	LU
Costs	Direct medical costs	Direct medical costs	Direct medical costs	Direct medical costs
Patient outcomes	Proportion at 40% WAR by week 8		Wound closure at 20 weeks. 47.6% vs 29.8% for comparator	WAR > 40% at 8 weeks. 65.5% vs 39.4% for comparator.
Results	Saved €485.64/ responder in 8 weeks. Greater cost/ patient but higher response rate results in a lower cost/responder.	Sucrose octasulfate dressing dominant	Average gain of 0.74 life-years without ulcer and 0.18 QALYs, saving €34,215 per patient	Average gain of 5.9 life-years without ulcer and of 0.5 QALYs, saving €25,798 per patient

A critical review of the included models was carried out, using a tool adapted from the literature, and used by the National Institute for Health and Care Excellence (NICE) when assessing devices in their Medical Technologies Evaluation process (MTEP) (Drummond and Jefferson, 1996). The results of this are presented in Table 5.2.

Table 5.2. Critical review of included economic studies of sucrose octasulfate dressing

	Augustin et al., 2016	Maunoury et al., 2012	Maunoury et al., 2017 DFU)	Maunoury et al., 2017 (LU)
Study design	Tree	Markov	Markov	Markov
Research question stated?	Yes	No	Yes	Yes
Economic importance of research stated?	Yes	Yes	Yes	Yes
Viewpoint of analysis stated and justified?	Yes	Yes	Yes	Yes
Rationale given for interventions?	Yes	Yes	Yes	Yes
Comparators clearly described?	Yes	Yes	Yes	Yes
Evaluation justified?	Yes	No	Yes	Yes
Effectiveness estimates sources stated?	Yes	No	Yes	Yes
Design/results of effectiveness source given?	Yes	No	Yes	N/A
Primary outcome measure clearly stated?	Yes	Yes	Yes	Yes
Stated method to value health states/benefits?	No	No	Yes	Yes
Resource quantity separate from unit cost?	Yes	No	Yes	Yes
Stated method for estimating quantities/costs?	No	No	Yes	Yes
Currency & price data recorded?	Yes	No	Yes	Yes
Adjustments for inflation/currency conversion?	N/A	Yes	Yes	Yes
Model choice and key parameters justified?	Yes	No	Yes	Yes
Time horizon of cost and benefits stated?	Yes	Yes	Yes	Yes
Discount rate stated and justified?	N/A	Yes	Yes	Yes
Approach to sensitivity analysis described?	Yes	Yes	Yes	Yes
Choice of variables for sensitivity justified?	Yes	No	Yes	Yes
Ranges of parameters varied stated?	Yes	No	Yes	Yes
Incremental analysis reported?	Yes	Yes	Yes	Yes
Outcomes disaggregated and aggregated?	No	No	Yes	Yes
Answer to the study question given?	Yes	N/A	Yes	Yes
Conclusions align with data?	Yes	Yes	Yes	Yes
Generalisability issues addressed?	Yes	No	Yes	Yes

Of the included economic models; the critical analysis shows that in general the reporting was clear and thorough; with enough detail included to replicate the models if necessary- meaning it is appropriate to accept the results. All the models were in favour of the sucrose octasulfate dressing; showing dominance, greater response rate, or a cost saving. However; none of the models included data from the UK and were based on data from either Germany or France. Models that are designed for use by NICE are more likely to be representative and generalisable to DFU and LU patients in the UK.

5.2.2 Approaches to economic evaluation

There are several different types of economic analyses that can be carried out to evaluate an intervention. These include; budget-impact, cost-minimisation, cost-effectiveness and cost-utility. They all have slightly different methods and are suitable for different scenarios and are of benefit to different stakeholders; financial analyses that focus on the short-term impact to the bottom line are likely to be of more interest to planners and NHS commissioners than a lifetime model showing cost and clinical outcomes over the next ten or twenty years.

Budget-impact models (BIMs) are a type of economic analysis often performed by Health technology assessment (HTA) bodies to understand the expense associated with implementing a new intervention in a defined patient population. BIMs measure financial impact usually over 3 to 5 years, in line with forecasts made to plan resource allocation. The comparison made by a BIM is usually with standard care; that is- the continuation of current practices without the new intervention; and then the costs if the new intervention were introduced.

In England, NICE uses BIMs alongside evaluations of cost-effectiveness and has guidelines for manufacturers for carrying out the analysis (NICE 2013). In early 2017, NICE announced a budget-impact test for new interventions that it assesses (NICE, 2017). If a drug is set to cost more than £20 million in any of the first three years of use then commercial discussions are mandatory to balance the impact of the spend on the rest of the NHS (NICE, 2017). The role of budget-impact analyses is increasingly recognised for reimbursement decisions, not just in England, but also in other countries such as Australia and France (Mauskopf et al., 2013; Ghabri et al., 2017).

Methodological discussions regarding BIMs discuss to what extent disease complexity, treatment switching/sequencing and patient behaviour should be accounted for (Ghabri and

Mauskopf, 2018). Complex treatment pathways can be difficult given the calculations required for a budget-impact analysis using templates developed by NICE (NICE, 2015). Additionally, the link between a long-term cost-effectiveness model and calculating short term budget-impact can present a challenge as it has been argued that the cost-effectiveness threshold value should cancel out most budgetary issues (Claxton et al., 2015). However, high cost drugs with a large budget-impact may be discriminated against using this method and keeping budgetary impact separate from cost-effectiveness modelling may be a preferred option (Ghabri and Mauskopf, 2018). BIMs are a simple and effective way of assessing impact on the NHS' financial bottom line; but are best carried out in tandem with other analyses that allow for more in depth modelling of the patient pathway.

Cost-minimisation analysis, like budget-impact analysis, focusses on the cost of treatment, and any associated consequences. With cost-minimisation, the patient outcomes of using the technologies being compared has either been proven to be, or is assumed to be, equivalent (Dakin & Wordsworth, 2011). The goal of this type of analysis is to identify the least costly treatment option to achieve the desired health outcome. This method is useful when operating in a climate of economic stagnation- with strained budgets for healthcare. A limitation of cost-minimisation analysis is the assumption of equivalence; some treatments can offer patient benefits that are not reflected in a clinical outcome - for example less frequent dosing or easier administration. Differences between interventions, including patient preference, could possibly be overlooked if only the clinical outcome and cost is the driver for decision making. The inherent uncertainty of declaring interventions as the same, led to Briggs and O'Brien pronouncing 'the death of cost-minimisation analysis' in 2001 due to the rare circumstances in which it is appropriate (Briggs and O'Brien, 2001). A decade on from this declaration, a review found that cost-minimisation was still in use, and by using it instead of cost-effectiveness could lead to an over or under estimation of uncertainty (Dakin and Wordsworth, 2011) leading to less precise models to inform decision making. The move away from cost-minimisation analysis can be seen in the economic SLR presented in chapter 2; with only one study, the oldest, using this method (Apelqvist & Ragnarson-Tennvall, 1996).

Cost-effectiveness analysis not only evaluates the cost of a proposed intervention; but also, the outcomes that it offers to a patient. Cost-effectiveness is a method where the cost-per-item is presented in natural units; for example cost per healed wound (Dakin & Wordsworth,

2011). Decision makers strive for optimal resource allocation, which would be the maximisation of outcomes and minimisation of costs. Cost-utility modelling is a subset of cost-effectiveness, where the outcome is communicated in quality adjusted life years (QALY), rather than a natural unit specific to a disease area. QALYs can be calculated using utility scores; which are collected using tools such as EQ-5D, as presented in study 3; and this allows for a comparison across disease areas using a common unit (Peters et al., 2014). In England, NICE's main driver of decision making is asserted to be cost-effectiveness; measured using an incremental cost-effectiveness ratio (ICER), the ratio of the difference in costs over the difference in quality adjusted life years expressed as the cost per QALY gained (Rawlinds and Culyer, 2004).

A combined approach using a cost-effectiveness analysis and BIM would help to mitigate the limitations of each method. A BIM provides information on the real-world costs associated with adopting a new technology, which can be lacking in a cost-effectiveness analysis. However, a cost-effectiveness analysis provides a more precise cost-per-patient; and more detail in terms of individual patient journeys using health states with transition probabilities instead of whole population aggregated statistics.

5.2.3 Economic evaluation in the UK

NICE has a threshold for the ICER of an intervention; with the upper end being £20,000-30,000 per QALY gained (NICE, 2017). This is far from a definite threshold, with interventions for children, disadvantaged populations and very serious diseases given more flexibility (Rawlins et al., 2010). Different disease areas also attract varied median ICERs, that is- the cost at which an ICER has 50% probability of being accepted - which could be argued to be more representative of the true upper boundary of the threshold (Dakin et al., 2014). This begins at £20,356/QALY for respiratory disease, with a maximum of £55,512/QALY for musculoskeletal disease- surprisingly was higher than the level for cancer, where a cost of £46,082/QALY had a 50% probability of acceptance.

A review of NICE decision-making showed that cost-effectiveness, when considered in isolation and relative to the threshold, correctly predicted decision making in 82% of cases (Dakin et al., 2014). This implies cost-effectiveness is a key factor, if not the sole driver of decision making; with issues such as certainty of evidence and economic modelling, budget-impact and current

affairs also being of importance to NICE alongside government pressures relating to decision making.

A report published in 2015 by the Centre for Health Economics at the University of York asserted that the cost per QALY threshold set by NICE was too high. This would mean that the approval of new drugs relative to the £20,000-30,000 per QALY threshold would be causing an opportunity cost to the healthcare system. Relative to NHS expenditure, they found that just £13,000 of NHS spending results in one QALY added to the lives of patients (Claxton et al., 2015). For every additional £10 million in NHS spend, a net loss of 440 QALYs would be incurred. The implication of this research is that spending by the NHS based on NICE recommendations of new interventions is not representative of value for money if judged against the current threshold.

The economic modelling required for a NICE submission for Medical Devices is slightly different to the HTA process for pharmaceutical products. For MTEP the economic evaluation carried out by the manufacturer needs to not only prove cost-effectiveness but is held to a higher standard in that the new intervention must be dominant to standard care. Dominance is achieved when an intervention provides greater outcomes for a reduced cost. NICE suggests performing a simple analysis such as budget-impact or cost-consequence/cost-minimisation (NICE, 2017). The appraisal of medical devices establishes the clinical outcomes offered by a new intervention and then reviews the associated costs. Patient outcomes, including improvements in quality of life (QoL), can be hard to determine for certain devices, such as stents and implants. For innovations that do offer advantages to patients, these methods may not be extensive enough to truly demonstrate the full value of an intervention. The economic evaluation presented in this chapter (study 5) was carried out concurrent to a MTEP of the sucrose octasulfate dressing.

5.2.4 Economic evaluation of DFU and LU

Economic analyses of DFU and LU interventions are already explored in Chapter 2, through the economic SLR. This review concluded that interventions that are of a higher acquisition cost may in fact be cost-effective when considering improvements in patient outcomes and the reduction of the need for ongoing care; the cost of which is approximately £7000 per annum for DFU and LU patients with an open wound. This review also highlighted the variance in

standard care; as the studies did not have an aligned treatment protocol for the patients in the comparator arm.

For DFU, the costs associated with ulceration are considerable, not only in terms of cost, but also when considering patient QoL. A persistent complicated DFU presenting with critical ischaemia or infection can become life-threatening and can lead to an amputation for a patient to avoid sepsis or death because of their ulcer. These situations are quite extreme, but their prevalence is growing (Narres et al., 2017). Patients with DFU are likely to suffer from multiple comorbidities which could also interfere with the healing process and incur additional costs to the healthcare system (Iglay et al., 2016).

LU patients are at less of a risk of amputation, with ischaemia not being such a problem. Patients who present with a LU have issues with their cardiovascular system which has led to the breakdown of the veins, usually in the lower leg. Like DFU patients, these patients probably have comorbidities that result in additional visits to Health Care Providers (HCPs); causing a financial burden to the NHS, but also a treatment burden for the patient themselves, who may be required to see multiple HCPs in addition to having their wound dressings changed on a regular basis. The PRO study (study 3) in chapter 4 indicated that patients with a LU are approximately 10 years older on average than a patient with a DFU. Their increased age impacts the healing process, and patients with LUs tend to have wounds of a long duration that can persist for many years (Rai, 2014).

The current standard care protocols for DFU and LU have common components, including use of dressings, debridement and infection control, additionally LUs require compression and DFU management includes offloading. Regarding dressings, current UK guidance does not indicate a preferred dressing for patients with these wounds (NICE, 2016). Improved wound care management that results in better healing outcomes is asserted to be cost saving. Additionally, patients could experience a QoL benefit due to improved healing rates and reduced healing time.

5.3 Study aims

The aim of study 5 was:

– To evaluate outcomes and costs associated with the use of PMM interventions in DFU and LU.

The objectives of study 5 were:

– To examine the economic impact of PMM dressings, namely the sucrose octasulfate dressing,
– To generate evidence that could be used to support a change in clinical guidelines.

5.4 Methods

In accordance with the preference indicated by the NICE process and methods guides, this economic evaluation employs both budget-impact and cost-effectiveness models (NICE, 2013). Using both methods addresses the range of requirements that are needed to assess a new intervention- both the short-term financial impact that is better presented using a BIM, and a more complex cost-effectiveness model of the long-term outcomes associated with DFU and LU. LUs have a high recurrence rate, with the wound bed often breaking down or new wound sites emerging. DFUs have been associated with an increased risk of mortality for patients; especially with more severe wounds that have resulted in an amputation; 50% of patients do not survive more than 5 years after amputation because of a DFU (Weledji and Fokam, 2014). Due to this risk of recurrence, and the associated downward trend in patient health, DFU and LU can be considered as long-term problems that warrant modelling over a longer period- justifying the use of a cost-effectiveness model.

BIMs have become more relevant in the persistent climate of economic austerity that is currently being endured by the NHS. The presence of budget cuts and a need to ensure that maximal outcomes are achieved with minimum budget has led to a need to understand the costs associated with adopting any new technology; in a short-term manner focussing on the bottom-line figures. The NHS needs to continue the uptake of new innovations but cannot justify doing so if there is a risk of sacrificing the standard level of care on offer to patients. To assess affordability; a BIM is a simple, succinct method of doing so, in contrast with a more complicated cost-effectiveness analysis.

This section first explains the methods and data used by the BIMs built to assess the economic impact of incorporating an efficacious PMM dressing into the standard of care for DFU and LU.

Following this; an explanation of the methods used to build the cost-effectiveness model is presented; again, to assess the economic impact of these technologies. The use of both methods should allow a multi-dimensional view; and is reflective of the process used by NICE in health technology assessment.

5.4.1 Budget-impact models

The following sections explore the methods used to create the BIMs for DFU and LU, which are both examples of static BIMs; where patients do not change health states and mean values are applied to the total population.

BIM programming

The BIMs for DFU and LU were created using the Microsoft Excel software, saved in a .xlsm format to enable macros in the document. The calculations were carried out in a sheet away from the main page, to enable clarity and transparency of the formulae. Macros were used to programme navigation of the document, and for a reset button to restore default values, meaning a user can customise the input values for individual scenario analysis.

BIM time horizon

In keeping with the budget-impact method; the models here present a 5-year view; with data presented for the current year, and years 1-4. A 5-year view is likely the longest time horizon that is feasible for a BIM; as the uncertainty around the extrapolation of data increases for every year into the future. Results for the cumulative budget-impact are presented at both year 3 and year 5; to counter the exponential uncertainty present in the model. A BIM is primarily a financial planning aid; and NHS financial plans and costing tools account for 5 years; so, the 5-year figure has been presented to provide information that is of relevance to decision makers.

BIM assumptions

The BIMs for DFU and LU make several assumptions in their calculations. Assumptions are a key part of economic modelling methods; due to the impossibility of forecasting accurately on an individual per-person basis. The models assume that all patients with a DFU and LU are treated the same; with the sole difference of primary treatment dressing. This assumption is justified as the models wish to assess the impact of the use of the PMM dressing, and not the impact of different treatment pathways or variations on standard care. Despite this not being

entirely reflective of the way that patients flow through the system in real life; as presented in study 4, the chart extraction, it allows the difference detected to be attributed to the impact of the study dressing. Additionally the outcomes data that power the model is drawn from the Reality study (Münter et al., 2017), a large pooled analysis of several observational trials, the result of multiple care pathways aggregated.

An assumption in the BIM is that all patients are the same and follow the same healing trajectory. The BIM does not distinguish between patient groups and does not allow for subgroup analysis as the budget-impact is calculated nationwide, including all patients currently diagnosed, or to be diagnosed in the time horizon, with a DFU or LU. Again; this assumption is justified given the data sources. The data powering the resource use and healing time has been aggregated from large patient groups (Munter et al., 2017; Guest et al., 2018a; Guest et al., 2018b). Included in these real-world evidence studies is a range of patients that are arguably representative of the wider patient population as they are not dictated by the rigorous inclusion and exclusion criteria of a randomised controlled trial (RCT).

BIM population

The two indications explored by this thesis are distinct and separate, needing different approaches in identifying patients that would be eligible for treatment with the sucrose octasulfate dressing. First, the method used to identify the DFU population is explained, followed by the method used by the LU model.

DFU BIM population

For the BIM focussing on DFUs a population funnel has been applied to filter down from the entire population of the UK to identify the patients for whom the PMM dressing would be a relevant intervention. This is represented in Figure 5.2 which shows the layers of filtration applied to the population.

First, the total UK adult population was ascertained using figures from the Office for National Statistics (ONS); neither DFU nor LU are expected to be seen in children and young people and this assumption was validated by experts (Office for National Statistics, 2016). A multiplier to account for annual population growth was applied, of 0.57% per year, to ensure that the model was representative of the growing population of the UK (Office for National Statistics, 2017).

The process then identified all patients in the UK who are currently diagnosed with diabetes, this figure was obtained from the Quality and Outcomes Framework (QOF) official statistics, captured by the NHS and published by NHS Digital measuring prevalence of various diseases including diabetes (NHS Digital, 2017). There are estimates of the number of people living with diabetes who remain undiagnosed; but these have not been included in the BIM due to the uncertainty associated with accounting for these patients. In addition to the prevalent population published by the QOF, this BIM also included new patients who received a diagnosis for diabetes during the time horizon, the incident population. A large observational study performed in 2012 of more than 50,000 subjects over approximately 10 years was used to derive the figure that was used in the model, 0.6% (Andersen, 2012).

To calculate the number of diabetic patients who develop an ulcer annually; incidence figures of 5-7% were obtained from literature, and this has been applied to the figure of diabetic patients to estimate the number of people per year who have a DFU (Kerr, 2012).

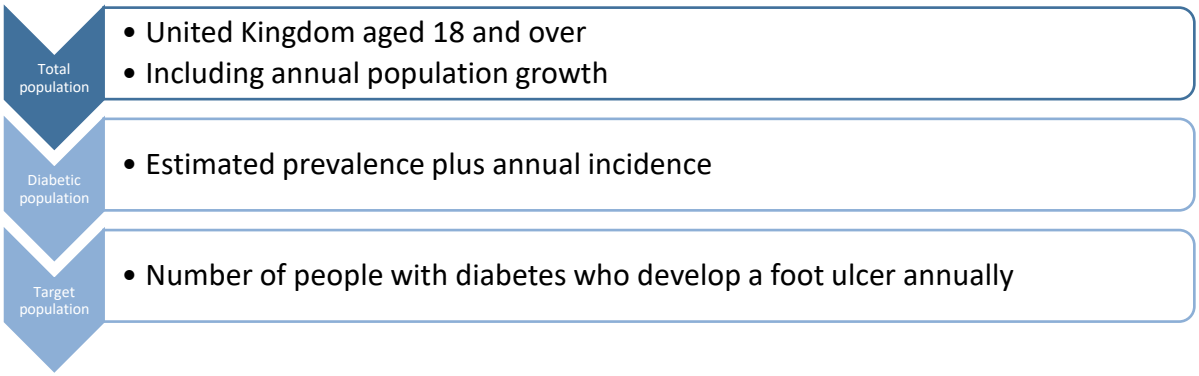


Figure 5.2. DFU BIM population funnel

LU BIM population

For the BIM that concentrated on patients with LUs, the same method was applied to identify the relevant patients. Figure 5.3 shows the stages that were used to filter the population.

In the same way as the DFU BIM, the LU model used the total UK population of adults aged 18 and over. Children were once again excluded because LUs are not seen in children in routine practice, and the prevalence figures used only included an adult population (Office for National Statistics, 2016). Again, a multiplier of 0.57% per year was applied to the total population to account for growth (Office for National Statistics, 2017).

To identify the patients in the UK who had a LU, a study of the adult population from The Health Improvement Network (THIN) database was consulted (Guest et al., 2015). This study examined 1000 patients who had a wound in a one-year period; the study categorised LUs as either being of venous, arterial, mixed or unspecified aetiology.

The focus of this thesis is on LUs, however, wounds determined as venous in origin only accounted for approximately a third of the LUs reported by the study. It was decided to include these figures in the prevalence estimate for LU as all LUs would be eligible for treatment with the PMM dressing. This gave an estimate of 1.5% annual prevalence among the adult UK population.

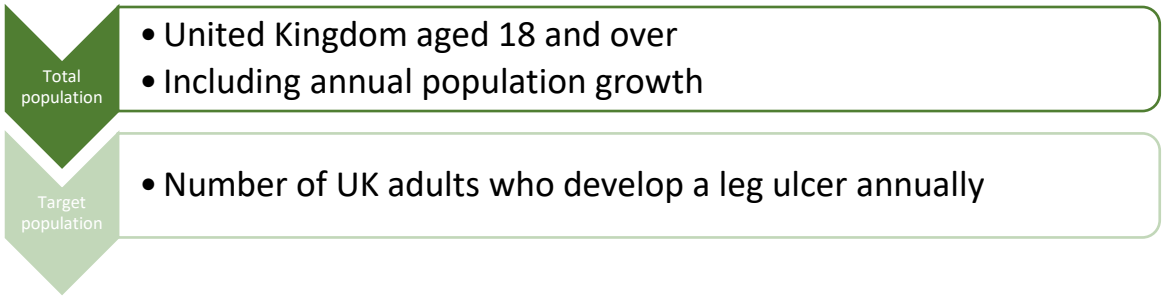


Figure 5.3. LU BIM population funnel

BIM treatment mix

The treatment mix input denotes what proportion of the eligible population receives the new technology versus the proportion that continues with standard care alone. For both the DFU and LU model, it was decided to assume 0% uptake in the first year. This would then be indicative of the full population costs of using standard care to treat a DFU or LU.

After discussion with the manufacturer about projected uptake, figures for years 2-5 were determined as shown in Table 5.3. The same proportions were used for both DFU and LU.

Table 5.3. Treatment mix applied to BIMs

	Current year	Year 2	Year 3	Year 4	Year 5
Sucrose octasulfate and standard care	0%	15%	25%	40%	60%

Standard care alone	100%	85%	75%	60%	40%

BIM effectiveness calculations

Both the DFU and LU models rely on a mean days-to-healing calculation, as opposed to a proportion of wounds healed by a set time-period. Using a mean time to healing calculation enables the model to calculate the number of weeks that a patient is using resources from the NHS to manage and heal their wound. Each of the models used a different source, due to the availability of data. These are shown in Table 5.4.

Table 5.4. Effectiveness data used in BIMs

Indication	Dressing	Mean time to healing (days)	Source
Diabetic foot ulcer	Sucrose octasulfate dressing and standard care	112	(Edmonds et al., 2018)
	Neutral dressing and standard care	210	(Edmonds et al., 2018)
Leg ulcer	Sucrose octasulfate dressing and standard care	115	(Münter et al., 2017)
	Neutral dressing and standard care	135	(Münter et al., 2017)

The study used to determine the effectiveness for the DFU model was the Explorer study, a double-blind RCT of 260 patients over 20 weeks that measured full wound closure as the primary endpoint (Edmonds et al., 2018). RCTs are the gold-standard of clinical evidence, at the top of several evidence classifications ranking the reliability of sources (Guyatt et al., 2008).

An RCT was not available to provide data on full wound closure for LUs being treated with the sucrose octasulfate dressing. Due to this, a large pooled analysis of observational studies was used to compare the active dressing with the control of standard care (Münter et al., 2017). The study included 7,903 LUs and had a primary endpoint measuring time to wound closure.

BIM resource use

Due to the two indications, DFU and LU, having differing interventions required to treat them; the two models have varied resource use, in terms of the HCPs and devices used. First, the resource use and associated costs are shown for the DFU model and subsequently for the LU model.

DFU BIM resource use

For the BIM focussed on DFU, items that were considered fell into the broad categories of hospital resource use, outpatient visits, medications prescribed, and devices used. A retrospective cohort analysis of 130 patients in the UK with a newly diagnosed DFU was analysed to estimate the annual resource use of managing a DFU in the NHS (Guest et al., 2018b). The study presented the costs over a one-year period, and to obtain a mean weekly cost for each item, the figures were divided by 52 to provide a figure that could be applied to the number of patients in the model. Using figures from a single source was deemed to provide internal validity, as all resource items have been measured from the same cohort of patients in routine practice.

The unit costs of the items were determined from a range of sources, all specific to the NHS. This included the NHS schedule of reference costs 2015-16, the manual of Unit Costs of Health and Social Care 2016 and the British National Formulary (BNF) Drug Tariff for medications and devices. The items and the number of units per week calculated from the Guest (2018) paper are shown in Table 5.5.

LU BIM resource use

For the BIM focussed on LU, items that were considered fell into the same categories of hospital resource use, outpatient visits, medications prescribed, and devices used as in the DFU BIM. A retrospective cohort analysis of 505 patients in the UK with a LU was analysed to estimate the annual resource use of managing a LU in the NHS (Guest et al., 2018a). The study presented the costs over a one-year period, and to obtain a mean weekly cost for each item, the figures were divided by 52 to provide a figure that could be applied to the number of patients in the model. As per the DFU model, the Guest et al., (2018b) study provided all resource use figures, derived from the THIN database.

The unit costs of the items were determined from the same range of sources as the DFU BIM with all costs specific to the NHS. This included the NHS schedule of reference costs 2015-16, the manual of Unit Costs of Health and Social Care 2016 and the BNF Drug Tariff for medications and devices. The items and the number of units used, calculated from the Guest (2018a) paper are shown in Table 5.6.

Table 5.5. DFU BIM weekly resource use and unit cost

Item	/Week	Unit cost	Cost source
Hospitalisation			
Admissions	0.0050	£2330.52	National Schedule 2015/16. Weighted average of Diabetic lower limb complication codes
Amputation	0.0042	£5507.72	National Schedule 2015/16. Weighted average of Amputation codes
Outpatient visits			
GP	0.0385	£38.00	PSSRU: Unit Costs of Health & Social Care 2017. Table 10.3b
Hospital	0.0398	£138.00	PSSRU: Unit Costs of Health & Social Care 2017. Chapter 7.1
Podiatrist	0.0050	£45.00	PSSRU: Unit Costs of Health & Social Care 2017. Chapter 13, band 6
Practice nurse	0.1560	£50.05	National Schedule 2015/16. Weighted average of TVN codes
Community nurse	1.0979	£14.65	PSSRU: Unit Costs of Health & Social Care 2017. Chapter 10, band 6
Medications and devices			
Antibiotics	0.1383	£1.57	BNF: Cefalexin, 1 course 28 tablets
Analgesia	0.4398	£2.07	BNF: gastro-resistant Diclofenac Sodium, 1 course 28 tablets
Primary dressing	2.8458	£4.20/ £3.13*	Urgo Medical dressing costs
Secondary dressing	2.8458	£3.13	Urgo Medical dressing costs
*Two costs available as two treatment arms in the model- either using the sucrose octasulfate dressing or a neutral dressing.			
Abbreviations: BNF: British National Formulary, GP: General Practitioner; PSSRU: Personal Social Services Research Unit, TVN: Tissue Viability Nurse			

Table 5.6. LU BIM weekly resource use and unit cost

Item	/Week	Unit cost	Cost source
Hospitalisation			
Admissions	0.0039	£452.18	National Schedule 2015/16.
GP	0.0323	£38.00	PSSRU: Unit Costs of Health and Social Care 2017. Table 10.3b.
Hospital	0.0169	£138.00	PSSRU: Unit Costs of Health and Social Care 2017. Chapter 7.1.
Outpatient visits			
Practice nurse	0.2952	£50.05	National Schedule 2015/16. Weighted average of TVN codes.
Community nurse	2.8683	£20.43	PSSRU: Unit Costs of Health and Social Care 2017. Chapter 10, band 6.
Medications and devices			
Antibiotics	0.1140	£1.57	BNF: Cefalexin, 1 course 28 tablets.
Analgesia	0.1767	£2.07	BNF: gastro-resistant Diclofenac Sodium, 1 course 28 tablets.
Primary dressing	2.8860	£4.20/ £3.13*	Urgo Medical dressing costs.
Secondary dressing	2.8860	£3.13	Urgo Medical dressing costs.
Compression	0.7163	£6.96	Urgo Medical. K-Four kits, 15-25cm.
Hosiery	0.2656	£11.73	Urgo Medical. Thigh length, class 2 compression hosiery.
*Two costs available as two treatment arms in the model- either using the sucrose octasulfate dressing or a neutral dressing.			
Abbreviations: BNF: British National Formulary, GP: General Practitioner; PSSRU: Personal Social Services Research Unit, TVN: Tissue Viability Nurse			

BIM data analysis

The methods used for the budget-impact calculations were the same for both the DFU and LU models. Once the population funnel has been used to establish the number of patients eligible for treatment with the new intervention, the proportions assigned in the treatment mix are applied to reach a final figure for each treatment arm, namely using sucrose octasulfate and standard care versus just standard care alone. For years 2-5 the multiplier was applied to simulate population growth, using the total population figure from the previous year (Office for National Statistics, 2017). The calculations used are presented below and are supported by the International Society of Pharmacoeconomic and Outcomes Research (ISPOR).

For DFU in year 1

$$\Big(\big((TotalPop \times diabetesprevalence) + (TotalPop \times diabetesincidence)\big) \times DFU\ incidence\Big) \times treatmentmix = number\ of\ patients\ eligible\ for\ treatment$$

(ISPOR, 2017)

For DFU in years 2-5

$$\Big(\Big(\big((PriorYearTotalPop \times 1.0057) \times diabetesprevalence\big) + (TotalPop \times diabetesincidence)\Big) \times DFU\ incidence\Big) \times treatmentmix = number\ of\ patients\ eligible\ for\ treatment$$

(ISPOR, 2017)

For LU in year 1

$$(TotalPop \times LUincidence) \times treatmentmix = number\ of\ patients\ eligible\ for\ treatment$$

(ISPOR, 2017)

For LU in years 2-5

$$\left((PriorYearTotalPop \times 1.0057) \times LUincidence\right) \times treatmentmix = number\ of\ patients\ eligible\ for\ treatment$$

(ISPOR, 2017)

Using the mean days until healing as ascertained through literature for both the sucrose octasulfate dressing and standard care, this is divided by 7 to represent the number of weeks taken for healing. Multiplying the healing time by the number of patients in each arm gives the number of weeks in treatment for each intervention over the year.

$$\left({}^{Mean\ days\ to\ healing}/_{7}\right) \times number\ of\ patients\ eligible\ for\ treatment = treatment\ weeks$$

(ISPOR, 2017)

Once the number of treatment weeks has been established for both arms in both the DFU and LU models, the cost of the resource use is calculated. For each item in the category, the unit cost was multiplied by the number of units used, and again multiplied by the number of treatment weeks when using each intervention.

$$(unit\ cost\ \times weekly\ unit\ use) \times treatment\ weeks\ = annual\ cost$$

(ISPOR, 2017)

The sum of all annual costs, for both treatment arms, results in the annual budget-impact. This is calculated for the full 5-year time horizon.

The results of the BIM can be expressed in various ways. The results can be presented as an annual figure or aggregated for the first 3 or 5 years. This study presents a cost-comparison result; which is the difference between the costs associated with the new intervention versus the costs of 100% of patients remaining on standard care for each of the 5 years. A mean cost per patient across the entire population eligible for treatment, regardless of the intervention they were assigned is also calculated.

Further to the financial results that are presented, the health outcomes can also be calculated using the BIM. The number of days with an active ulcer can be calculated across the entire

population; and again, using a comparison against a scenario where 100% of patients receive standard care, the number of days with open ulcer that are gained/avoided by uptake of the sucrose octasulfate dressing can also be calculated.

BIM sensitivity analysis

Sensitivity analyses were carried out to test the certainty of the results presented by the BIM. This consisted of pre-defined scenario analyses that differed dramatically from the base case to stress-test the inputs in the model.

The variations in the inputs for the scenarios that have been tested in the DFU model in addition to the base case are shown in Table 5.7. These scenarios have been chosen and designed to test the impact of making certain parameters either more conservative or more optimistic for the sucrose octasulfate dressing.

Table 5.7. DFU BIM scenarios for sensitivity analysis

Input	Base case	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5
Annual incidence of DFU	6.0%	2.5%	4.0%	6.0%	7.5%	10.0%
Treatment uptake years 1-5	0% / 15% / 25% / 40% / 60%	10% /25% / 50% / 60% / 80%	0% /5% / 15% / 25% / 40%	5% / 15% / 25% / 50% / 70%	0% /10% / 20% / 30% / 40%	0% / 5%/ 10% / 15% / 20%
Cost of standard care dressing	£3.13	£0.35 (BNF, 2019)	£1.21 (BNF, 2019)	£3.54 (BNF, 2019)	£1.93 (BNF, 2019)	£0.82 (BNF, 2019)
Mean days to healing: sucrose octasulfate	115	120	125	85	100	130
Mean days to healing: standard care dressing	135	130	140	100	120	140

Similarly, the scenarios that were tested in the LU model in addition to the base case are shown in Table 5.8. These scenarios have been chosen and designed to test the impact of making certain parameters either more conservative or more optimistic for the sucrose octasulfate dressing.

Table 5.8. LU BIM scenarios for sensitivity analysis

Input	Base case	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5
Estimated prevalence of LU	1.5%	0.5%	2%	0.7%	2.5%	3%
Treatment uptake years 1-5	0% /15% / 25% / 40% / 60%	10% /25% / 50% / 60% / 80%	0% / 5% / 15% / 25% / 40%	5% / 15% / 25% / 50% / 70%	0% / 10% / 20% / 30% / 40%	0% /5% / 10% / 15% / 20%
Cost of standard care dressing	£3.13	£0.35 (BNF, 2019)	£1.21 (BNF, 2019)	£3.54 (BNF, 2019)	£1.93 (BNF, 2019)	£0.82 (BNF, 2019)
Mean days to healing: sucrose octasulfate	112	120	150	90	160	100
Mean days to healing: standard care dressing	210	150	180	220	190	170

5.4.2 Cost-effectiveness analyses

Next in this chapter, the methods for the cost-effectiveness analyses (CEA) carried out for DFU and LU is explained. Both cost-utility analyses in this thesis are examples of Markov models; with patients moving through different health states associated with different costs and health outcomes. A Markov model was chosen in preference to a decision tree due to the chronic

nature of the condition; presenting repetitive events, such as wound recurrence and moving between health states such as infection or complication can be difficult using a decision tree model that is better when a disease has a single clear direction of travel.

CEA programming

The cost-utility models for DFU and LU were created using Microsoft Excel software, saved in a .xlsm format to enable macros in the document. The front-end of the models has a menu powered by the Visual Basic Application (VBA) code that joins the cover page, input pages, calculations pages and the presentation of results. The calculations tab includes links to the Markov chains that power the model to enable transparency for a user. Due to the complexity of the calculations, one-way deterministic and probabilistic sensitivity analyses have been carried out using macros programmed in the backend of the document.

CEA Model structure

The models are constructed using the Markov analytical framework. Markov models use different health states that represent the possible outcomes of an intervention when used in a specific indication. Health states are mutually exclusive, so a patient can only reside in one at a time and subjects move between health states at the end of a cycle, which is a pre-defined length (York Health Economics Consortium, 2019). The transition matrices provide the probabilities that drives the movement between health states, and these are calculated from relevant clinical data drawn from the clinical studies of the sucrose octasulfate dressing (Meaume et al., 2012; Edmonds et al., 2018). The structure, health states and transition probabilities were validated by clinical experts, discussed in section 5.4.3.

DFU CEA model structure

In the cost-utility model designed to examine the impact of the sucrose octasulfate on the DFU population, there are 3 core health states which are: 'open wound', 'closed wound' and 'complicated wound'. The model also makes a distinction for patients who have not had an amputation- 'pre-amputation', versus patients who have an amputation 'post amputation'. Open wounds are defined as DFUs that have been diagnosed by a clinician; this health state makes no distinction between wounds of different ages or sizes, between new wounds or a recurrence of a previous DFU or between wounds that are following different healing trajectories. Closed wounds are wounds that have achieved full healing, or, in the case of after

an amputation, where the wound has been closed in the operating room by the surgeon. Complicated wound is a health state that represents wounds that are infected, but also those that have become ischaemic or gangrenous. Complicated wounds are defined as those who have been identified as being very unlikely to follow a normal healing trajectory. An amputation is often a consequence of a persistent complicated DFU, in this model amputation is not a health state, but has been programmed as an event, which incurs the cost of surgery, subsequent physiotherapy and a prosthesis, in the case of a major amputation.

The model structure assumes that a patient starts with an open wound; and this wound can either close or become complicated. Complicated wounds can either heal, or result in an amputation event, causing a patient to move to the post-amputation block of health states. After amputation, patients have a closed wound (healing by primary intention, closed at the operating room); or their wound persists as an open wound (post-amputation) which could either close, or become complicated before closure. Closed health states have a risk of recurrence; which is higher post-amputation. In all health states, patients have a risk of death. The model structure is shown in Figure 5.4.

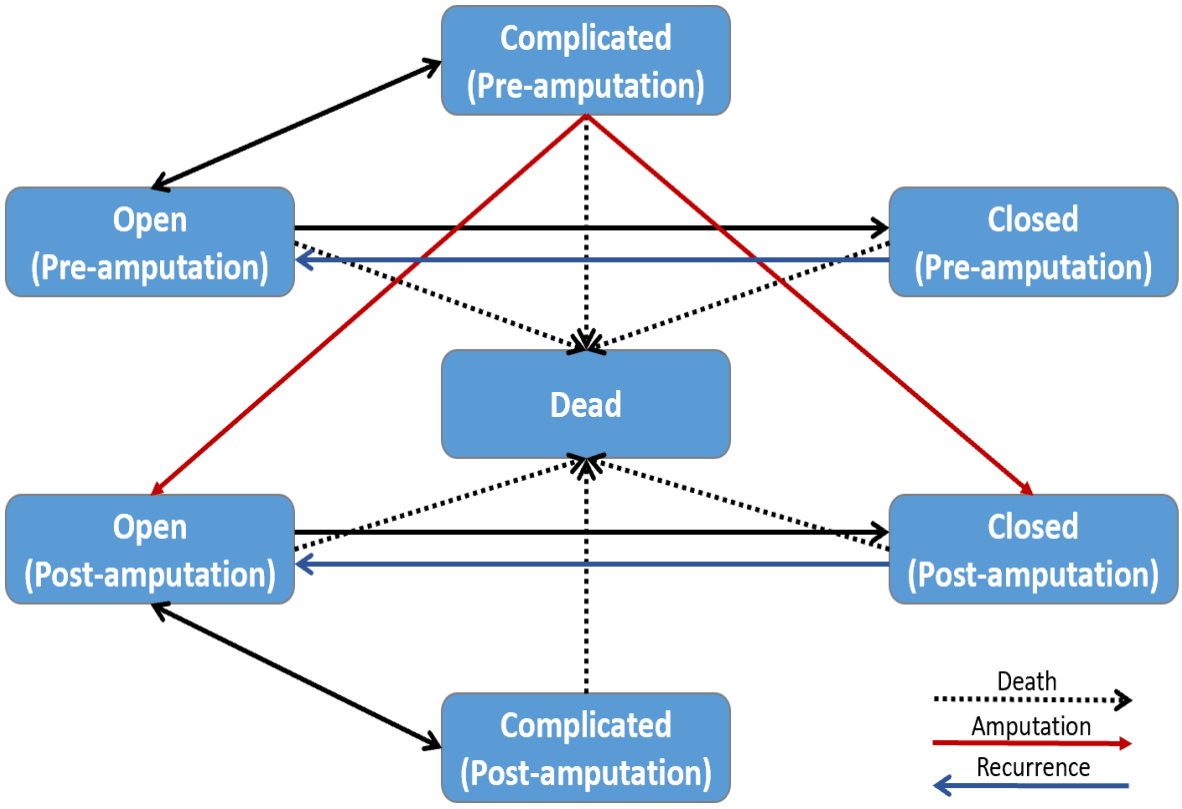


Figure 5.4. DFU cost-utility model structure

LU CEA model structure

In the cost-utility model developed for LU patients, there health states follow a similar, but simplified version of the health states for DFU. This is because LUs are not as high risk for amputation as DFU; due to complications with diabetes, such as neuropathy or the heightened risk of ischaemia.

In the model, patients were in one of the following health states: 'open wound, 'closed wound' and 'infected wound'. Open wound refers to any LU that has not healed, and is not infected, regardless of wound duration, size or other risk factors associated with healing. Closed wounds are those that have achieved full healing, confirmed by a clinician. Wounds that are infected present with symptoms such as excessive slough or exudate, itching, increased pain; these wounds are also not going to heal unless the infection is resolved using medications, either oral prescriptions or a topical application of an antimicrobial agent.

In the model designed for this study, a patient starts with an open wound; which can either heal and become a closed wound or can become infected and the patient moves to the

infected wound health state. Wounds that are infected incur higher costs to the healthcare system and result in lower QoL for the patient. The infection, when treated, resolves and the patient returns to the open wound health state. From here, a wound can then close and the patient has healed. LUs have a high chance of recurrence, so patients can move from the closed wound state back to the open wound state. In all health states, patients have a risk of death. The model structure is shown in Figure 5.5.

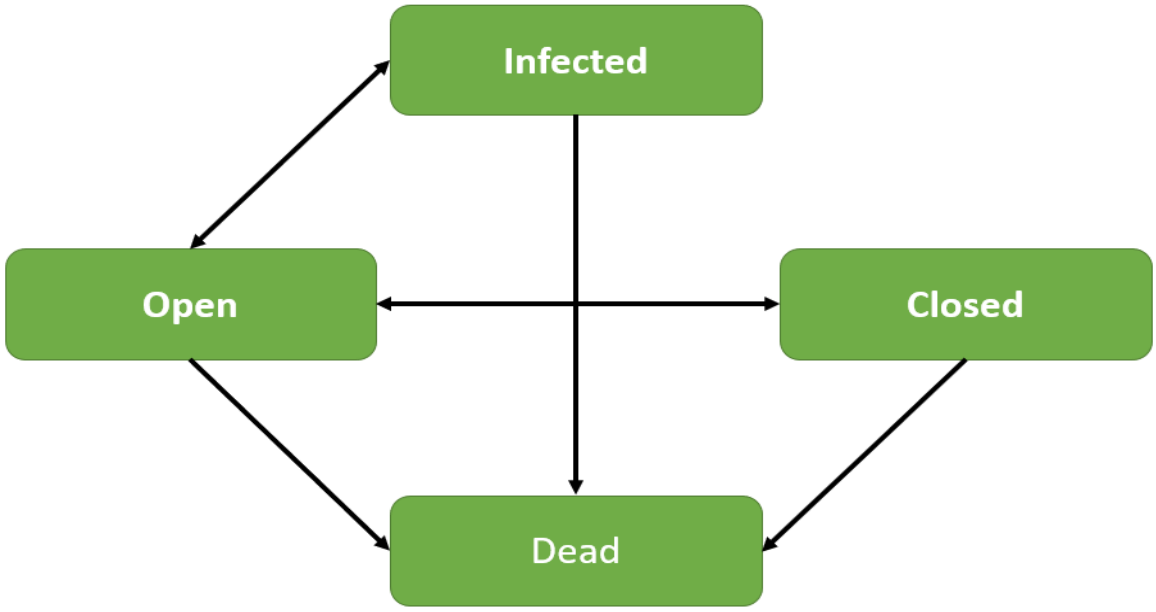


Figure 5.5. LU cost-utility model structure

CEA model features

Both models, DFU and LU, had a base case time-horizon of 1 year. This was chosen as it best represents one wound episode for a patient. Another factor is that for a shorter time horizon, there is less of a need to extrapolate clinical trial data, which can cause inherent uncertainty in a model with a longer time-horizon. To allow for transparency and clarity, both excel models had the functionality to change the time horizon, a user could choose to see results for: 6 months, 1 year, 2 years, 5 years and 10 years. The longer time-horizons would allow an observation of long-term health and cost-consequences, however, are associated with higher uncertainty than the base-case of 1-year.

Discounting of future costs and outcomes was applied at 3.5% beyond the first year, in line with instruction in the NICE methods guide (NICE, 2013). The perspective applied to the model was that of the NHS; excluding societal costs such as social care, welfare payments, patient

transport and productivity losses. Using the perspective of the NHS, the models only applied direct medical costs. The cycle length was determined to be 1 week, which is informed by clinical practice and validated by expert opinion. Wound status can change in a short period of time, so a longer cycle length would not be representative of the real-world.

CEA assumptions

Methods using the Markov framework necessitate the use of assumptions with regards to certain aspects of the patient characteristics, treatment pathway and resource use. These assumptions are necessary to restrict calculations to those which could have an impact on the outcomes. Assumptions need to be reasonable and justifiable in their use, as they apply for all patients included in the model. All the assumptions built into the economic models presented here have been validated by experts as discussed in section 5.4.3

Both models assumed that all patients begin in the open wound health state. For the DFU model, there is the ability to determine the proportion of the population that has already had an amputation and begins in the post-amputation block. This assumption is because patients with a closed wound are not treated and are not likely to be under treatment. The reality of the situation is that many wounds are recurrences, as shown in the PRO study (study 3) in Chapter 4. This assumption is unlikely to impact the results and is reasonable and justifiable.

Another assumption applied to both the DFU and LU model is that the deceased health state does not incur any costs. There may be some costs billed after a patient's death in actuality- but for the purposes of the model, costs are applied at the time of resource use.

For the DFU model, there is an assumption that all patients who have an amputation were previously in the complicated health state and a regular open DFU does not pose a risk of amputation. This assumption has been validated externally by clinicians who confirmed that a wound would not undergo an amputation without persistent infection or critical ischaemia. With regards to amputation, the DFU model also assumes that an amputation can only occur once. In real-world practice, there is a risk of patients who have had an amputation having to undergo further amputations, either on the same limb or bilaterally. This assumption was applied as the model base case was one year, and for a patient to undergo an amputation more than once in any given year was deemed very rare by clinical experts.

For the post-amputation health-states, the DFU model makes some assumptions around resource use. For patients who have undergone amputation, which is divided into either major or minor amputation, it was assumed that every patient would require some physiotherapy. Due to difficulties with mapping the level of physiotherapy required for each type of amputation, a uniform figure was applied to all amputations. This assumption has been validated by clinicians who work with patients after an amputation because of a DFU. Similarly, the model assumes that the provision of a prosthesis would only be available after a major amputation; this assumption was informed by a NICE costing report that measured resource use associated with DFUs (NICE, 2015).

In some cases, it is necessary to make assumptions in the absence of data. When this is the case, it is preferable to make conservative assumptions that are unlikely to have a misleading impact when interpreting the results of the cost-utility model. In the DFU model, it was assumed that a closed wound would have the same estimated resource use in both the pre- and post-amputation blocks. This is a conservative assumption as consultation with clinicians implied that closed wounds post-amputation could incur higher costs. However, no data or literature could be found to support a differentiation; so, the assumption was to keep these the same.

The LU model had less assumptions than the DFU model, in main part because it used a different model structure, where patients followed a simpler pathway. The assumption that all wounds that were infected would not move directly to healing unless the infection was resolved was validated by clinicians. Another assumption regarding infections that was validated by the consulted clinical experts was the fact that the average infection lasted 2 to 4 weeks, so the model used a 3-week infection period as a base case.

CEA clinical parameters and variables

The models used data from the clinical evidence to inform the cost analysis. A core element of the Markov model framework is to create a transition probability matrix; a table to inform the model of the chance of moving to one health state from another. For the DFU model, transition probabilities were calculated using data from patients in the Explorer study. These patients also had a confirmed neuro-ischaemic DFU, and at baseline there were no statistically significant differences between the treatment arm and the control arm (Edmonds et al., 2018).

The LU model used transition probabilities calculated using data from patients in the Challenge study (Meaume et al., 2012). These patients also had a LU with no statistically significant differences between the two study arms at baseline. Prior to calculating the transition probability, probability and hazard rates were estimated. This was calculated as below, where P equals probability:

$$Rates = \frac{[-In(1-P)]}{Time}$$

(Briggs et al., 2006)

The annual probability for each transition was then calculated as below, where r equals hazard rate, and u equals cycle length:

$$Annual\ probability = 1 - \exp(-ru)$$

(Briggs et al., 2006)

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

$$\frac{7 \times Annual\ probability}{365.25}$$

(Briggs et al., 2006)

In both the DFU and LU model, the transition probabilities do not change over time; and are assumed to be representative of patients with wounds of varying duration. The studies that the transition probabilities were derived from included patients with wounds of varied duration. For a DFU, the mean duration was 7.3 months with standard deviation of 6.5 and for LU, a mean duration of 15.1 months with standard deviation of 8.7 (Meaume et al., 2012; Edmonds et al., 2018).

The relative efficacy of each treatment arm was derived from the studies. The Explorer study which examined patients with a DFU measured wound healing as the primary endpoint, so no extrapolation calculations were necessary. Conversely, for LU, the Challenge study did not measure full wound healing as an endpoint of the study and measured Relative Wound Area Reduction (RWAR) as a surrogate endpoint for the healing rate. In the published literature there are well documented links between the initial healing at 8 weeks and the likelihood of

healing at 24 weeks (Kantor and Margolis, 2000). A 2008 paper found that the majority of LUs exhibited surface area reduction via an exponential decay model and provided a formula to calculate the healing rate from the initial measured change in wound area (Cardinal et al., 2008). This formula is as below:

$$Healing\ rate\ (\%) = \frac{LN(1 - Mean\ surface\ area\ reduction\ in\ \%)}{Weeks}$$

(Cardinal et al., 2008)

With regards to the patient characteristics, the Explorer study informed the DFU model about patient age at inclusion and amputation history (Edmonds et al., 2018). The Challenge study informed the LU model about patient age at inclusion (Meaume et al., 2012). Age at inclusion is an important parameter as it determines the rate of age-related mortality applied to the cohort.

All-cause mortality among diabetic foot patients was informed by data from the Third Annual Report of The National Diabetes Foot Care Audit (NHS Digital, 2018). At 12 weeks, 520 patients were confirmed deceased from a cohort of 22,653. This data was transformed into weekly transition probabilities as per the above calculations. For patients with LUs, the literature does not show a higher mortality rate when compared with control (Nelzen et al., 1999). Considering this; a weekly transition for standard age-related mortality has been calculated for patients to move into the deceased health state (Office for National Statistics, 2018).

The risk of recurrence was calculated for the DFU model and the LU model. The DFU model was informed by a prospective follow up of 73 patients over 3 years, where 42 patients experienced a recurrent DFU (Dubský et al., 2013). The LU model used another prospective follow up of patients using standard care; over 12 months, 16.1% of patients had experienced a recurrent ulcer (Clarke-Moloney et al., 2014).

All variables used in the DFU and LU cost-utility models can be found in Appendix C.

CEA Resource use

To establish relevant resource use data for the management of DFU and LU by the NHS; a search of the literature was undertaken. After an appraisal of the identified studies it was found that only 1 study for each DFU and LU included multiple health states, as was required by the

cost-utility modelling in the present study. The same studies that were identified as relevant for the BIMs were utilised for the cost-utility analyses (Guest et al., 2018a; Guest et al., 2018b). Using the same sources for resource use can be argued to provide enhanced internal validity of the CEA and BIMs that make up this economic evaluation.

For DFU, the retrospective real-world evidence study using the THIN database was chosen to estimate health resource use for healed, unhealed and amputated wounds (Guest et al., 2018b). Not only did this study include multiple health states, but it was also published shortly before the development of these cost models, meaning that it is data is the most up to date. However, this study did not present any standard deviation of the mean values in the results, meaning that a generic ±30% was used in sensitivity analysis. A second source of data, NICE costing report for DFU provided information about NHS costs and usage assumptions for patients that had experienced an amputation (NICE, 2015).

For LU, the paper that reported on 505 patients with a LU in the THIN database was used (Guest et al., 2018a). This paper was selected due to the provision of health state estimates, and this data is again the most recently published so is likely to be of most relevance to provide information on decision making for the NHS. For the LU paper, standard deviation of the mean was provided for the resource use estimates, which were used in sensitivity analysis.

Neither of the included papers included absolute values for health resource use for infected wound or complicated wound health states; these were aggregated with the unhealed health states for both DFU and LU. To combat this, and to provide a differentiation between the resource use for open and complicated/infected wounds, the published values were varied around the mean to estimate resource use for open and complicated/infected wounds. Despite not revealing the values, the publications do explain that open DFUs cost 67% less than infected/complicated DFUs and open LUs cost 69% less than infected LUs.

Table 5.9 shows the weekly resource use for the DFU health states and Table 5.10 for the LU health states. These figures have been derived by transforming the reported annual values into weekly values (*7/365.25).

For DFU these figures were adjusted for the reported difference in open and complicated/infected health states multiplying by 0.5, and 1.5 respectively, to allow the open

wounds to cost 67% less. For LU the adjustment for open and infected health states was to multiply by 0.475 and 1.525 respectively, to allow the open wounds to cost 69% less.

This method of variation let to certain anomalies and expert opinion questioned the use of antibiotics in a non-infected/complicated health state. The sensitivity analysis for these items included testing the use of 0 antibiotics, unless in the infected or complicated health states, to mitigate the uncertainty arising from this method.

The use of secondary dressings was informed by data retrieved from the chart extraction study presented in chapter 4. This data showed that in open DFUs and infected DFUs 22% and 9% fewer secondary dressings were used than primary; and in open LUs and infected LUs 57% and 30% fewer secondary dressings were used than primary.

Table 5.9. DFU weekly resource use for health states

	Open pre	Complicated pre	Closed pre	Open post	Complicated post	Closed post
Admissions	0.0002	0.0006	0.00	0.0144	0.0433	0.00
GP	0.0239	0.0718	0.0294	0.0158	0.0473	0.0294
Outpatient	0.0192	0.0577	0.0196	0.0433	0.1298	0.0196
Podiatrist	0.0032	0.0095	0.0040	0.0017	0.0052	0.0040
Practice Nurse	0.0998	0.2994	0.0937	0.0826	0.2478	0.0937
Community Nurse	0.8103	2.4309	0.3789	0.5869	1.7608	0.3788
Antibiotics	0.0795	0.2386	0.0627	0.1204	0.3612	0.0627
Analgesia	0.3268	0.9805	0.2410	0.1324	0.3972	0.2410
Primary dressing	2.0800	6.2400	1.0392	1.5084	4.5251	1.0392
Secondary dressing	1.6224	5.6784	0.8106	1.1765	4.1178	0.8106
Orthosis	Assumed 1 per year. (0.0192 per week for all health states)					

Table 5.10. LU weekly resource use for health states

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

CEA Unit costs

Unit costs for resource use were collected from published data sources. Like the BIMs, the costs were split into: Hospital inpatient, outpatient visits, medication and devices. Additionally, for the DFU model. one-off costs associated with an amputation event were costed from published literature. The resources, unit costs and data sources for the DFU model can be seen in Table 5.11 and the resources, unit costs and data sources for the LU model are shown in Table 5.12.

Table 5.11. DFU cost-utility model unit costs

Item	Cost	Source
Admissions	£2330.52	National Schedule 2015/16.
GP	£38.00	PSSRU: Unit Costs of Health and Social Care 2017.
Hospital	£138.00	PSSRU: Unit Costs of Health and Social Care 2017.
Podiatrist	£45.00	PSSRU: Unit Costs of Health and Social Care 2017.
Practice nurse	£50.05	National Schedule 2015/16.
Community nurse	£20.43	PSSRU: Unit Costs of Health and Social Care 2017.
Antibiotics	£1.57	BNF: Cefalexin, 1 course 28 tablets
Analgesia	£2.07	BNF: gastro-resistant Diclofenac Sodium, 28 tablets
SO dressing	£4.28	Urgo Medical dressing costs
Neutral Dressing	£3.13	Urgo Medical dressing costs
Orthoses	£525.00	NICE costing report: diabetic foot care (August 2015)
Minor Amputation	£4440.32	National Schedule 2015/16.
Major Amputation	£9269.23	National Schedule 2015/16.
Physiotherapy	£532.80	NICE costing report: diabetic foot care (August 2015). £15,230,000/28585 patients.
Prosthesis	£2876.00	NICE costing report: diabetic foot care (August 2015). £16,968,000/5900 patients.
Abbreviations: BNF: British National Formulary; PSSRU: Personal Social Services Research Unit; SO: Sucrose octasulfate		

Table 5.12. LU cost-utility model unit costs

Item	Cost	Source
Admissions	£452.18	National Schedule 2015/16.
GP	£38.00	PSSRU: Unit Costs of Health and Social Care 2017.
Hospital	£138.00	PSSRU: Unit Costs of Health and Social Care 2017.
Practice nurse (TVN)	£50.05	National Schedule 2015/16.
Community nurse	£20.43	PSSRU: Unit Costs of Health and Social Care 2017.
Antibiotics	£1.57	BNF: Cefalexin, 1 course 28 tablets
Analgesia	£2.07	BNF: gastro-resistant Diclofenac Sodium, 28 tablets
SO dressing	£4.28	Urgo Medical dressing costs (UrgoStart)
Neutral Dressing	£3.13	Urgo Medical dressing costs (UrgoTul)
Compression	£6.96	Urgo Medical. K-Four kits, 15-25cm
Hosiery	£11.73	Urgo Medical. Thigh length, class 2 compression hosiery
Abbreviations: BNF: British National Formulary; PSSRU: Personal Social Services Research Unit; SO: Sucrose octasulfate		

CEA utility scores

To facilitate a cost-utility analysis, it is necessary to prescribe a utility score to the different health states in the model. The utility scores represent patient QoL. The two interventions are then compared not only on cost difference, but in the difference of outcomes expressed in quality adjusted life years. Utility scores can be derived from generic patient reported outcome measures; but the preference stated by NICE is to use EQ-5D (NICE, 2018). Study 3 of this thesis, presented in chapter 4, used EQ-5D to derive utility scores in a cross-sectional analysis of DFU and LU patients.

DFU CEA utility scores

For the DFU cost-utility model; the scores collected from the PRO study (study 3) in chapter 4 are used as the base case for the health states. Due to the uncertainty, explained in chapter 4, in the closed wound group; the health states for a closed wound has been sought from literature (Redekop et al., 2004). The utility score given to the deceased health state is assumed to be 0; as per standard practice. The values used in the DFU model are shown in Table 5.13.

Table 5.13. DFU health state utility scores

Health states	Utility score	Source
Open Pre-amputation	0.456	PRO study
Complicated Pre-amputation	0.525	PRO study
Closed Pre-amputation	0.797	(Redekop et al., 2004)
Open Post-amputation	0.620	PRO study
Complicated Post-amputation	0.554	PRO study
Closed Post-amputation	0.498	(Redekop et al., 2004)
Deceased	0.000	Assumption

Additionally, in the DFU model; a disutility was applied after an amputation event to reflect the period after an amputation when a patient experiences pain and is possibly immobilised until they recover from the surgery. The disutility value, -0.28, was found in literature, and applied for a 4-week period after the amputation event (Clarke et al., 2002).

LU CEA utility scores

For the LU cost-utility model; the scores collected from the PRO study in chapter 4 are used as the base case for the health states. Due to the uncertainty in the results, explained in chapter 4, the health states collected from the PRO study have been combined with existing utility scores sought from literature to provide a mean value (Palfreyman, 2008). The utility score given to the deceased health state is assumed to be 0; as per standard practice. The values used in the LU model are shown in Table 5.14.

Table 5.14. LU health state utility scores

Health states	Utility scores	Source
Open wound	0.456	PRO study and (Palfreyman, 2008)
Infected wound	0.525	PRO study and (Palfreyman, 2008)
Closed wound	0.797	PRO study and (Palfreyman, 2008)
Deceased	0.000	Assumption

CEA incremental cost-effectiveness ratios

The results of the models will be presented using an incremental cost-effectiveness ratio (ICER) value. The ICER is a figure used extensively by NICE in the appraisal programmes to compare different interventions across disease areas. NICE has a stated willingness-to-pay threshold of £20,000 - £30,000 per QALY gained. For both the DFU and LU models the incremental cost-effectiveness ratio was calculated using the below formula.

$$\frac{Incremental\ cost}{Incremental\ QALYs} = ICER$$

(Briggs et al., 2006)

CEA sensitivity analysis

Uncertainty around assumptions and variable parameters in the models were tested by both one-way deterministic and probabilistic sensitivity analyses. Deterministic sensitivity analysis (DSA) is a method that varies a specific parameter to observe the changes on the output values caused by an individual factor, to see how 'sensitive' the model is to this parameter (York Health Economics Consortium, 2016). Probabilistic sensitivity analysis (PSA) is a different method and explores uncertainty around all parameters and the impact on the results; random sampling from set distributions is used in multiple runs of the model and the variance of the results is linked to the sensitivity of the model (York Health Economics Consortium, 2016). Using both methods together allows for a greater analysis of the results; DSA interrogates parameters individually to highlight the drivers of uncertainty, a result not produced by PSA; where the outcome is a distribution of outputs relative to the distribution of inputs. Arguably, PSA is a more real-world view; where all parameters are likely different for each patient presenting to the NHS.

In this study, DSA was used first to identify key cost drivers. If a parameter caused more than 5% variance to the base-case cost increment, it was determined to be a cost driver. Any parameter causing less than a 5% variance to the base case cost was excluded, and PSA was used to vary the remaining parameters using 1000 runs of the model.

To perform both DSA and PSA, it is necessary to vary the parameters in the model. If the variable had a confidence interval or standard deviation available from the published literature,

then this was used for the distribution. If this was not available for any variable, a 30% variance was applied; unless rationally another value should be used.

To calculate the range from the standard deviation, the 68–95–99.7 rule was used; meaning that the range of 95% of the data was assumed to be within 2 standard deviations of the mean (Pukelsheim, 1994). For DSA the range was calculated, and minimum and maximum values set; no negative values were allowed, if the range was larger than the mean value the minimum was set at 0 and the maximum at the range value. For PSA, a stochastic was calculated using the mean and standard deviation; if this returned a negative value it was set at 0. Negative values were not allowed due to needing the model to be representative of real-world treatment; and in clinical practice it would not be possible for a patient to require a negative amount of resource in a week.

The full list of ranges used to perform DSA and PSA on the DFU and LU cost-utility models are presented in Appendix C. The items in Table 5.15 were omitted from all sensitivity analysis as they were deemed to be constant; or in the case of minor amputations; this was dependent on the proportion of major amputations and was varied accordingly so the two values equal 100%. Furthermore, any parameter that failed to cause more than 5% variance to the base case in the DSA was omitted from the PSA.

Table 5.15. Items excluded from all sensitivity analysis

Category	Constant
Hospital costs	The cost of a hospital admission episode
Outpatient costs	The cost of a GP appointment
	The cost of a hospital outpatient appointment
	The cost of a Podiatrist appointment
	The cost of a Practice Nurse appointment
	The cost of a Community Nurse appointment
Medication costs	The cost of a prescription for antibiotics
	The cost of a prescription for analgesics
	The cost of a minor amputation
	The cost of a major amputation
	The cost of a course of physiotherapy
	The cost of a prosthesis
Device costs	The cost of a compression system
	The cost of a pair of hosiery
	The cost of a bespoke orthosis
Dependent value	The proportion of minor amputations

5.4.3 Expert validation

The cost-utility analyses presented here were validated by experts. Two external clinicians reviewed the model structure, the suitability of assumptions, the transition probabilities and the resource use levels and costs. These clinicians were involved in the expert advice panel using the Delphi methodology as reported in chapter 3. One was a Diabetologist who had extensive experience with patients with DFUs and the other a Vascular Surgeon who was an expert in treating LUs. In addition, two clinical experts who worked for Urgo Medical, the manufacturer of the sucrose octasulfate dressing were consulted, given their knowledge of the trials and expertise with the product and disease areas. The four clinical experts were sent a questionnaire to ascertain their opinions on key parameters of the model. They supported the structure and choice of evidence to provide inputs for the models. There were some comments

regarding the resource use in different health states; however, this was addressed by extending sensitivity analysis to include the values suggested by the clinicians whilst retaining the literature values as the base case. The model structure and methods were also peer reviewed and validated by Health Economists; both within Manchester Met (FF & IO) and from an international partner (Creativ-Ceutical). Further to this, as presented in section 5.7, external validation from NICE and the External Assessment Centre (EAC) has been granted.

The BIMs use lot of the same data as the cost-utility models with regards to the resource use, and have made some of the same assumptions, but were not individually validated by external clinicians due to time and resource considerations. These models were still reviewed by the two Urgo Medical clinical experts and by the Manchester Met Health Economics Professors (FF & IO).

5.5 Results

This economic evaluation of the sucrose octasulfate dressing consisted of using two different methods; budget-impact and cost-effectiveness. Both methods have been used to analyse the costs and consequences associated with DFUs and LUs. The different patient populations have been kept separate as the disease pathology, standard care, and expected outcomes differ drastically between the indications. The methods, parameters, inputs, and assumptions for the base-case analysis have been described in the previous section.

This section presents the results of the economic models. Firstly, the results of the BIMs measuring the cost of introducing the sucrose octasulfate dressing into the standard of care for DFU and LU are explored. Following this; the results of the cost-effectiveness models for LU and DFU is presented.

5.5.1 Budget-impact models

The two BIMs allowed for an analysis of cost outcomes and health outcomes in the DFU and LU populations. The base-case results are presented, including the size of the eligible and treated populations; the cost outcomes include the total budget-impact per year and cumulatively at years 3 and 5; this is also presented as the per-patient cost of treatment, along with a cost comparison between the sucrose octasulfate dressing and a neutral alternative. Health outcomes are reported, which includes the number of days with ulcer, and the days with ulcer avoided by using the sucrose octasulfate dressing.

DFU BIM population

The mid-2016 population figure provided by the Office for National Statistics (ONS) was 51,757,543; only including adults aged 18 and over (Office for National Statistics, 2016). The total population was subject to an annual growth of 0.57%, applied to the previous year total population (Office for National Statistics, 2017).

The estimated prevalence of diabetes was 6.7% according to the Quality and Outcomes Framework (QOF) audit reported by NHS digital (NHS Digital, 2017). There is also an annual incidence rate of new diagnoses for diabetes, at 0.6% (Andersen, 2012). When a patient has diabetes, there is a 6% annual incidence of developing DFU (Kerr, 2012). Table 5.16 shows the results of applying the population funnel to reach the eligible DFU population for the current year until year 5.

Table 5.16. DFU BIM eligible population

	Current year	Year 2	Year 3	Year 4	Year 5
Total population	51,767,543	51,770,494	51,773,445	51,776,396	51,779,347
Prevalent diabetic population	3,468,425	3,763,500	4,058,592	4,353,701	4,648,826
Incident diabetic population	295,075	295,092	295,109	295,125	295,142
Total diabetic population	3,763,500	4,058,592	4,353,701	4,648,826	4,943,969
Patients who develop a DFU: The eligible population	225,810	243,516	261,222	278,930	296,638

From the eligible population, the pre-determined treatment mix was applied to obtain the number of patients who were treated with the sucrose octasulfate dressing and standard care, versus those receiving standard care alone. Table 5.17 shows the number of patients treated in each arm of the DFU model.

Table 5.17. DFU BIM treated population

	Current year	Year 2	Year 3	Year 4	Year 5
Sucrose octasulfate and standard care	0	36,527	65,306	111,572	177,983
Standard care alone	225,810	206,88	195,917	167,358	118,655

LU BIM population

The LU model used the same total population figure as the DFU model, 51,757,543, as it also excluded people under the age of 18 from the model (Office for National Statistics, 2016). The same annual growth rate of 0.57% was applied to this model; to reflect the change in the national population of the UK (Office for National Statistics, 2017).

The LU prevalence figure was derived from a whole population sample, and LUs are not only found in people with a specified co-morbidity, unlike DFUs that are only found in people who also have a diagnosis of diabetes. The estimated prevalence of leg ulceration was 1.5% of the adult population (Guest et al., 2015). Table 5.18 shows the results of applying the population funnel to reach the eligible LU population for the current year until year 5.

Table 5.18. LU BIM eligible population

	Current year	Year 2	Year 3	Year 4	Year 5
Total population	51,767,543	51,770,494	51,773,445	51,776,396	51,779,347
Annual leg ulcer prevalence: The eligible population	776,513	776,557	776,602	776,646	776,690

From the eligible population, the pre-determined treatment mix was applied to obtain the number of patients who were treated with the sucrose octasulfate dressing and standard care, versus those receiving standard care alone. Table 5.19 shows the number of patients treated in each arm of the LU model.

Table 5.19. LU BIM treated population

	Current year	Year 2	Year 3	Year 4	Year 5
Sucrose octasulfate and standard care	0	116,484	194,150	310,658	466,014
Standard care alone	776,513	660,074	582,451	465,988	310,676

BIM cost outcomes

The budget-impact is the total amount that hits the NHS budget for treating DFU and LU, respectively. The budget-impact is expressed as an annual cost; and as a cumulative amount at the end of years 3 and 5. In addition to budget-impact, the cost-consequence was calculated. This is a comparative analysis that compares the annual cost of introducing the new intervention with a scenario where standard care remains the same. To enable understanding, the cost-per-patient is also presented.

DFU BIM cost outcomes

The DFU BIM showed an increase in costs year-on-year until year 5. The costs of introducing the sucrose octasulfate dressing to the standard of care are shown in Table 5.20. The cumulative budget-impact at year 3 was found to be £1,177,375,87 and at year 5 was £2,064,669,169. The annual costs are also shown in Figure 5.6.

Comparing the costs of introducing the sucrose octasulfate dressing with the cost of continuing standard care for all patients shows the cost-consequence associated with this intervention. The calculation uses the same treatment mix for the uptake of the new intervention. The results of the cost comparison are shown in Table 5.21. The increased use of the sucrose octasulfate dressing was associated with cost savings when compared to the continuation of standard care for all patients.

To translate the national costs represented by the budget-impact into a format more easily understood; the per-patient cost of treatment is also shown in Table 5.22. The figures have again been calculated using the same treatment mix as prescribed by the base-case. Should 100% of the population receive the sucrose octasulfate dressing, the annual cost per patient

would be £1445.90, versus £1638.48 for standard care. The cost-consequence calculation shows that the introduction of this intervention would save up to £192.57 per patient per year.

Table 5.20. DFU budget-impact results

	Sucrose octasulfate and standard care	Standard care	Budget impact
Current Year	£0	£369,984,589	**£369,984,589**
Year 2	£52,814,987	£339,145,463	**£391,960,450**
Year 3	£94,425,456	£321,004,792	**£415,430,249**
Year 4	£161,322,079	£274,211,863	**£435,533,941**
Year 5	£257,346,017	£194,413,922	**£451,759,940**

Table 5.21. DFU cost-consequence results

	Budget impact	Standard care	Cost consequence
Current Year	£369,984,589	£369,984,589	**£0**
Year 2	£391,960,450	£398,994,663	**-£7,034,213**
Year 3	£415,430,249	£428,006,390	**-£12,576,141**
Year 4	£435,533,941	£457,019,771	**-£21,485,830**
Year 5	£451,759,940	£486,034,806	**-£34,274,866**

Table 5.22. DFU per patient cost

	Cost per patient
Current Year	**£1,638.48**
Year 2	**£1,609.59**
Year 3	**£1,590.33**
Year 4	**£1,561.45**
Year 5	**£1,522.93**

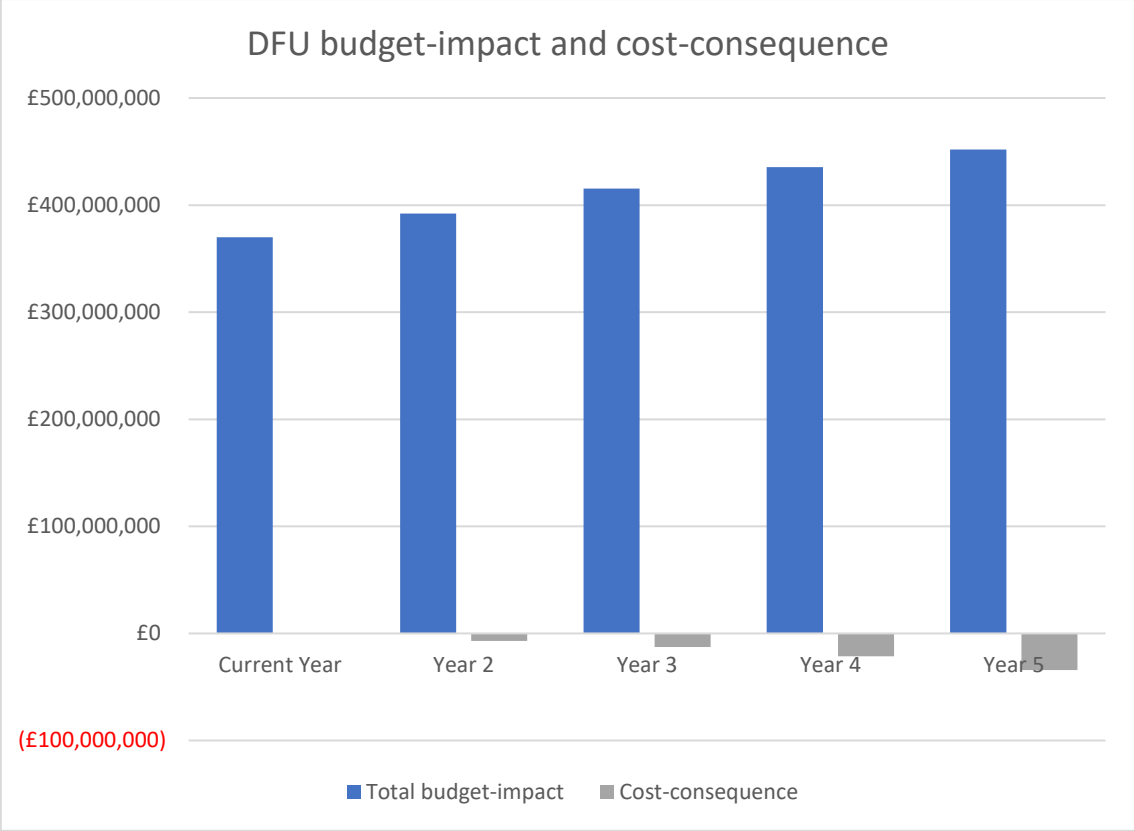


Figure 5.6. DFU budget-impact annual costs

LU BIM cost outcomes

The LU BIM showed a decrease in costs year-on-year until year 5. The costs of introducing the sucrose octasulfate dressing to the standard of care are shown in Table 5.23. The cumulative budget-impact at year 3 was found to be £6,767,184,844 and at year 5 was £10,382,732,268. The annual costs are also shown in Figure 5.7.

Comparing the costs of introducing the sucrose octasulfate dressing with the cost of continuing standard care for all patients shows the cost-consequence associated with this intervention. The calculation uses the same treatment mix for the uptake of the new intervention. The results of the cost comparison are shown in Table 5.24. The increased use of the sucrose octasulfate dressing was associated with cost savings when compared to the continuation of standard care for all patients.

To translate the national costs represented by the budget-impact into a format more easily understood; the per-patient cost of treatment is also shown in Table 5.25. The figures have again been calculated using the same treatment mix as prescribed by the base-case.

Should 100% of the population receive the sucrose octasulfate dressing, the annual cost per patient would be £1540.54.90, versus £3114.67 for standard care. This cost-consequence calculation shows that the introduction of this new intervention would save up to £1547.13 per patient per year.

Table 5.23. LU budget-impact results

	Sucrose octasulfate and SoC	SoC alone	Budget impact
Current Year	£0	£2,418,583,307	**£2,418,583,307**
Year 2	£179,447,709	£2,055,912,991	**£2,235,360,700**
Year 3	£299,096,562	£1,814,144,275	**£2,113,240,837**
Year 4	£478,581,777	£1,451,398,145	**£1,929,979,922**
Year 5	£717,913,585	£967,653,916	**£1,685,567,501**

Table 5.24. LU cost-consequence results

	Budget impact	Standard care	Cost consequence
Current Year	£2,418,583,307	£2,418,583,307	**£0**
Year 2	£2,235,360,700	£2,418,721,166	**-£183,360,466**
Year 3	£2,113,240,837	£2,418,859,033	**-£305,618,196**
Year 4	£1,929,979,922	£2,418,996,908	**-£489,016,986**
Year 5	£1,685,567,501	£2,419,134,791	**-£733,567,290**

Table 5.25. LU per patient cost

	Cost per patient
Current Year	**£3,114.67**
Year 2	**£2,878.55**
Year 3	**£2,721.14**
Year 4	**£2,485.02**
Year 5	**£2,170.19**

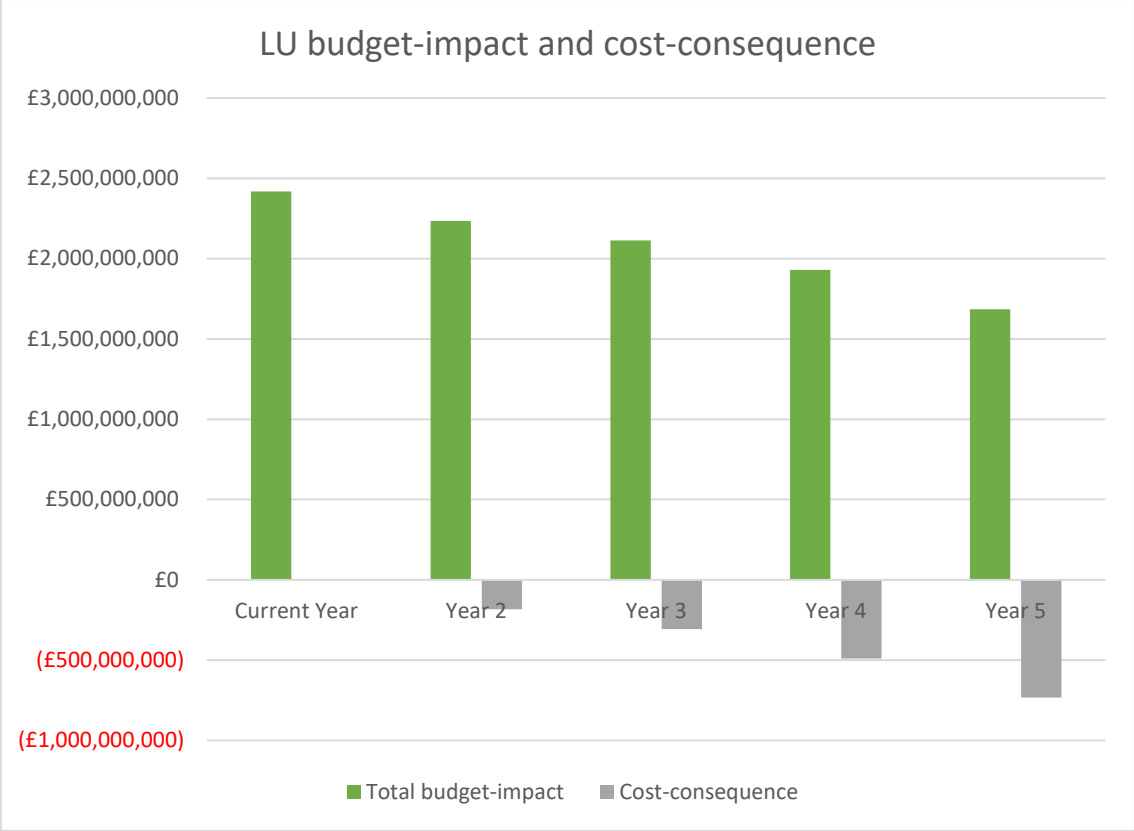


Figure 5.7. LU budget-impact and cost-consequence

BIM health outcomes

In addition to a reduced cost to a healthcare system, it is important to calculate the patient impact of introducing a new intervention. The effectiveness measure that was used in the BIMs was the mean days to healing for the sucrose octasulfate dressing used in combination with standard care, and the mean days to healing recorded for standard care alone. The model calculated how many days that a patient has an open wound, and is therefore experiencing symptoms, and has calculated how many days of ulceration have been avoided by the introduction of the sucrose octasulfate dressing.

DFU BIM health outcomes

By introducing the sucrose octasulfate dressing, patients experience fewer days with an open DFU, because of the shorter mean time to healing. Table 5.26 shows the number of days with ulcer avoided by introducing the new intervention; the days with ulcer row has been calculated using the progressive uptake as specified in the treatment mix used in the base-case. Should 100% of the population receive the sucrose octasulfate dressing, then in year 5, a total of

5,932,762 days with ulcer would have been avoided. Figure 5.8 shows the number of days with ulcer avoided as calculated by the DFU BIM.

Table 5.26. DFU days with ulcer results

Health Outcomes	Current Year	Year 2	Year 3	Year 4	Year 5
Days with ulcer	30,484,353	32,144,050	33,958,866	35,424,056	36,486,488
Days with ulcer avoided	N/A	730,547	1,306,110	2,231,437	3,559,657

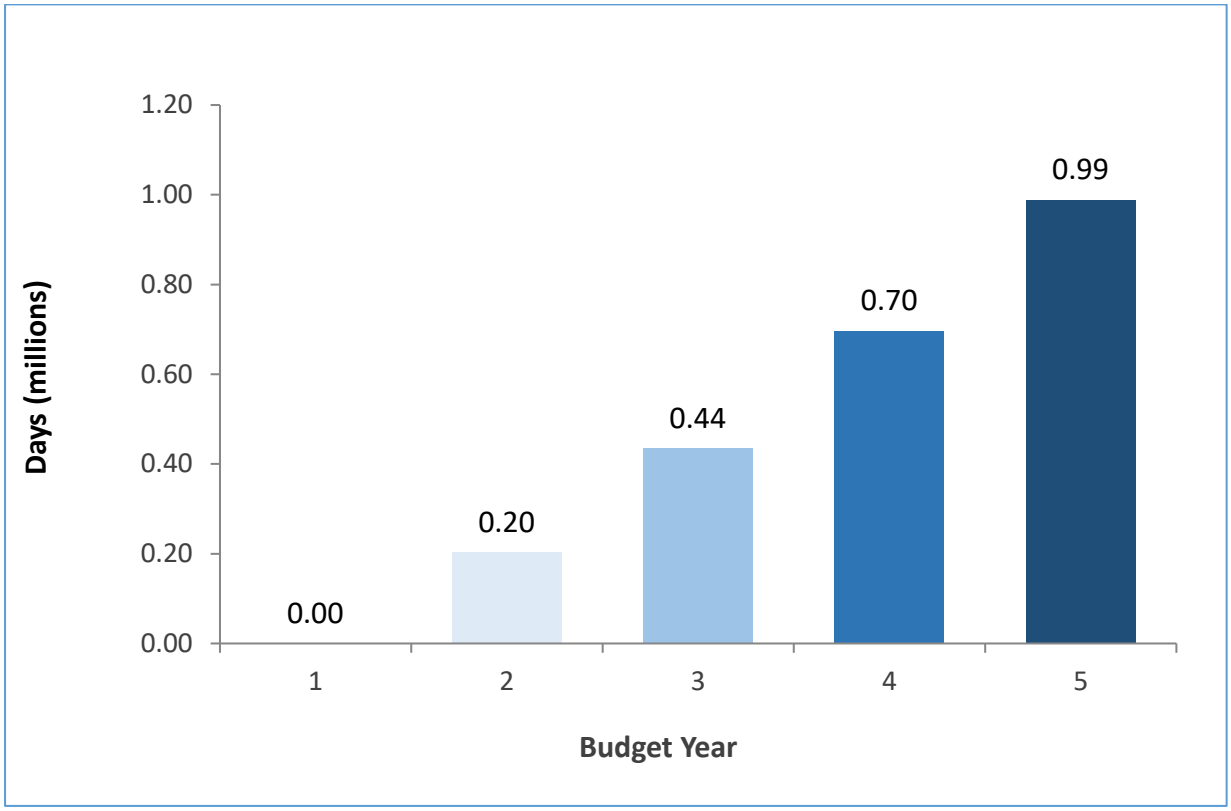


Figure 5.8. DFU days with ulcer avoided

LU BIM health outcomes

By introducing the sucrose octasulfate dressing, patients experience substantially fewer days with an open LU, because of the shorter mean time to healing. Table 5.27 shows the number of days with ulcer avoided by introducing the new intervention; the days with ulcer row has been calculated using the progressive uptake as specified in the base-case treatment mix. Figure 5.9 shows the number of days with ulcer avoided as calculated by the LU BIM.

Table 5.27. LU days with ulcer results

Health Outcomes	Current Year	Year 2	Year 3	Year 4	Year 5
Days with ulcer	163,067,760	151,661,661	144,059,610	132,651,126	117,435,559
Days with ulcer avoided	N/A	11,415,394	19,026,741	30,444,521	45,669,384

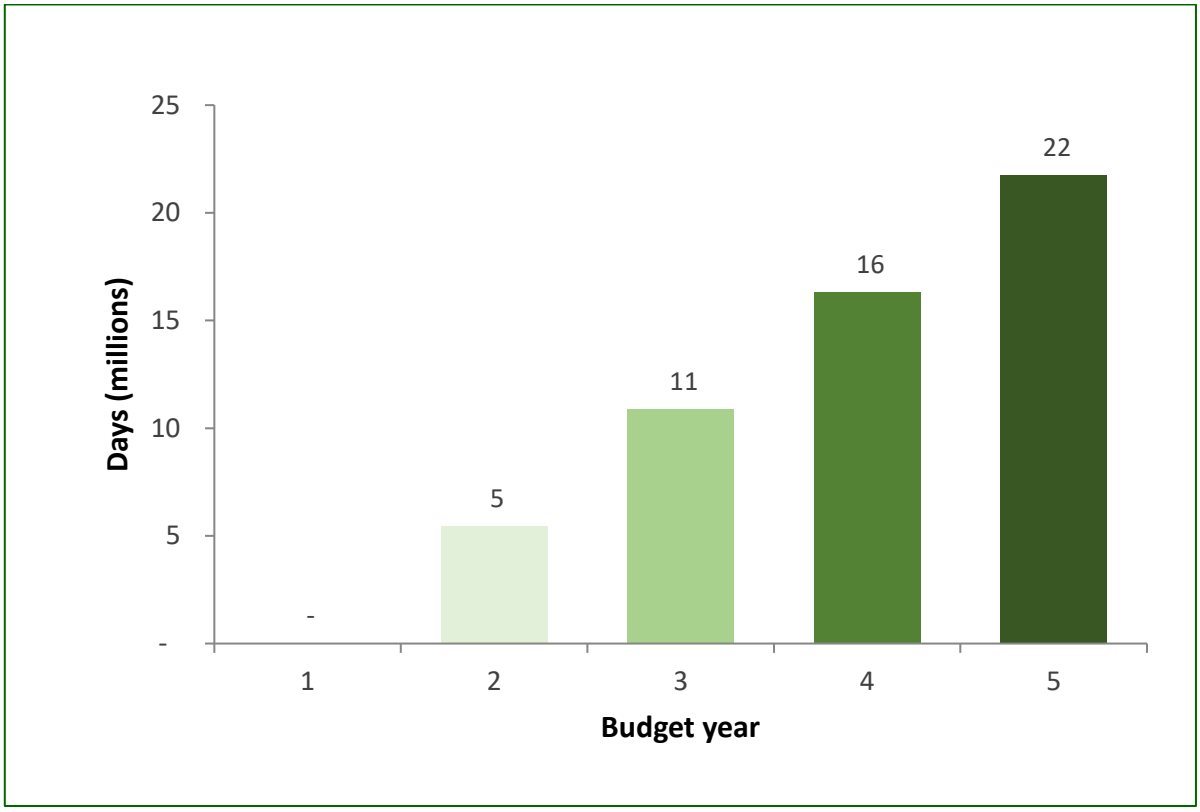


Figure 5.9. LU days with ulcer avoided

Should 100% of the population receive the sucrose octasulfate dressing, then in year 5, a total of 76,115,640 days with ulcer would have been avoided.

DFU BIM Sensitivity analysis

The sensitivity analysis carried out on the DFU BIM consisted of applying a pre-defined set of scenarios to vary key parameters of the models. The scenarios used to test the DFU BIM are shown in Table 5.7 earlier in this chapter. The results for the five scenarios tested are shown. Table 5.28 shows the cost outcomes, the annual budget-impact, annual cost-consequence and the annual per patient cost.

These results show the importance of the reduced mean time to healing; as in some scenarios where this was adjusted, the sucrose octasulfate dressing was no longer cost saving; as the dressing was more expensive than the comparator.

If the price of the dressing was lowered to reflect some of the most inexpensive dressings available (£0.35 per dressing) then the cost benefits of the sucrose octasulfate dressing were lost. If the mean time to healing in the real-world was the same as in the RCT that informed the model, then the sucrose octasulfate dressing is still cost saving even when compared with the lower cost dressings.

When testing the five scenarios the health outcomes were also measured. Table 5.29 shows the health outcomes, measured by the days with ulcer avoided.

LU BIM Sensitivity analysis

The sensitivity analysis carried out on the LU BIM consisted of applying a pre-defined set of scenarios to vary key parameters of the models. The scenarios used to test the LU BIM are shown in Table 5.8 earlier in this chapter. Table 5.30 shows the cost outcomes, the annual budget-impact, annual cost-consequence and the annual patient cost.

The results show that in all scenarios, the sucrose octasulfate dressing continued to be cost saving. Even when the dressing was substantially more expensive than the comparator (£4.20 vs £0.35). The cost saving is reflective of the size of the population and the much-improved time to healing reported in the real-world observational study when compared with standard care. If the mean time to healing by the sucrose octasulfate dressing only 1 day faster than standard care, with other parameters matching the base-case, the dressing is still cost saving with a lower cost per patient.

When testing the five scenarios the health outcomes were also measured. Table 5.31 shows the health outcomes, measured by the days with ulcer avoided. A key factor that influences the number of days with ulcer avoided is the number of patients who are part of the eligible and treated populations.

Table 5.28. DFU scenario analysis cost outcomes

	Item	Current year	Year 2	Year 3	Year 4	Year 5
Scenario 1	Budget-impact	£121,642,634	£132,538,102	£144,602,424	£155,441,320	£167,514,921
	Cost-consequence	£839,265	£2,262,678	£4,854,404	£6,220,165	£8,820,090
	Cost/patient	£1,292.87	£1,306.25	£1,328.55	£1,337.47	£1,355.31
Scenario 2	Budget-impact	£222,890,530	£240,314,024	£257,673,831	£275,019,189	£292,285,412
	Cost-consequence	£0	-£53,100	-£170,885	-£304,114	-£517,474
	Cost/patient	£1,480.61	£1,480.28	£1,479.63	£1,478.97	£1,477.99
Scenario 3	Budget-impact	£279,737,028	£297,673,731	£315,030,400	£324,939,293	£335,830,596
	Cost-consequence	-£1,853,268	-£5,995,743	-£10,719,509	-£22,892,310	-£34,083,960
	Cost/patient	£1,238.82	£1,222.40	£1,205.99	£1,164.95	£1,132.12
Scenario 4	Budget-impact	£378,045,822	£403,705,925	£428,788,631	£453,293,893	£477,221,660
	Cost-consequence	£0	-£3,982,044	-£8,543,173	-£13,683,437	-£19,402,885
	Cost/patient	£1,339.34	£1,326.26	£1,313.18	£1,300.10	£1,287.01
Scenario 5	Budget-impact	£540,518,641	£584,446,489	£628,601,636	£672,984,100	£717,593,901
	Cost-consequence	£0	£1,546,392	£3,317,666	£5,313,842	£7,534,940
	Cost/patient	£1,436.21	£1,440.02	£1,443.83	£1,447.64	£1,451.45

Table 5.29. DFU scenario analysis health outcomes

	Scenario	Current year	Year 2	Year 3	Year 4	Year 5
Days with ulcer avoided	1	94,088	253,662	544,213	697,324	988,794
	2	-	121,758	391,833	697,324	1,186,552
	3	169,358	547,910	979,583	2,091,972	3,114,700
	4	-	608,789	1,306,110	2,091,972	2,966,381
	5	-	202,930	435,370	697,324	988,794

Table 5.30. LU scenario analysis cost outcomes

	Item	Current year	Year 2	Year 3	Year 4	Year 5
Scenario 1	Budget-impact	£480,891,780	£471,975,401	£457,095,137	£451,157,985	£439,256,608
	Cost-consequence	-£5,962,187	-£14,906,317	-£29,814,333	-£35,779,239	-£47,708,372
	Cost/patient	£1,857.89	£1,823.34	£1,765.75	£1,742.72	£1,696.65
Scenario 2	Budget-impact	£2,469,053,253	£2,452,548,402	£2,419,395,126	£2,386,238,062	£2,336,428,777
	Cost-consequence	£0	-£16,645,587	-£49,939,607	-£83,237,423	-£133,187,468
	Cost/patient	£2,384.75	£2,368.67	£2,336.52	£2,304.37	£2,256.14
Scenario 3	Budget-impact	£1,171,331,290	£1,095,316,078	£1,019,292,198	£829,123,670	£676,980,954
	Cost-consequence	-£38,038,820	-£114,122,966	-£190,215,785	-£380,453,254	-£532,664,916
	Cost/patient	£3,232.39	£3,022.45	£2,812.51	£2,287.65	£1,867.76
Scenario 4	Budget-impact	£3,403,762,898	£3,348,398,855	£3,293,028,488	£3,237,651,799	£3,182,268,786
	Cost-consequence	£0	-£55,558,058	-£111,122,450	-£166,693,175	-£222,270,236
	Cost/patient	£2,630.04	£2,587.11	£2,544.18	£2,501.26	£2,458.33
Scenario 5	Budget-impact	£3,412,924,046	£3,349,276,766	£3,285,622,219	£3,221,960,404	£3,158,291,322
	Cost-consequence	£2,197.60	£2,156.49	£2,115.38	£2,074.28	£2,033.17
	Cost per patient	£0	-£63,841,817	-£127,690,911	-£191,547,284	-£255,410,937

Table 5.31. LU scenario analysis health outcomes

	Scenario	Current year	Year 2	Year 3	Year 4	Year 5
Days with ulcer	1	776,513	1,941,394	3,883,008	4,659,876	6,213,522
	2	-	1,553,115	4,659,610	7,766,459	12,427,043
	3	2,355,423	7,066,672	11,778,459	23,558,260	32,983,444
	4	-	3,882,787	7,766,017	11,649,689	15,533,804
	5	-	5,435,902	10,872,423	16,309,565	21,747,326

5.5.2 Cost effectiveness analysis

The two cost-utility models allowed for a more detailed analysis of cost and health outcomes in the DFU and LU populations than the BIM. This is because of the inclusion of health states, and a treatment pathway; rather than only aggregated costs as presented by the BIMs. The base-case results are explored, first presenting the population characteristics and then showing costs per resource category and health state.

Health outcomes are also reported, reported in variation of quality adjusted life years (QALYs) between the treatment groups. Additionally, the number of wounds healed are presented, and in the case of DFU; the number of amputation events in the treatment group using the sucrose octasulfate dressing and standard care versus the control group just using standard care. Finally, the per-patient incremental cost-effectiveness ratio (ICER), is determined.

CEA Population

The cost-utility models relied on the RCT data from the Explorer and Challenge clinical trials for DFU and LU patients respectively (Meaume et al., 2012; Edmonds et al., 2018). Therefore, the models are based on patient populations that matched the clinical trials. See chapter 2, section 2.3.4 for reporting of the inclusion and exclusion criteria for these studies.

As per the Explorer study (Edmonds et al., 2018), the patients in the DFU cost-utility analysis had a mean age of 65, with a sex distribution of 84% male and 16% female. The proportion who had previously experienced an amputation was 50%. As per the Challenge study (Meaume et al., 2012), the patients in the LU cost-utility analysis had a mean age of 73, with a sex distribution of 33% male and 67% female.

CEA Cost outcomes

The base case for the DFU and LU cost-utility models uses the data inputs presented earlier in this chapter. These values are believed to be those that are most representative of the clinical and resource use parameters that a patient would experience in the NHS if they were to present with a DFU or LU.

Total costs are presented as a per-patient cost and extracted at the base-case time horizon of one year. The total costs associated with the use of the sucrose octasulfate dressing and standard care with a neutral dressing are shown in Table 5.32 for DFU and Table 5.33 for LU.

Table 5.32. DFU cost-utility per-patient cost

DFU	Total per patient cost (£)
Sucrose octasulfate dressing	£3184.35
Neutral dressing	£3850.86

Table 5.33. LU cost-utility per-patient cost

LU	Total per patient cost (£)
Sucrose octasulfate dressing	£1582.58
Neutral dressing	£1856.83

The DFU cost-utility model reported that the sucrose octasulfate dressing incurred £666.51 less cost than the neutral dressing and the LU cost-utility model reported that the sucrose octasulfate dressing incurred £274.25 less cost than the neutral dressing. The costs split by resource use category and reported on a per patient basis are shown in Table 5.34 for DFU and Table 5.35 for LU, and further split by resource use item in Figure 5.10 for DFU and 5.11 for LU.

Table 5.34. DFU costs per resource use category

Item	Sucrose octasulfate	Standard care	Increment	% change
Primary dressing	£390.72	£359.63	£31.09	+9%
Inpatient	£597.61	£811.94	-£214.33	-26%
Outpatient	£1280.27	£1564.24	-£283.97	-18%
Medication	£37.95	£44.69	-£6.74	-15%
Devices	£734.94	£802.96	-£68.02	-8%
Amputation	£142.86	£267.40	-£124.54	-47%
Total	**£3184.35**	**£3850.86**	**-£666.51**	**-17%**

Table 5.35. LU costs per resource use category

Item	Sucrose octasulfate dressing	Standard care	Increment	% change
Primary dressing	£157.77	£151.94	£5.83	+4%
Inpatient	£4.60	£4.53	£0.07	+2%
Outpatient	£1140.25	£1370.58	-£230.33	-17%
Medication	£8.19	£9.78	-£1.59	-16%
Devices	£271.78	£320.00	-£48.22	-15%
Total	**£1582.58**	**£1856.83**	**-£274.25**	**-15%**

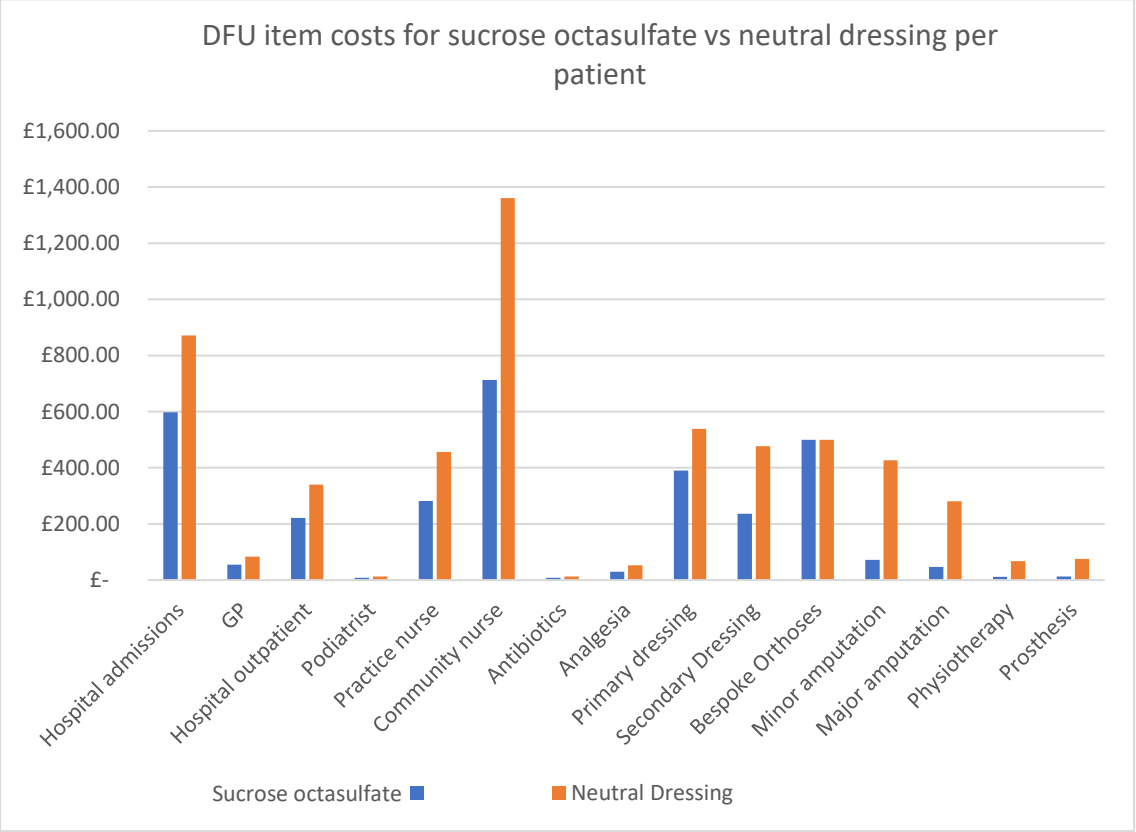


Figure 5.10. DFU costs per resource use item

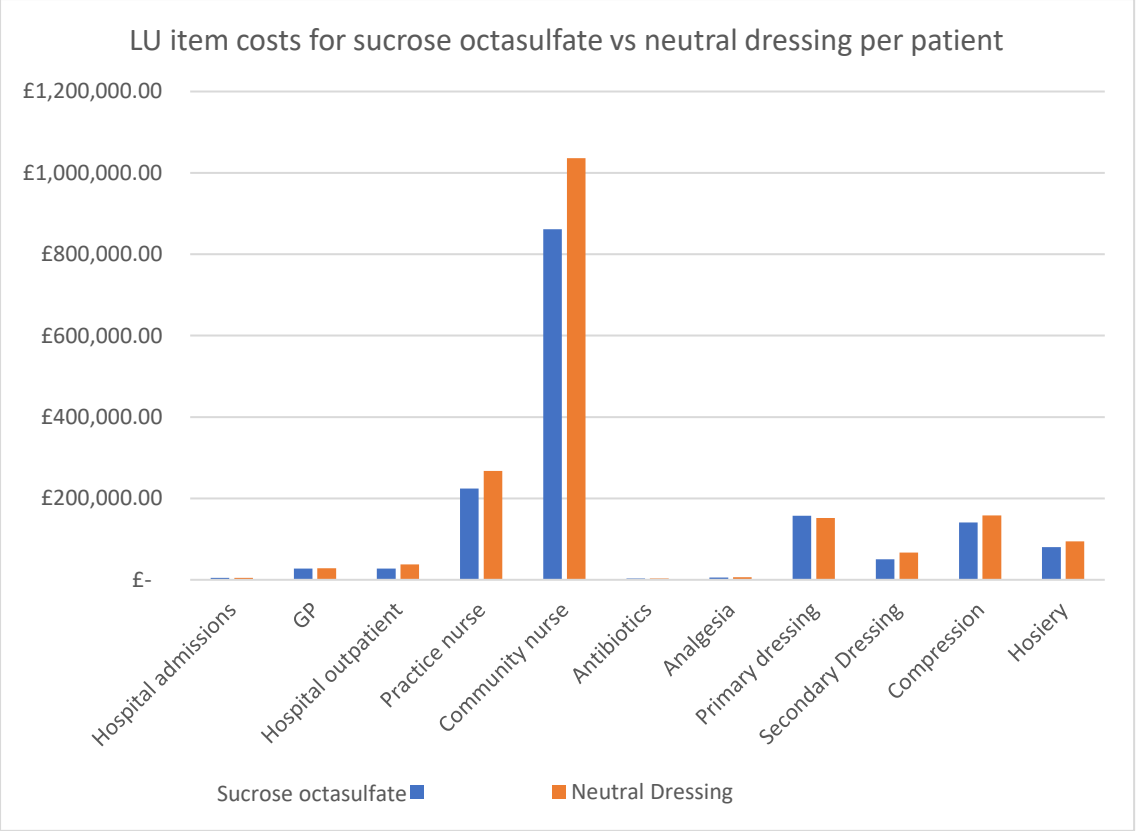


Figure 5.11. LU costs per resource use item

Both models found that the cost of the primary dressings was higher when using the sucrose octasulfate dressing; by 9% in the DFU model and 4% in the LU model. This cost is offset by the savings made across the other categories.

In the DFU model, the biggest relative change was seen in the cost of amputation events, which was 47% less in the sucrose octasulfate group than the standard care only group. The largest absolute change in costs in the DFU model was seen in the outpatient category, with a saving of £283.97 when using the sucrose octasulfate dressing.

In the LU model; in addition to the primary dressing, the inpatient category experienced a modest cost increase of £0.07 (2%). All other categories saw a cost saving when using the sucrose octasulfate dressing, with the greatest relative change, 17%, in the outpatient category, which was also the largest absolute change, at a saving of £230.33. This accounted for the clear majority (81%) of the overall savings for the sucrose octasulfate dressing in the LU model.

A summary of costs split by health state and reported on a per patient basis are shown in Table 5.36 and Figure 5.12 for DFU. Amputation event costs are included in the table for the DFU model; despite these not being a health state.

Table 5.36. DFU costs per health state

Health state	Sucrose octasulfate	Standard care	Increment	% change
Open pre-amputation	£464.04	£556.70	-£92.66	-17%
Complicated pre-amputation	£433.58	£771.50	-£337.92	-44%
Closed pre-amputation	£403.79	£206.09	£197.70	+96%
Open post-amputation	£758.98	£834.95	-£75.97	-9%
Complicated post-amputation	£545.13	£877.62	-£332.49	-38%
Closed post-amputation	£435.96	£336.60	£99.36	+30%
Amputation costs	£142.86	£267.40	-£124.54	-47%
Total	**£3184.35**	**£3850.86**	**-£666.51**	**-17%**

When costs are disaggregated in this manner, it becomes clear that more patients reside in the closed wound health states, as increases in cost can be seen here, +96% pre-amputation and +30% post amputation. A summary of costs split by health state and reported on a per patient basis are shown in Table 5.37 and Figure 5.13 for LU. Consistent with the findings in the DFU model, more costs were incurred for the closed wound health state, an increase of 37%, for the sucrose octasulfate dressing.

Table 5.37. LU costs per health state

Health state	Sucrose octasulfate	Standard care	Increment	% change
Open	£489.07	£1009.64	-£520.57	-52%
Infected	£51.43	£84.02	-£32.59	-39%
Closed	£1042.09	£763.17	£278.92	+37%
Total	**£1582.58**	**£1856.83**	**-£274.25**	**-15%**

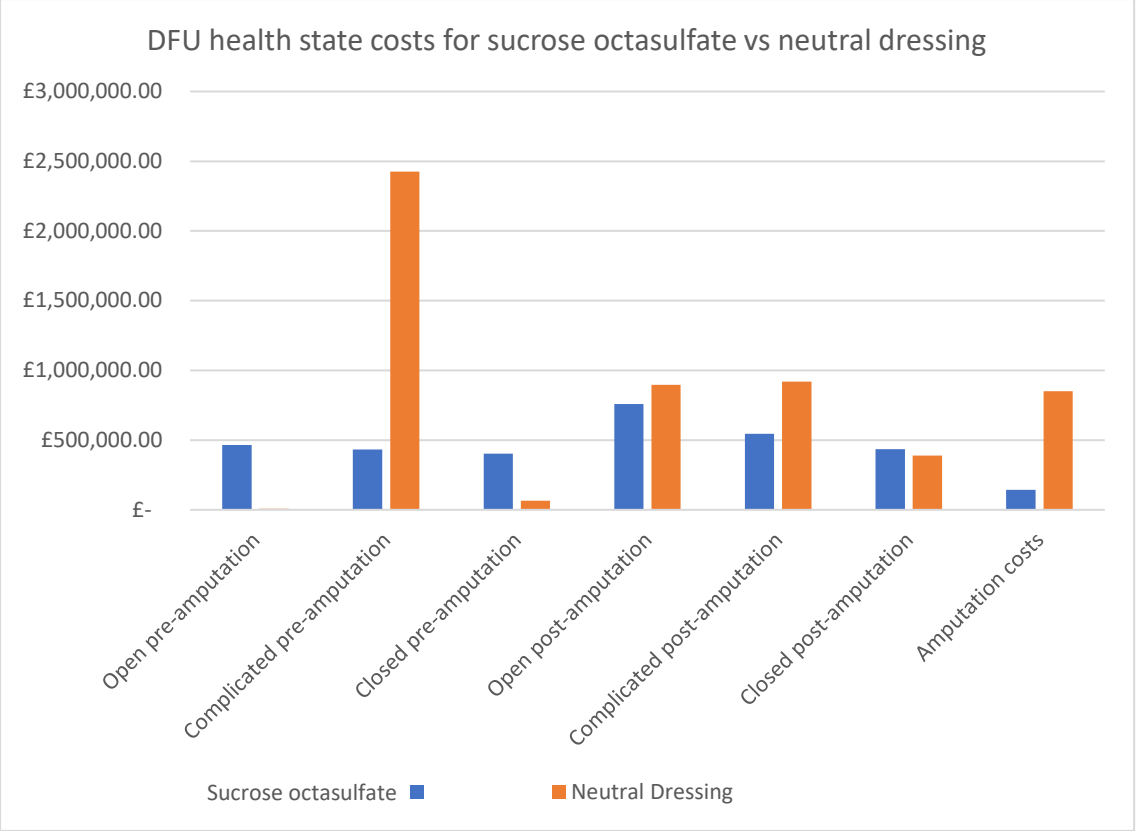


Figure 5.12. DFU costs per health state

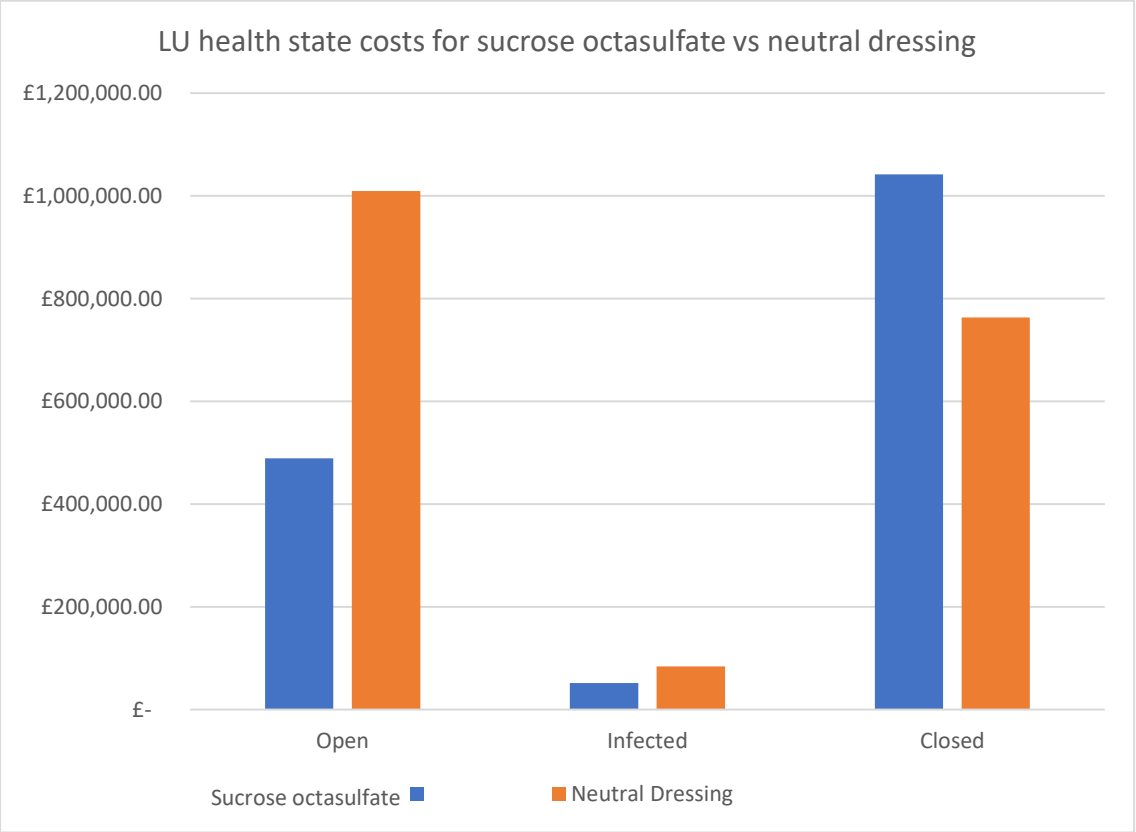


Figure 5.13. LU costs per health state

CUA health outcomes

At the base-case time horizon of one year, the models calculated the cumulative number of QALYs attributed to each treatment arm. These are shown in Table 5.38.

Table 5.38. QALYs gained in cost-utility models

	Sucrose octasulfate dressing	Standard care	Increment
DFU	0.682	0.665	0.017
LU	0.726	0.658	0.069

DFU CUA health outcomes

The DFU cost-utility model calculated the number of wounds that had healed by the time horizon. For the sucrose octasulfate dressing, 653 wounds had healed at one year compared with 473 wounds healed in the standard care arm. Figures 5.14 and 5.15 show this, split by pre- and post-amputation.

A cost per healed wound was calculated by the model; resulting in a cost of £4879.84 per healed wound using the sucrose octasulfate dressing and a cost of £8136.19 per healed wound using standard care alone.

Additionally, for the DFU model, it was possible to calculate the number of amputation events that took place in each treatment arm. At one year, 21 amputations had taken place in the sucrose octasulfate treatment group, compared with 40 in the standard care group, shown in Figure 5.16.

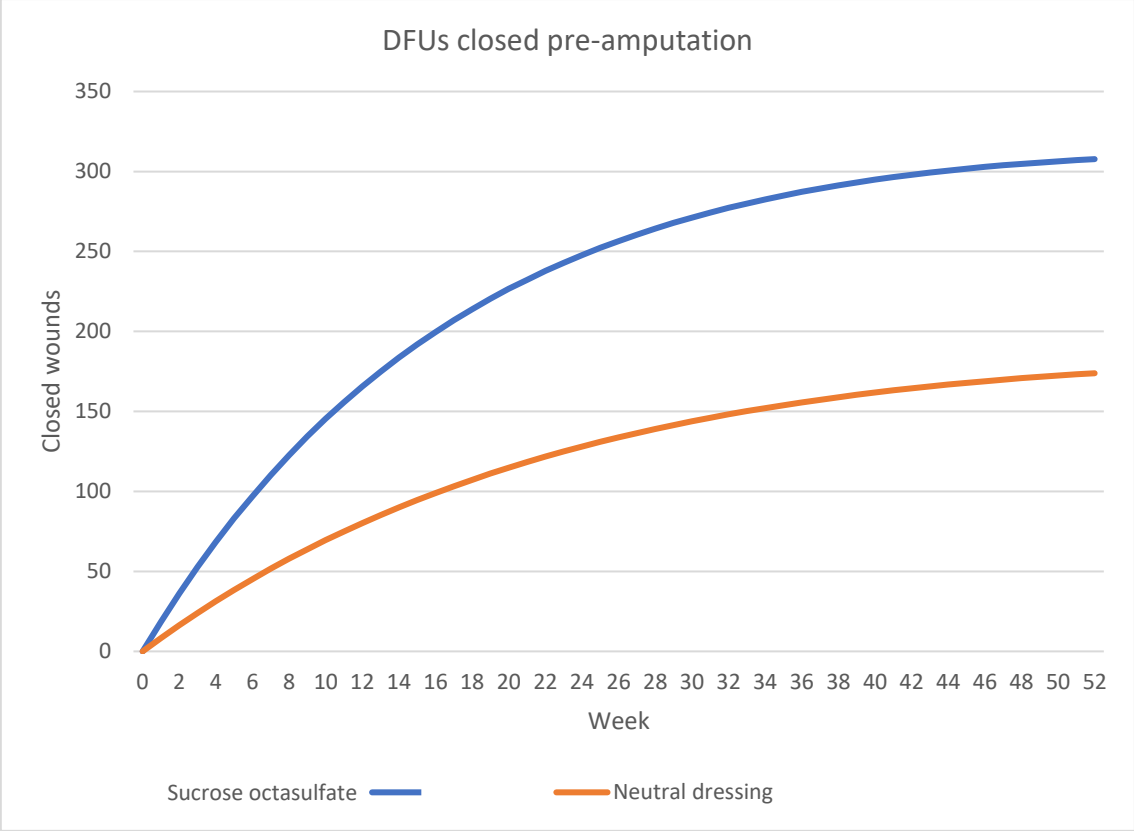


Figure 5.14. DFUs closed pre-amputation

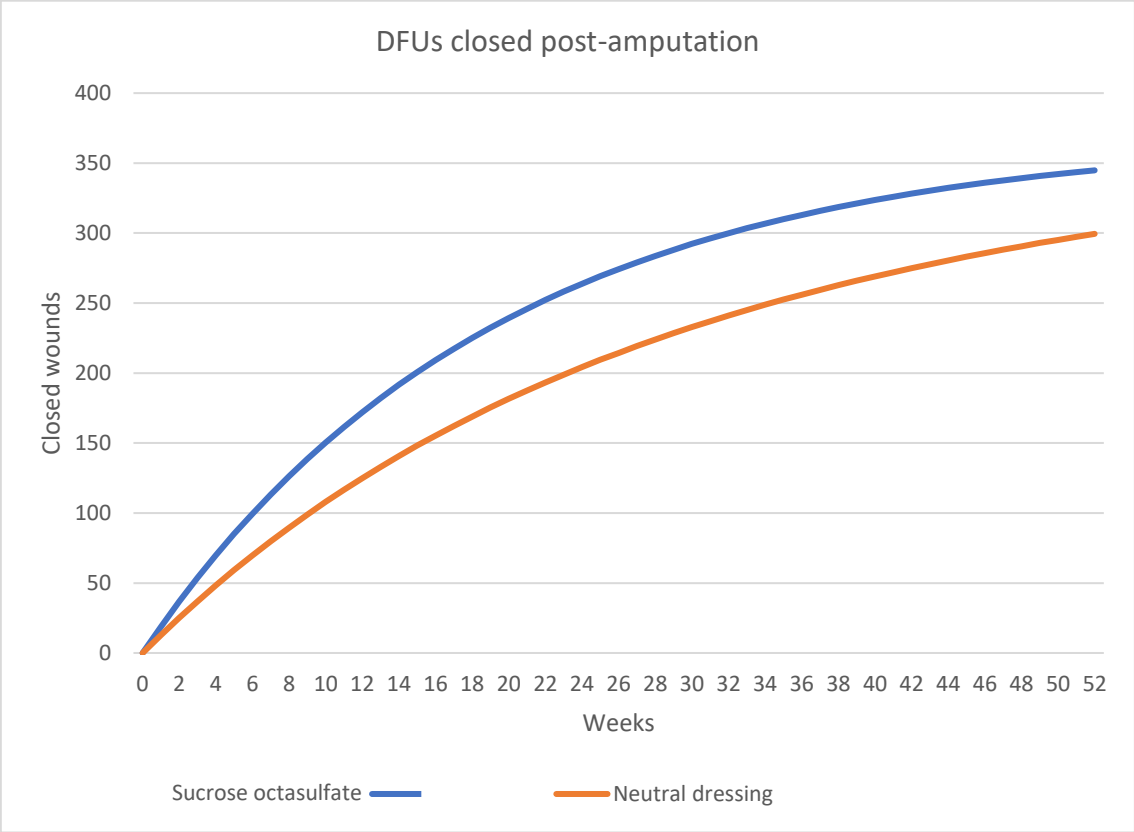


Figure 5.15. DFUs closed post-amputation

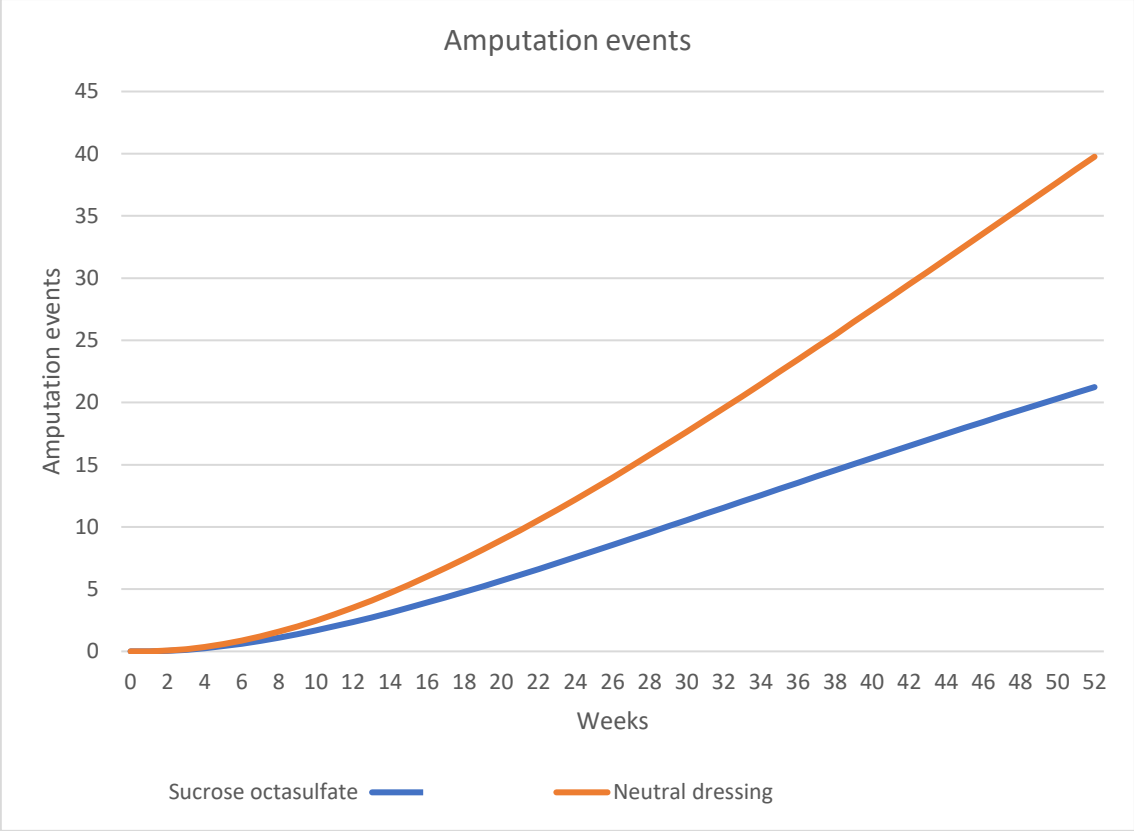


Figure 5.16. DFU model amputation events

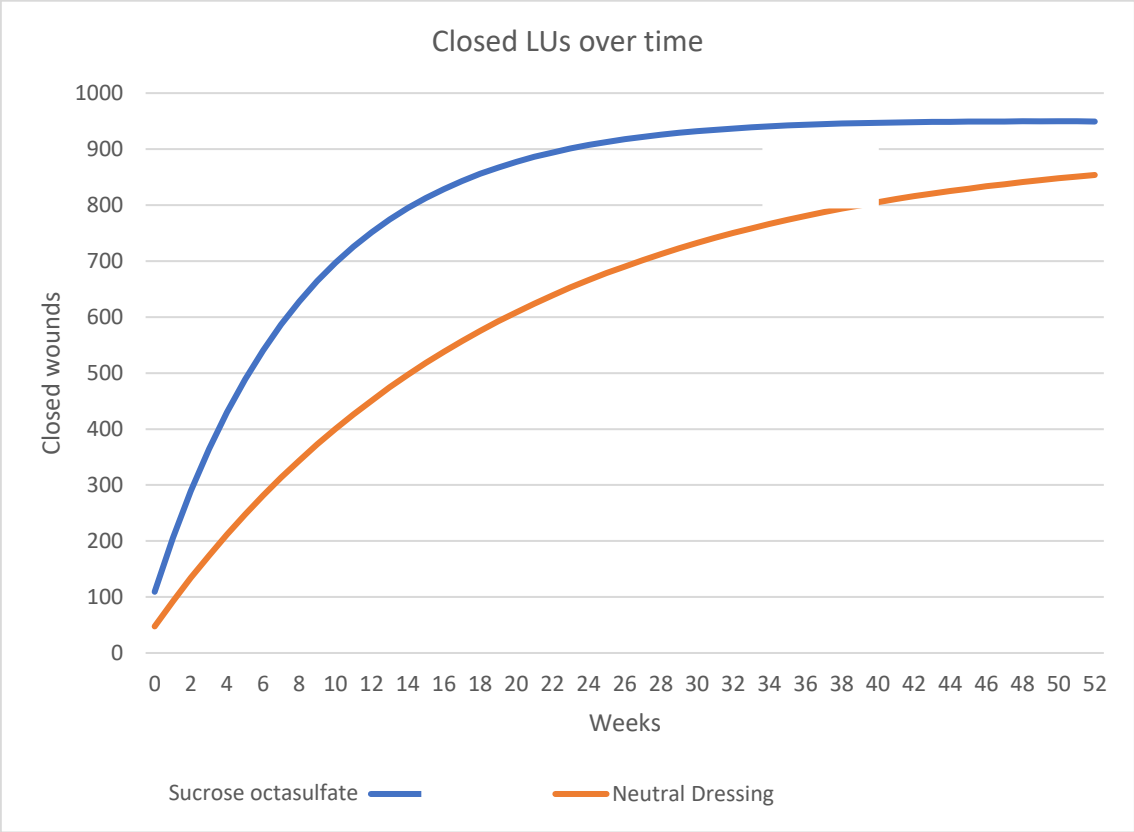


Figure 5.17. LUs closed

LU CUA health outcomes

The LU cost-utility model calculated the number of wounds that had healed by the time horizon of one year. For the sucrose octasulfate dressing, 949 wounds had healed compared with 854 wounds healed in the standard care arm shown in Figure 5.17.

A cost per healed wound was calculated by the model; resulting in a cost of £1666.80 per healed wound using the sucrose octasulfate dressing and a cost of £2174.89 per healed wound using standard care alone.

CUA Incremental cost-effectiveness ratios

For both the DFU and LU models the ICER was calculated.

For the DFU model, the calculation was as below:

$$\frac{£666.51}{0.017} = -£39{,}900.07$$

For the LU model, the calculation was as below:

$$\frac{£274.25}{0.069} = -£3996.72$$

When an intervention is both more effective, and less costly than the comparator, it is declared to be the dominant intervention; this is also shown by the negative ICER value. When considering both the DFU and LU indications, the sucrose octasulfate dressing was the dominant intervention.

CUA sensitivity analysis

The sensitivity analysis to test the robustness of the results was carried out in two stages. The first part was the DSA, where each parameter was varied individually according to the assigned minimum and maximum values. After this, values that caused a ≥5% variance were deemed to be key driving variables, and these were taken forward to be used in the PSA. For the PSA, the range values and estimated standard deviation of each parameter were used for the model to generate stochastic values to be used in each of 1000 runs of the model.

Figure 5.18 presents the results of the DFU DSA, for variables that caused a ≥5% variance and Figure 5.19 presents the results of the LU DSA, for variables that caused a ≥5% variance. For the tabulated results of the DFU and LU DSA please see Appendix C.

The DFU PSA, which showed that in all cases the sucrose octasulfate dressing resulted in a cost saving and a QALY gain. The results of the DFU PSA are shown in Table 5.39. The results of the LU PSA are shown in Table 5.40. Figure 5.20 presents the results of the LU PSA, which showed that in approximately 90% of cases the sucrose octasulfate dressing resulted in a cost saving and a QALY gain.

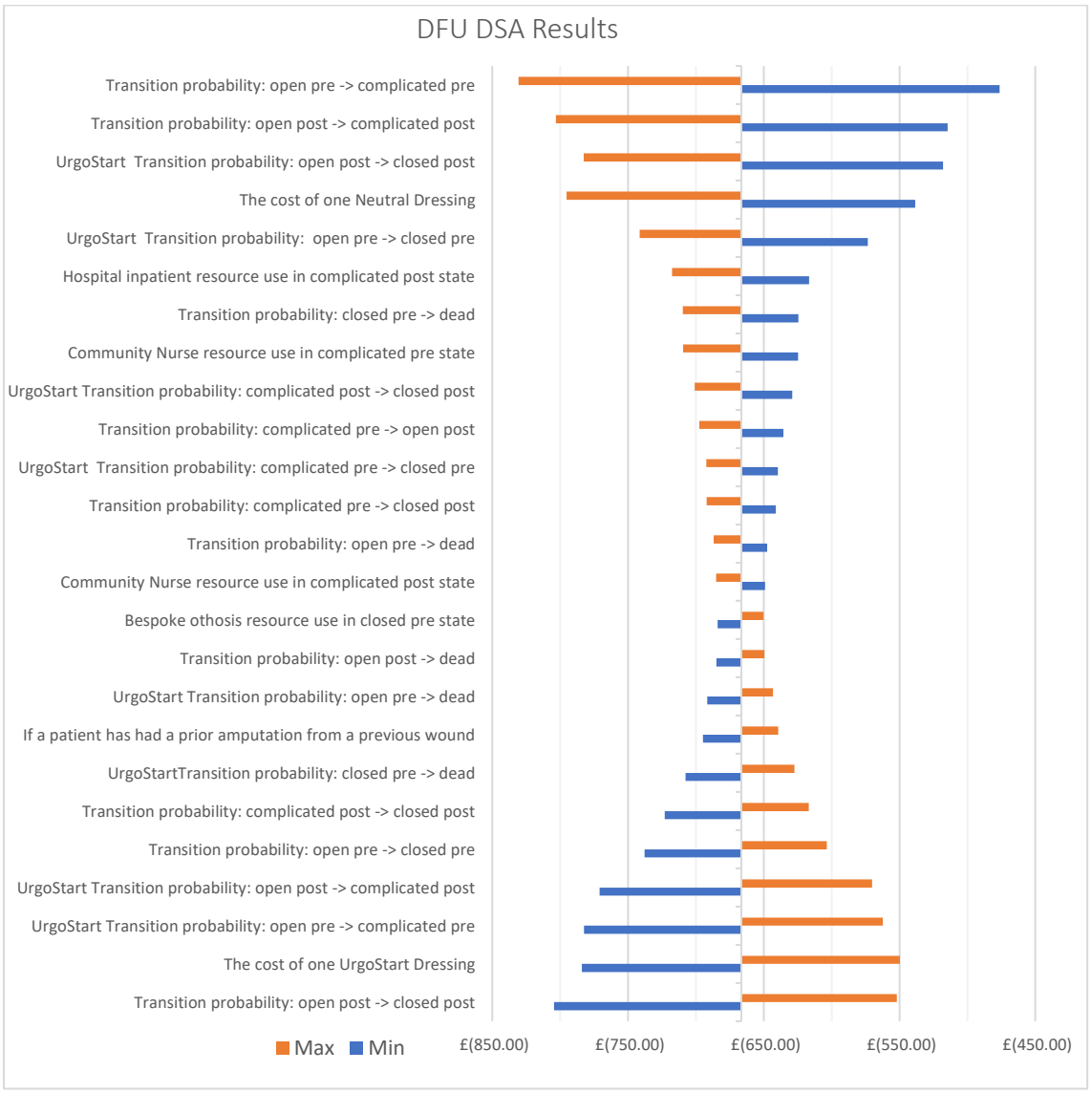


Figure 5.18. DFU DSA results

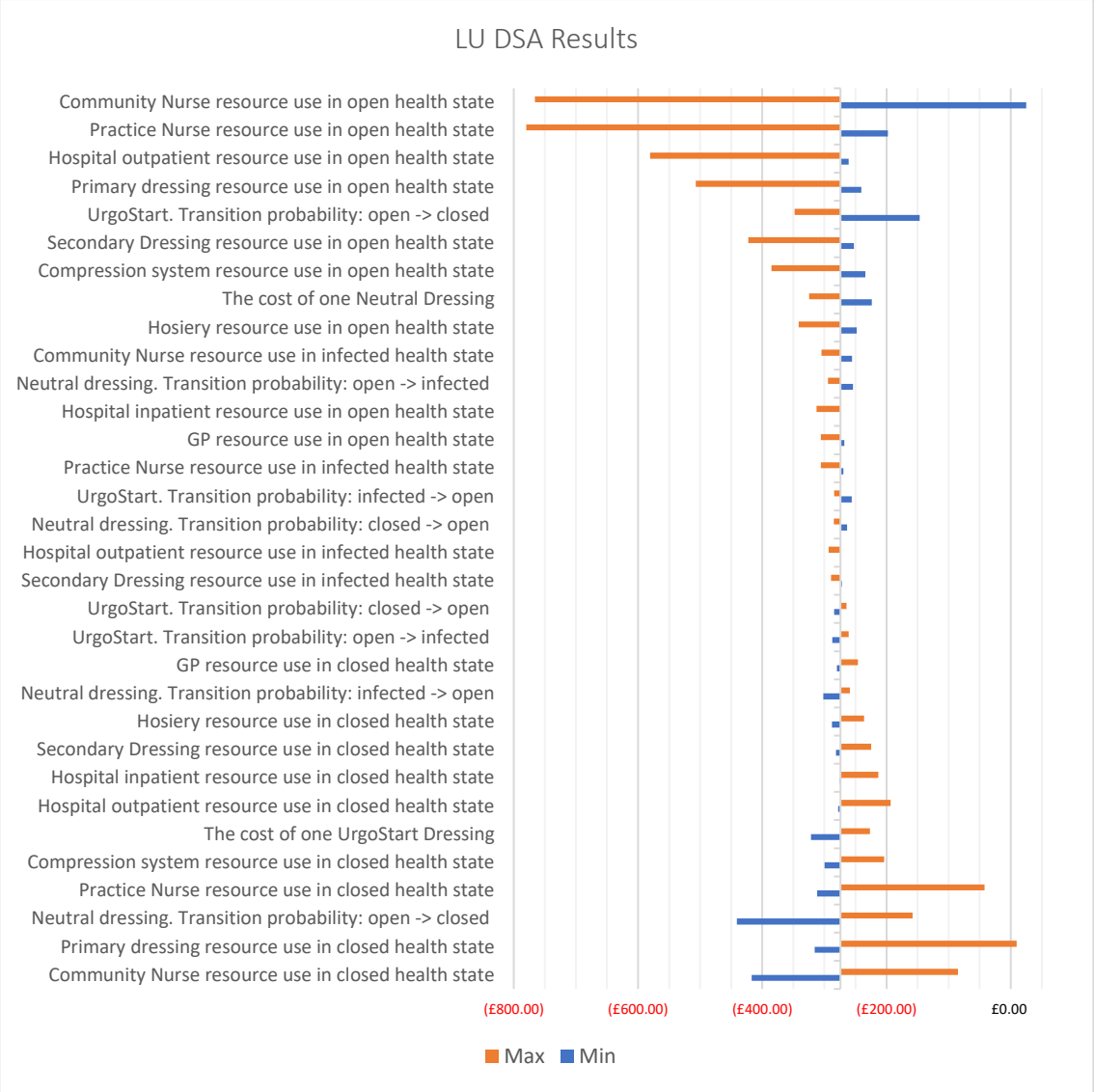


Figure 5.19. LU DSA results

Table 5.39. DFU PSA results

	Cost increment	ICER
Minimum	-£1352	-£92,789
Median	-£661	-£31,193
Maximum	-£1	-£99
Mean	-£664	-£31,713
Standard deviation	£212	£9,085
2.50%	-£1092	-£49,704
97.50%	-£262	-£15,209

Table 5.40. LU PSA results

	Cost increment	ICER
Minimum	-£1857	-£36,964
Median	-£305	-£10,577
Maximum	£427	£58,872
Mean	-£335	-£10,632
Standard deviation	£302	£9184
2.50%	-£1000	-£29,202
97.50%	£150	£5225

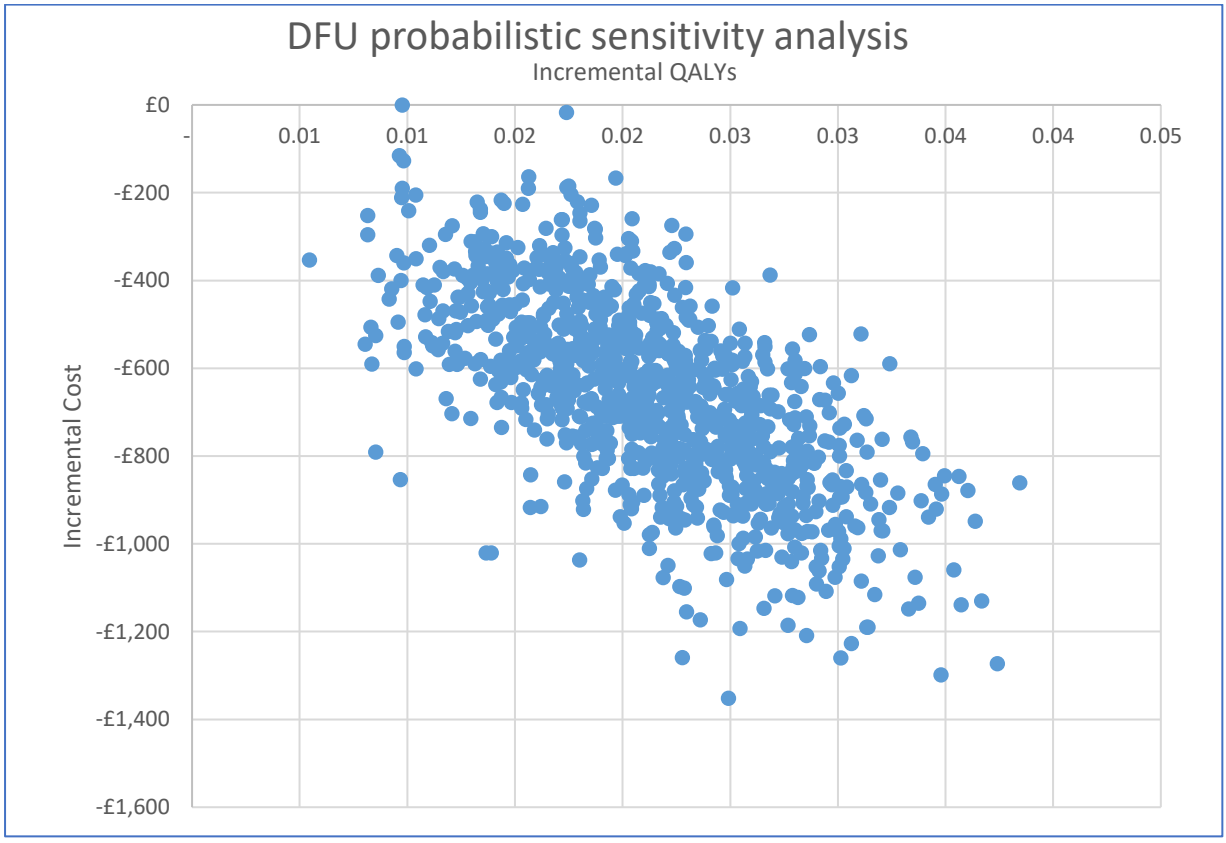


Figure 5.20. DFU PSA Results

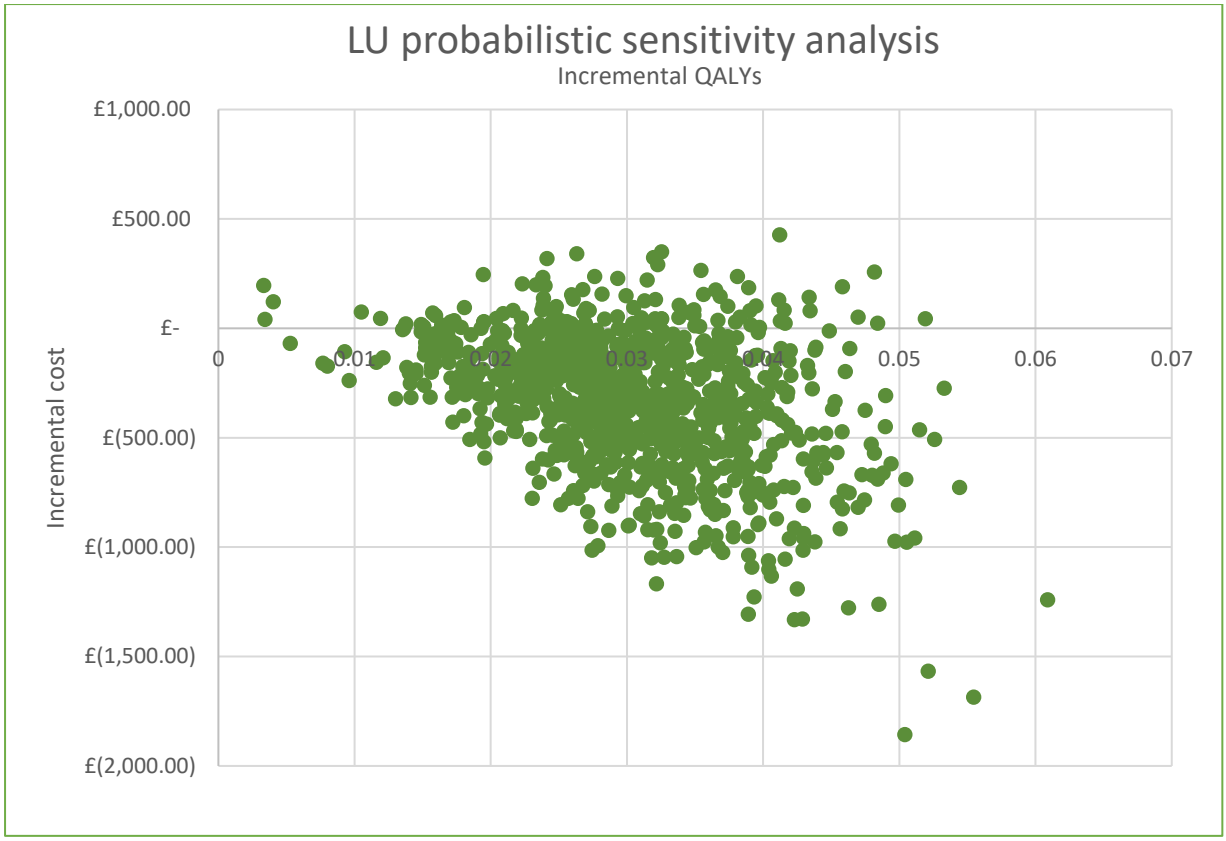


Figure 5.21. LU PSA Results

The DSA showed that when varying parameters individually the cost of the dressings was a key driver, as were transition probabilities for the sucrose octasulfate dressing and standard care. Despite these being influential factors, these could be varied within the set ranges and the sucrose octasulfate dressing would remain cost saving in any scenario. Scenario analysis also showed that if the comparator product were free (£0) the sucrose octasulfate dressing would remain cost saving (-£239.05) due to the increased efficacy and shorter healing time.

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

The DSA showed that when varying parameters individually then resource use during the open health state cause the largest variance in costs. In only two scenarios does the sucrose octasulfate dressing incur costs- with community nurse visits set at 0, £24.59 per patient is incurred and with primary dressing use at maximum in the closed health state, the sucrose octasulfate dressing incurs £9.68 per patient cost. The sucrose octasulfate dressing remains cost saving in all other scenarios tested. Scenario analysis also showed that if the competitor

product were free (£0) the sucrose octasulfate dressing would remain cost saving (-£105.80) due to the increased efficacy and shorter healing time.

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

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

5.6 Discussion

The economic evaluation in this chapter was designed to assess the cost implications of using the sucrose octasulfate dressing in combination with standard care, rather than using a neutral dressing with standard care. Two different methods of economic analyses were performed, budget-impact and cost-utility. The BIMs provided a population-level overview of the costs associated with integrating the sucrose octasulfate dressing into standard care. The BIMs were designed as static models; meaning that patients did not move through different health states or cost levels - they had a wound that healed in the period specified by the clinical data. The cost-utility model further analysed the consequences of using the sucrose octasulfate dressing. These models used health states that were representative of different stages of having a wound; and patients moved through these states using transition probabilities defined from published literature. These two models were chosen as they have different focuses; but together provide a clear overview of the costs and consequences of the new intervention. This selection is representative of the process used by NICE during HTA; and as such can be considered an appropriate evidence package to guide decision making.

The results of the analysis were in clear favour of the sucrose octasulfate dressing; with the increase in acquisition cost being overshadowed by the savings made in other areas; driven by the improved rate of healing reported in the clinical evidence.

The published clinical data showed improved outcomes for patients when using the sucrose octasulfate dressing, which the model demonstrates (Meaume et al., 2012; Munter et al., 2017; Edmonds et al., 2018). It is this efficacy, leading to shorter healing times, that drives the cost saving results. Wounds treated with the sucrose octasulfate dressing are more likely to heal, and thus less likely to spend time in the complicated/infected health states, where more resources are used. Particularly, for DFU patients, the avoidance of amputation is a driver of cost savings. The literature used specifies that wounds are more expensive to the healthcare system post-amputation (with a much higher likelihood of hospital admission) and by healing patients faster, some of these consequences are avoided.

5.6.1 Findings in context

The models agree with previous studies that were discussed in chapter 2 and in the scoping literature review reported at the start of this chapter in section 5.2. The models found that interventions that improve healing outcomes for patients result in savings to the healthcare system; even if the intervention is costlier that the direct comparators. The resource use data used here is from two studies of the THIN database published in March 2018 (Guest et al., 2018a; Guest et al., 2018b). Using a single source of information for the resource use, across indications and health states, is very useful in strengthening the internal validity of the results; as the data has been taken from the same cohort of patients. This cohort was a sample from real-world practice in the NHS; and as such the resource use levels applied in the model are generalisable to the wider population. The DFU study informed by the THIN database reports a cost range of £2140 - £16,900 dependent on the wound status (Guest et al., 2018b). The model built for this study shows an average per patient cost of £3627.76/£4172.54 (sucrose octasulfate/neutral dressing) which falls within these bounds. In the model, patients move between the health states, incurring the relevant weekly cost. In the Guest et al., (2018b) study DFU patients were shown to receive compression, this was excluded from the costs used in this current study model as it is not recommended for the treatment of DFUs. In the paper, 13% of costs come from amputations, which is higher than the 3-5% shown in our model. It is possible that the likelihood of amputation in the general population is higher than the sample population in the Explorer clinical trial (Edmonds et al., 2018).

The LU article from Guest et al., (2018a), estimated the costs of treating a LU as between £3000-£13,500 dependent on wound status. The model presented in this study shows a more

modest cost of £1579.23/£1856.56 (sucrose octasulfate/neutral dressing) despite using resource use values from this study published in this paper. This is likely driven by the large standard deviations of the resource use mean values, which were used in the base-case. When performing sensitivity analysis, the standard deviation was used to estimate the range of values, and the highest cost for neutral dressing was £3737. The healing rate applied from the RCT (Meaume et al., 2012) was higher than the healing rate reported in literature; and is perhaps reflective of the benefits of a highly protocolised treatment regimen as used in RCTs.

There are no previous published examples of UK focussed cost-utility models for the sucrose octasulfate dressing; with the work presented in this chapter being the first study to assess this dressing using the methods prescribed by NICE (NICE, 2013).

Further real-world data collection regarding use of the technology could provide data to show the effectiveness of the sucrose octasulfate dressing in patients receiving wound care outside of RCTs.

5.6.2 Budget-impact models

The BIMs found a slight cost increase in some scenarios, where the time to healing benefit was significantly reduced, and the least costly dressing used as part of standard care. However; these scenarios still resulted in fewer days with ulcer for patients. Given that clinical decision making is not be made on cost alone; it would be necessary to consider the improved outcomes for patients in any analysis.

5.6.3 Cost-utility analyses

The cost-utility analyses were more decisive in their results, with the sucrose octasulfate dressing dominating standard care, that is offering a cost saving and clinical benefits, in both the DFU and LU models. Extensive sensitivity analysis of the DFU model found that in all scenarios the sucrose octasulfate dressing remained cost saving; even in the case where the competitor product was provided free of charge. For the LU model, this was true in approximately 90% of cases, and where costs were incurred, they were still accompanied by health gains for patients. This is compelling evidence to support the assertion that improving clinical outcomes reduce cost to the healthcare system; even when the intervention being tested is not the least costly available, with regards to acquisition cost.

5.6.4 Discussion of methods

The economic evaluation presented here was part of an evolving process, with the models being developed from scratch to support the needs of this research. The study initially set out to perform a budget-impact analysis and a cost-utility analysis, two models that incorporated both indications of interest, DFU and LU. Combining the two indications in one model proved to overcomplicate the programming, without offering any tangible benefits. The models were based on different data, and the indications had different resource use, and in the case of the cost-utility analysis, the DFU model included more health states due to the need to incorporate the amputation event. This led to the decision to separate the models by indication; but they were designed on the same frameworks and aesthetically were near identical to show that they were part of the same larger body of work.

5.6.5 Additional analyses

The individual methods; budget-impact and cost-utility, were also adapted through the process to provide slightly different results that would be useful for a decision maker. The BIM was modified to compare the cost associated with uptake of the sucrose octasulfate dressings with a scenario where standard care remained the same. This provided a cost-consequence analysis which when reported, showed that using the new intervention resulted in savings when compared to not using it. Cost-utility analysis traditionally only reports the ICER value, with the results expressed in QALYs. The cost-utility analyses presented in this chapter were programmed to count the number of healed wounds for DFU and LU and in the case of DFU, the number of amputations, in each treatment arm. This allowed for a meaningful comparison of health outcomes; expressed in healing and amputation rates. Using the cost data in the model, it was also possible to assign a cost-per event; so, a cost-effectiveness calculation was performed to model the cost per healed wound.

5.6.6 Strengths and limitations

This research has several key strengths, with one being the use of contemporary data that is published and peer reviewed. The double-blind clinical trials are of high quality, as discussed in chapter 2, and this supports the results of the models. Further to this, multiple methods have been used; and these all have been tested with multiple sensitivity analyses; DSA, PSA and scenario analysis. Expert validation has been undertaken extensively with different groups of experts; clinical, economic, and health policy. As will be discussed in section 5.7; these

models have been externally reviewed and accepted by NICE and are now a part of UK clinical guidance (NICE 2019).

As with all methods; the economic evaluations performed in this study to assess the sucrose octasulfate dressing have their limitations, and strategies to overcome these have been implemented.

The static BIMs make assumptions that all patients treated cost the same per week until healing, with no provision to separate wounds that could cost more, such as complicated DFUs and infected LUs. The population funnel that identifies patients is also based on an annual incidence figure that covers the entire diabetic population and the model assumes that all these patients seek treatment from a health care professional. Another limitation that may reduce real-world applicability of the results is the fact that product list-prices have been used; which are possibly higher than the confidential net price that the NHS pays a manufacturer. These limitations do not nullify the results of the BIMs, as they have been developed and reported in line with the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) good practice guidelines for BIMs (ISPOR Task Force Report, 2014). The taskforce recommended using a cost calculator approach and to use published data to inform the models, both principles have been followed by the DFU and LU BIMs in this chapter.

The cost-utility models developed for this analysis are also subject to some inherent limitations because of employing the Markov method. Markov assigns probabilities to moving between the included health states, reported in a transition matrix, however, the model has no memory; meaning that past health states do not influence future transitions. This is potentially problematic when considering long lasting wounds, that are shown to be harder to heal (Margolis et al., 2004). Again, the model relies on list prices for resource use; which overlooks the impact of any patient access scheme or confidential price discount agreed between the manufacturer and the NHS. However, these limitations have been addressed by the design of the models and the fact that have been created using peer reviewed and published data. The patient characteristics that were programmed into the cost-utility models as reflective of the clinical trial populations of the Explorer and Challenge RCTs (Meaume et al., 2012; Edmonds et al., 2018). These trials included patients with varied wound duration, wound size and of different ages; all items that could impact healing rates or risk of mortality.

Additionally, the DFU cost-utility analysis used the same weekly cost for patients with closed wounds both pre- and post-amputation. Discussion with clinical experts highlighted the fact that a closed wound post-amputation is likely to incur a higher weekly cost; however, without the data available, this was left at the same level. This is a conservative assumption and will have affected both groups in the analysis and as such does not serve to undermine the cost-saving of the sucrose octasulfate dressing.

The LU cost-utility analysis relies on the mean values from the Guest (2018a) paper, which mostly have a large standard deviation. These values were tested using the sensitivity analysis, where the sucrose octasulfate dressing remained cost saving in all but two scenarios.

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

5.6.7 Further areas for research

Further work in this area could build on the results of the economic models presented in this chapter. The overall budget-impact of wounds is high, a significant area of spending for the NHS- and wound management should remain a priority item to ensure that patients receive optimal health outcomes whilst the health system manages the budget by prioritising interventions that can improve healing. With regards to the sucrose octasulfate dressing, further work could be done to assess the impact of the dressing on subgroups; such as those identified in chapter 4, patients with severe wounds that suffer lower quality of life because of their DFU or LU. Other risk factors for healing as identified in literature, such as wounds that are larger, long duration, or patients with comorbidities that could impact healing should be tested using economic modelling; to see if treating these groups with the sucrose octasulfate dressings result in health gains and cost savings. To achieve this; further clinical studies of effectiveness could be carried out, assessing the impact of the sucrose octasulfate dressing in real-world practice, in the NHS. A limitation of the LU model in presented in this chapter was the need to extrapolate the relative wound area reduction using statistical methods that introduce uncertainty; a further RCT of the dressing in the LU population would reduce uncertainty if this had a primary endpoint of full closure.

The model frameworks presented in this chapter, approved by a NICE EAC, can be repurposed in the future as they have been extensively validated to ensure they are representative of both DFU and LU. Given this; further work can be done to refine populations and reduce uncertainty to provide more robust evidence for medical decision making that can be communicated to the healthcare system and to practicing clinicians.

5.7 Health technology assessment

The cost-utility models were extensively tested, and peer reviewed as part of the HTA assessment made of the sucrose octasulfate dressing by NICE in 2018. NICE relies on external academic groups to assess economic submissions made during HTA. This is partly due to the capacity of the NICE team, but also to utilise the world class expertise in health economics and modelling at academic centres in the UK. The centre that was selected to assess the cost-utility models was King's Technology Evaluation Centre, (KiTEC); a collaboration between the King's College London School of Biomedical Engineering & Imaging Sciences, the School of Population Health and Environmental Sciences, and King's Health Economics, as well as the Guy's and St Thomas' NHS Foundation Trust Medical Physics department. KiTEC is a specialist External Assessment Centre (EAC) that works on NICE's MTEP.

The EAC checked the electronic models for errors and ascertained that the model was valid and believed the model structures adequately captured the required health states to examine the costs and consequences of the technology and comparators for patients with DFUs and LUs. The EAC reported that the assumptions in the model are reasonable and valid. They asserted that there are cheaper neutral dressings that may be equivalent to the comparator used in the models; however, this was addressed by the sensitivity analysis; the EAC asserted that the sensitivity analyses were appropriate.

The EAC critique of the DFU model used in this study, included some amendments to the resource use assigned to health states, and some unit costs - however none of the changes resulted in the sucrose octasulfate dressing being cost incurring. The EAC concluded that even with amendments, that the sucrose octasulfate dressing was dominant, saving cost and generating health gains. The EACs amended base case resulted in an annual cost saving of £342 for DFU patients; less than was found in the base case model presented above. For sensitivity

analysis the sucrose octasulfate dressing was cost saving in all analyses except for one analysis in which healing rates estimated from the Explorer trial (Edmonds et al., 2018) were reduced by 50%. In this scenario the sucrose octasulfate dressing generated a modest cost increase compared to standard care.

As per the review of the DFU model, the EAC amended some resource use assumptions and unit costs for the LU model. There were also concerns about using the exponential transformation rate to convert relative wound healing rates into healing rates, but in the absence of full healing data for the LU population it was accepted as the best option. The key change made by the EAC was the inclusion of the assumption that healed ulcers had zero weekly resource use. The EAC concluded that even with amendments, that the sucrose octasulfate dressing is dominant, saving cost and generating health gains. The EACs amended base case resulted in an annual cost saving of £541 for LU patients; a far greater saving than that of the base case model presented in this chapter. This is a result of the assumption that healed wounds incur no costs. Additionally, the EAC found that the sucrose octasulfate dressing was cost saving in all sensitivity analyses.

5.7.1 Publication of NICE guidance

Following the peer review and analysis carried out by KiTEC, the NICE MTEP committee reviewed the models and supporting submission of clinical evidence supporting the adoption of the sucrose octasulfate dressing. A positive NICE guidance for the sucrose octasulfate dressing was published on the 31st January 2019 (NICE, 2019). The NICE guidance reports that:

> *Evidence supports the case for adopting UrgoStart dressings to treat diabetic foot ulcers and Leg ulcers in the NHS, because they are associated with increased wound healing compared with non-interactive dressings.*
>
> *NICE (2019). Full guideline available at: https://www.nice.org.uk/guidance/mtg42*

This guidance should have the implication that clinicians who treat DFU and LU patients should now consider using the sucrose octasulfate dressing, as it has been declared as better for patients in terms of healing outcomes, but also results in savings to the NHS. As a result; this

research has directly impacted treatment guidelines and serves to improve outcomes for patients.

5.8 Chapter summary

This chapter presents the final study (study 5) of this thesis. The BIMs and cost-utility models that are described and reported here draw on the learnings from the other studies that have been carried out as part of this thesis (see chapters 2-4).

The economic evaluations carried out in this chapter has demonstrated that sucrose octasulfate dressings are proven to improve healing, but also are associated with cost savings to the healthcare system; even when tested with robust sensitivity analyses. This result has been externally validated by a NICE EAC and subsequence NICE guidance has been published to support the use of these dressings. The budget-impact analyses showed that by adopting the sucrose octasulfate dressing, the health care system can experience potentially large savings whilst reducing the number of days with ulcers for patients.

The implications of this research are that patients should experience faster healing and the sucrose octasulfate dressing should be routinely offered to patients who present with either a DFU or LU. The increased wound healing rate means that less patients should experience infected or complicated wounds, and in the case of DFUs, amputations should be avoided.

This new NICE guidance recommending the sucrose octasulfate dressing is currently in opposition to advice in the guideline for treating DFUs NICE Guidance (NG) 19, which states that the least costly dressing is the one that ought to be used (NICE, 2016). This was due to no evidence of superiority for a single dressing at the point of publication of NG19. Further work in this field would be to ensure that a future update of NICE NG19 includes a reference to the sucrose octasulfate dressing being proven to increase wound healing and has been recommended by NICE for use in DFU and LU patients.

The next chapter presents the overall discussion of the thesis, to explore the outcomes relative to the primary aim and thesis objectives.

5.9 Dissemination

The results of these study have been presented at the ISPOR conference in Europe, Barcelona, 2018 (Appendix D) and are referenced in the NICE MTG42 guidance documents (https://www.nice.org.uk/guidance/mtg42).

Chapter 6 Overall Discussion

6.1 Introduction

This PhD thesis set out to evaluate the clinical and economic impact of protease-modulating matrix (PMM) dressings with regards to the management of diabetic foot ulcers (DFU) and leg ulcers (LU) in the United Kingdom (UK), with the intent of making recommendations for guidance.

6.2 Aims and objectives

The aim of this thesis was:

– To evaluate the clinical and economic impact of PMM interventions in DFU and LU to inform the development of treatment guidelines in the United Kingdom.

To achieve this aim the objectives of the thesis were:

A. To evaluate current treatment guidelines.
B. To gain consensus on guidelines, and treatment strategies for chronic wounds.
C. To document quality of life (QoL) for DFU and LU patients
D. To assess clinical and economic impact of PMM interventions in wound management.
E. To assess the clinical and economic impact of the proposed recommendations.

Five different studies that link together were carried out to address the primary aim of this research. Figure 6.1 presents the full research study and the flow of the five studies.

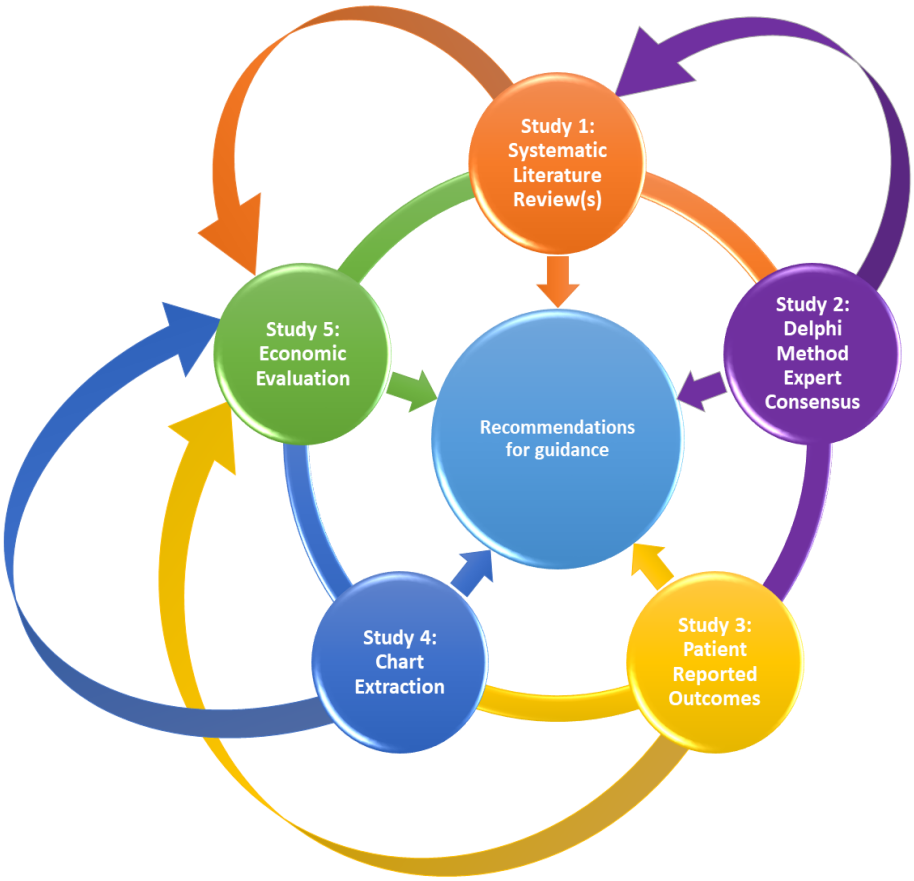


Figure 6.1. Overall PhD study framework

The aim and all thesis objectives have been successfully achieved, as outlined below. Further to this; the research that is presented here has culminated in a change of policy; in the form of a new clinical guideline regarding the use of the sucrose octasulfate dressing. The National Institute for Health and Care Excellence (NICE) has released guidance based on the body of evidence that was submitted as part of a medical technology evaluation process; NICE MTG42 guidance documents (https://www.nice.org.uk/guidance/mtg42). This guidance advises the use of the sucrose octasulfate dressing; acknowledging that it is a cost saving intervention that results in improved health outcomes for patients with DFU and LU (NICE 2019).

6.3 Discussion of thesis objectives

Each of the objectives are discussed in turn, highlighting the role of each of the studies; for further detail on the methodologies and results please refer to the corresponding chapters for each study.

6.3.1 Objective A: Evaluation of current treatment guidelines

Current treatment guidelines have been summarised in chapter 1 of this thesis; in the UK NG19 for DFU and SIGN120 for (v)LU. These documents, however, provide very little guidance with regards to the use of dressings, and as such this objective was achieved by evaluating current practice; in the absence of explicit guidance.

A varied approach to treatment is a key finding that recurs throughout this research. It is speculated that this is a direct result of a lack of clear guidance regarding wound dressings dictated by a national body such as NICE. In study 1, presented in chapter 2, the clinical systematic literature review (SLR), no meta-analysis was possible due to the heterogeneity of the included studies. This not only related to diverse patient populations but also the lack of uniformity across the standard care arms of included studies; there was no reference arm from which a strong network to power a meta-analysis could be built.

The economic SLR examined the use of standard care, and once again found that the standard care arms of the included studies in the economic SLR were not aligned; presenting multiple examples of 'standard care', that included a vast array of different protocols. Such heterogeneity is unhelpful; for clinicians and patients as there is not a consistent treatment protocol. Heterogeneity is also troubling for payers and industry as it makes a meta-analysis impossible. Meta-analysis is a key part of the NICE health technology assessment methodology to provide statistically robust comparisons with other interventions (NICE, 2013). Unchecked heterogeneity and a lack of meta-analysis introduces uncertainty that limits the extent of the guidance that can be published (Hakoum et al., 2017). If one assumes that payers and manufacturers want to encourage robust meta-analyses and minimise uncertainty; it implies that the reason for the divergence in standard care is due to a lack of consensus where there is no mandated guideline to adhere to.

Study 4 in chapter 4 also presented evidence to confirm the suspicion that standard care is in fact, not standard. The real-world data, representative of multiple clinical settings, found that treatment switches occur in nearly 80% of visits; making the variance in treatment between patients, or even between visits for the same patient, very explicit. Again, this variance is mutually detrimental; where no stakeholder is served well. Payers end up spending more on dressings due to longer healing times, patients suffer with wounds for longer, and the burden

on the health care providers is increased as patients' wounds do not heal. Manufacturers do not benefit, given that the high rate of treatment switching contrasts with the recommendation that a dressing be used for a set time (usually 6-8 weeks) to replicate the outcomes seen in clinical trials (Urgo Medical Ltd, 2019). When a dressing is switched earlier, the outcomes reported in clinical trials, where strict treatment protocols have been followed in narrow pre-defined populations, are unlikely to be replicated; an effect that can be considered as a bias (Kim et al., 2018).

The incidence of chronic wounds is increasing, further adding to the burden felt by all parties, requiring more effective treatment strategies (Diabetes UK, 2018; Office for National Statistics, 2018).

With such a variance found in treatment; both in real-world data and SLRs, should an optimal strategy be used, it is unlikely to be implemented uniformly throughout the UK, and will likely be outweighed by the volume of sub-optimal strategies still in practice. This claim is supported by a recent real-world evidence study, that found continued use of compression in patients with a DFU; despite this being contra-indicated (Guest et al., 2018). A further example is the £5.4 million spent on silver dressings for over 20 million patients in 2015; despite studies showing limited clinical benefit and a subsequent Cochrane review reporting that these treatments neither promote wound healing nor reduce infection (Storm-Versloot et al., 2010; NHS Presqipp, 2015). The result of this is resources being used sub-optimally, and the NHS budget being unable to maximise the health gain to the population due to clinical practice continuing to use out-dated practices that have limited benefits, instead of those with proven clinical and economic benefits.

In accordance with current guidelines (NICE, 2016) a clinician is encouraged to use "the least costly" dressing, an instruction that the economic SLR has demonstrated is unlikely to result in cost-effective treatment pathways. Current guidance falls short of a mandated treatment pathway for wound care dressings; which may be negatively impacting patient outcomes, as evidenced by the results of the chart extraction study in chapter 4, and supported by real-world studies in the literature, where healing outcomes also do not match randomised controlled trials (RCTs) (Guest et al., 2018).

Therefore, this research does not support the continuation of current NICE (2016) and SIGN (2010) guidance in its current form, as the resulting variation does not offer the best value to patients, payers, or the healthcare system. Variations, by their nature, mean that some patients are not receiving optimal care, and interventions that help to improve outcomes are not routinely used. This lack of mandated treatment guidance regarding wound care dressings is theorised to have come from the lack of high quality RCTs in this area. Guidance needs to be evidence-based; and without evidence, the guidance cannot be confirmed to be clinically nor cost effective.

6.3.2 Objective B: Consensus on guidelines and treatment strategies for chronic wounds

The literature reviewed in the Delphi panel in chapter 2 found a lack of consensus regarding wound care dressings, and the uncertainty surrounding new interventions. The Delphi panel that was convened to address this uncertainty arrived at a consensus regarding: the role of matrix metalloproteinases (MMPs); the need for management plans associated with shorter treatment periods and fewer adverse events; and a recommendation for early investment in treatment to improve patient QoL and provide a reduction in long-term costs. Consensus was reached swiftly, with multiple statements being endorsed unanimously by the panel. The consensus statement explicitly stated that prolonged futile treatment is costlier. The independent experts also highlighted the need for a long-term view from decision makers when making decisions about wound care dressings.

There are relatively few examples of Delphi panels being convened in the field of wound care (Serena et al., 2012; Schultz et al., 2017). Delphi studies often use a single type of expert; and Serena et al., (2012) is an example of this, focusing only on researchers gaining consensus regarding wound care research. Schultz et al., (2017) sought diversity in their panel, which aimed to answer a clinical question surrounding biofilms and their contribution to delayed healing of chronic wounds. Both studies, and the one presented in this thesis, are successful examples of the Delphi methodology, as all reached a consensus agreed by the experts which has since been published.

Advice surrounding Delphi methodology includes a recommendation to use a group of homogenous experts (Atkins et al., 2005). Contrary to this proposed methodology, the study presented in this thesis has used a multi-disciplinary approach; selected to represent the varied

group of stakeholders that treat patients with wounds. It was reasoned that to include just one type of health care provider (HCP) would risk excluding other HCPs from the final output; if a group was not involved in the development, they may be hesitant to follow the recommendations.

There is also the risk that if groups do not interact with those outside of their direct sphere, they may fail to see limitations that could be obvious to others (Karlsen et al., 2017). To avoid this 'echo chamber' effect and to produce a consensus statement meaningful to multiple stakeholders; a range of stakeholders were invited to participate. The Delphi methodology is also well suited to multi-disciplinary groups; especially when the groups involve HCPs of differing seniority; the anonymity afforded in the early rounds allows an equal weighting to be given to all opinions; without politics dictating that the group defers to the most senior person in the room.

Unfortunately, expert opinion is often subject to low levels of evidence classifications, due to its typically uncontrolled nature, yet as shown in study 2 this can be counterbalanced using a Delphi methodology. The anonymous, iterative approach protects from many of the risks of a traditional expert panel; including the risk of undue bias or pressure from the research sponsor. Such is this risk, Clause 22 of the Prescription Medicines Code of Practice Authority (PMCPA) Code of Practice is dedicated to meetings with HCPs, with further advice published specifically on advisory boards (PMCPA, 2016; 2019). This guidance does not always result in compliant interactions between industry and HCPs, as presented in section 3.2.5. Given the resulting poor reputation of the pharmaceutical and related industries, it is important to uphold scientific values and principles that can be offered by the Delphi methodology when compared to a traditional unstructured advisory board (House of Commons Health Committee, 2005; Goldacre, 2012; Morriss, 2019).

Furthermore, thesis objective B "to gain consensus on guidelines and treatment strategies for chronic wounds" has been achieved by the publication of guidance by NICE in January 2019 recommending the use of the sucrose octasulfate dressing. The publication of Medical Technologies Guidance 42 (MTG42) represents consensus between the members of the Medical Technologies Evaluation Process (MTEP) committee, the evidence review group, expert stakeholders, patient groups, academic institutes, and the manufacturer. A positive

NICE recommendation represents the highest commendation, globally, for an intervention and reflects the consensus that shorter healing times lead to improved outcomes; both in terms of clinical healing, patient QoL and financial benefits for the health care system (All-Party Parliamentary Group on Global Health, 2015).

6.3.3 Objective C: QoL in patients with DFU and LU

Another finding that is critical to stress, is the high burden to patients that is a consequence of having a chronic wound. This is not a revelation by this study and has been widely reported in literature; with chronic wound patients reporting a 'loss of self', depression anxiety, and problems with everyday activities (Walshe, 1995; Kinmond et al., 2003; Green & Jester, 2009; 2010). Study 3 in this thesis found that QoL was greatly impacted by having a DFU or LU, aligning with previous findings in literature (Jeffcote et al., 2009; Meaume et al., 2018). However, the research presented here has gone further and quantified the impact on QoL using the latest version of the EuroQol tool; the EQ-5D-5L that offers improved sensitivity to small changes in patient QoL (Janssen et al., 2018).

DFU patients had a lower mean index score when compared to patients with a LU, implying that patients with a DFU have a worse QoL than patients with a LU. There are many potential reasons why DFU patients report worse QoL than LU patients, including the fact that they tend to be younger and may have higher expectations of their health; additionally the DFU is also likely to be just one of a series of co-morbidities suffered by the patient. However, further qualitative research to investigate the relative differences found between DFU and LU would be able to provide more insight. The comparison of different types of wound can be made due to the use of a generic tool collected in a real-world setting. The study compared the utility scores of these patients with other chronic diseases and found that they scored lower, indicative of a worse QoL, than epilepsy, heart failure, asthma and chronic obstructive pulmonary disorder (COPD) (Peters et al., 2014).

QoL is not only measured using utility scores, there is also a financial impact on a patient, a wound has tangible costs that could include productivity costs from not being able to attend work. Patients may also need to purchase different clothing or shoes to accommodate the ulcer or pay transport costs associated with attending various appointments with HCPs based at different locations. These costs are not reported in any of the literature reported in the

economic models; with Tabolli et al., (2007) asserting that carer burden is under reported for these patients. The pressure exerted by these costs may negatively impact a patient's QoL.

Despite this burden; chronic wounds and the impact they have is not very prominent in the media, a simple Google news search only returns 32,400 and 6,720 results for DFU and venous LU and 65,500 for chronic wounds; however, searching for epilepsy returns 538,000 hits, asthma over 6.5 million, COPD over 17 million and heart failure over 22.5 million results (Google, 2019). This is a demonstration of the relatively limited coverage that these wounds receive and could explain why the severe patient burden is not acknowledged, and despite the high patient burden and cost to the healthcare system; chronic wound management is not a clinical priority area for the National Health Service (NHS) (NHS England, 2019). Without prioritising chronic wound management there is a risk that the current problems could continue, and potentially increase as the size of the diabetic and aging population grows.

6.3.4 Objective D: Clinical and economic impact of PMM interventions in wound management

The clinical SLR in chapter 2 found evidence of some PMM interventions being effective versus control in clinical studies. This study also found that not all PMM interventions are the same, with the results of the included RCTs suggesting that the sucrose octasulfate dressing is superior to oxidized regenerated cellulose. Versus control, the sucrose octasulfate dressing had favourable outcomes in trials measuring full wound closure and relative wound area reduction (Meaume et al., 2012; Edmonds et al., 2018). The sucrose octasulfate RCTs are considered as high quality; they achieve a higher level of evidence by using double blinded methods which are typically challenging in wound care studies. This means the results should be considered robust and relevant to clinical practice.

The chart extraction study, presented in chapter 4, also demonstrates the benefits offered by PMM dressings, by providing baseline real-world outcomes achieved by the current treatment practices. In this study 25% of DFUs healed within 20 weeks; this healing rate is similar to the control arm in the sucrose octasulfate RCT; where 30% of wounds healed when using a neutral dressing versus the sucrose octasulfate dressing which healed 48% of patients within 20 weeks.

Regarding economic impact; wounds are expensive to payers; they also exert a huge pressure on the resources of the healthcare system. Diabetes UK estimated that in 2014–2015 around £1 billion (or approximately £1 in every £140 the NHS spends) was spent on foot ulcers or

amputations with prescriptions for dressings accounting for £184 million of expenditure in 2012 (Diabetes UK, 2016). This had risen by 51% since 2004, a rate much higher than inflation in the same period; indicative of the increasing prevalence of wounds and the growing economic burden (Kerr, 2017). When considering that there is an intervention (the sucrose octasulfate dressing) that can improve outcomes; this spend feels poorly directed, when it could be used to address unmet needs of patients in other disease areas.

The chart extraction study, study 4, highlighted an infection incidence rate of nearly 20%. Infected wounds are more labour intensive to heal and require more frequent dressing changes; resulting in additional burden to the practitioners. The cost-utility analysis performed in study 5, showed that costs for HCP appointments, both inpatient and outpatient, accounted for 60% and 72% of annual costs for DFU and LU patients, respectively. This explicitly demonstrates that the cost of HCP time is the primary driver of costs, with wounds needing a high level of intervention to achieve closure; aligning with previous cost studies of chronic wounds; where nurse visits or inpatient stays accounted for most costs (Guest et al., 2005; 2015). It is not the cost of devices, but the cost of HCPs that drives the expense of chronic wounds; and in addition to the financial cost of the time; there is a further opportunity cost for the other patients that an HCP could be treating if a chronic wound healed quickly with minimal intervention.

6.3.5 Objective E: Clinical and economic impact of the proposed recommendations

The results of the economic SLR in study 1 highlighted the high cost to the healthcare system of nearly £4,000 for a DFU and over £1,500 for a LU (Guest et al., 2012; Craig et al., 2013; Jemec et al., 2014). Given the high, and growing, prevalence of wounds it should not be surprising that wounds contribute to a significant portion of healthcare spending in the UK, an estimated 5.5% of NHS expenditure was on wound care in 2016 (Phillips et al., 2016). This SLR also found that more expensive interventions are, in all included studies, cost-effective when compared to standard care. The sucrose octasulfate dressing, the most effective PMM intervention, was found to be associated with improved healing and faster onset of healing both of which contribute to the reduced healthcare system costs of chronic wounds.

If a wound heals faster, the patient will be in treatment for a shorter time; leading to a reduction in costs because of fewer HCP visits, as shown by previous economic models as well

as the evaluation performed in this study. As most costs have been shown to come from HCP visits, even a short reduction in healing time would offset the cost of using a more expensive dressing. The relative change in dressing cost may be initially large, but the absolute change is small when compared to the other high cost items; explaining why the sucrose octasulfate dressing was still cost saving in study 5 when the comparator price was set at £0.00. This is a powerful argument that demonstrates that making these changes is a low-risk strategy for payers; the sensitivity analyses performed on the cost-utility models found no scenarios where the sucrose octasulfate dressing is associated with a large cost increase.

The economic modelling assigned a standard care protocol that was derived from a large-scale real-world study of DFU and LU patients in the UK (Guest et al., 2018a; Guest et al., 2018b). An assumption was made that this real-world study included patients with various versions of standard care, and the aggregated results were assumed generalisable to a wider population. The active arm was identical to the standard care arm, except for the primary dressing as per the clinical trial protocols and justifies the assumption that the differences found were due to the sucrose octasulfate dressing and not confounding factors. These assumptions were validated by clinical and academic experts; and by the External Assessment Centre (EAC) and NICE committee during the production of the subsequent MTG42 guidelines (https://www.nice.org.uk/guidance/mtg42).

The budget impact models provided a population-level overview of the costs associated with integrating the sucrose octasulfate dressing into standard care and found that a saving was made for both DFU and LU populations, both in terms of costs and patient days with ulcer. When considering the cost-utility analyses, the results of the analysis were in clear favour of the sucrose octasulfate dressing; with the increase in acquisition cost being overshadowed by the savings made in other areas; driven primarily by the improved rate of healing reported in the clinical evidence. Compared to other cost studies found in literature; this result is similar; finding in favour of the active intervention, as per all the included studies in the economic SLR presented in chapter 2. This is because all the models were based on clinical studies where the intervention offered an improvement in healing outcomes, and thus reduced healing times in the model. As discussed in chapter 5, a reduction in healing time leads to a significant cost saving, one that can offset an increase in acquisition cost of a topical intervention or dressing. The difference between this model and those presented in chapter 2 is the fact that this model

is based on data from randomised double blinded trials which enhances the validity of the results.

The sucrose octasulfate dressing reduces the time to healing in both DFU and LU patients and as a result reduces the economic impact of these wounds. The economic modelling in study 5 confirms this assertion; which has since been taken forward by NICE and included in clinical guidance for the UK healthcare system (https://www.nice.org.uk/guidance/mtg42).

6.4 Strengths and limitations

This PhD thesis has several strengths, including methodological strengths and external support for the conclusions drawn. Methodologically, this research used a multi-method approach, drawing from different data sources and using different analysis methods to paint a complete picture surrounding the use of PMM interventions in wound care. This picture included evidence from patients, clinicians, existing research and evaluation of current practice. This is a key strength as the evidence produced here has been subject to evaluation by The King's Technology Evaluation Centre (KiTEC) NICE EAC, and subsequent appraisal by the NICE committee. The review by the EAC and NICE has resulted in the recommendation to use the sucrose octasulfate dressing being accepted into mainstream guidance published by NICE. This is unique, as before now no dressing has been recommended for use by NICE, other than the generic instruction to use that with the lowest acquisition cost.

Another strength of this research is the diverse range of stakeholders who have had input. Clinicians have been consulted throughout; in study 2 they were the source of the evidence and in study 5 their expertise was consulted to validate the assumptions and parameters used in the economic modelling. Clinician input is crucial as they have direct, front-line experience with patients, they can offer key insights that may be lacking from desk research such as the SLRs in chapter 2. Patients were also a crucial stakeholder, with study 3 focussed entirely on collecting their experience and quantifying this for use in the economic modelling study in chapter 5. Patients are the ultimate beneficiary of any changes to wound care strategies and have their own opinions and experiences with care; it is important to understand their perspective. The approach towards healthcare has moved away from doctor driven treatment mandates and towards a paradigm where patients are active participants in their care (European Patients Foundation, 2015). Patient data has also been recorded in study 4, but with

less involvement from the individuals. Furthermore, policy experts were consulted in study 2 and study 5; to provide insights regarding the health system and validate assumptions regarding resource use and uptake.

An important stakeholder when assessing the merits of this research is NICE; and a strength of this research is their validation after the endorsement by KiTEC, (external review group that independently assesses evidence for NICE to maintain consistent standards across the NICE processes and committees). NICE is a world leader in producing guidance on interventions, and the ratification of the economic evaluation structure and results provides strength to this research and enhances the validity of this thesis.

Current literature has been extensively reported on in this thesis, with the overall PhD having several SLRs of the evidence. These included the clinical SLR of PMM interventions and the broad economic SLR in study 1; the systematic literature search in study 2 that was used to develop the statements tested during the Delphi panel. Further scoping literature reviews in study 3 and study 5 were performed using a systematic approach to retrieval of articles. Therefore, this study has been guided by current literature and given that the results presented in this thesis are concordant with the existing evidence, provides a level of external validity to the results. This study does not stand alone but has made conclusions that align and build on the current body of evidence and further synthesizes the evidence, and collected new data, to update the body of knowledge with meaningful results that have had real impact on practice through a change in clinical guidance (NICE 2019).

In addition to secondary research synthesising current literature, this PhD also collected original data from varied sources to investigate the research topic further. This included the opinions solicited from experts in study 2, the use of validated patient reported outcome tools in study 3, and the retrospective real-world data collected in study 4; both presented in chapter 4. New data was necessary to fill the evidence gaps found through the literature searches to ensure the generalisability of this research to the patient population in the UK.

The economic evaluations performed in study 5 were heavily evidence-based, synthesising the results of the previous studies with all assumptions being valid, justifiable, and based on the learnings made throughout this research programme. An outcome of this process is that the

results of the economic evaluations can be interpreted as robust and with limited uncertainty; as proven by their resistance to sensitivity analysis and adoption by NICE.

During the development of this thesis, several outputs relating to each of the individual studies have been produced to disseminate the knowledge gained to a broad audience. This had the additional advantage of subjecting the methods and results to a peer review process before the development of the final economic evaluation; which gives the results of the economic analyses even more credence. The International Society of Pharmacoeconomic and Outcomes Research (ISPOR) is the leading professional society for health economics and outcomes research (HEOR) globally; with the mission of promoting excellence to improve decision making for health globally (ISPOR, 2019). ISPOR hosts annual conferences that are attended by thousands of HEOR experts. All studies that constitute this PhD thesis have published outputs, see Appendix D.

Despite the numerous strengths of this research; there are also inevitable limitations; that have been mitigated where possible. Studying wound care interventions is often difficult, due to the inherent challenges in performing a double blinded RCT. This is because the intervention is not just a pill or procedure; but a device that is attached to a patient by a healthcare provider. Dressings typically come in different packaging and experienced practitioners would be able to identify a type of dressing based on look and feel alone. As a result; many studies of wound care interventions are subject to low levels of evidence; which explains why the Cochrane review performed in venous LU (Westby et al., 2015) struggled to identify any superior dressings in line with their strict methodology that assesses study design and risk of bias. This has been overcome in this study, because of the level of evidence available to support the sucrose octasulfate dressing. The manufacturer could perform double blinded trials due to them offering a range of products; and were able to allocate identical dressings to the treatment arms, but with only one group receiving the dressing impregnated with the PMM, sucrose octasulfate.

An additional limitation of this research into chronic wounds is the variability in the diagnosis methods for LU. There is variance within LUs, regarding what is considered a venous LU and what is just a LU. The studies included in this PhD programme have taken a pragmatic approach to overcome this difficulty; the terminology has been broadened to ‘leg ulcer’ which can

include those of venous, arterial, mixed, or unspecified, origin. This decision has been taken, not only for pragmatic purposes, but also because the treatment regimen for these variations of LU is similar.

The economic evaluation presented in chapter 5 also takes the perspective favoured by the NICE methodology, which only includes direct medical costs (NICE, 2013). This perspective thus excludes costs incurred by the patient and carers; including transportation, time off work, and any modifications to their home or lifestyle required due to having a DFU or LU. Further, societal costs are excluded from this approach; which include time off work and any social care required by the patient. The decision was taken because of the evaluation taking place in the England, where the dominant HTA body, NICE, only considers direct medical costs when assessing the cost-effectiveness of an intervention. This standard is currently being challenged as part of the NICE methods and process review, which is considering the inclusion of other costs (NICE, 2019). The models in this thesis have been designed to accommodate the addition of these costs and future research can explore the extent of these costs.

All research results are subject to levels of uncertainty; however, the uncertainty in this programme has been mitigated through a variety of methods. This is by performing repeated literature searches to support the individual studies, where appropriate. Also, the economic models were validated by external experts; tested using multiple sensitivity analyses; and further validated by the independent evidence review group in the process of developing NICE guidance. Finally, having a series of studies that support the primary aim of the thesis allows for analysis of the results as a collective; and these results all support each other; with the strength of the conclusions supported by each study.

6.5 Lessons learned

Due to the interdependence of the studies in the thesis, a few minor amendments had to be made to the planned study that followed. Where necessary, if the results of a previous study highlighted an important finding this was included in the studies going forwards. The focus throughout the PhD, has been on the PMM dressings; and considering the findings of the clinical SLR (study 1), which highlighted that not all PMM interventions are the same; the focus was placed on the intervention found the be the most efficacious, the sucrose octasulfate dressing. This was then taken forwards into economic evaluation to ensure that the

intervention offering maximal benefit was assessed. Additionally, in study 1, a QoL SLR was planned; however, the review discovered that a SLR has been carried out by Green (2009 and 2010) which followed the same proposed design; assessing quantitative and qualitative evidence separately. This planned systematic review was then abbreviated and presented as a scoping review at the start of study 3; to contextualise the study and highlight how the original research carried out for this PhD added to current literature.

The changes made throughout the process sought only to strengthen the results and enhance the validity of the research and to improve any recommendations that could be made using the body of evidence produced. The changes were minor and only served to clarify the scope, in the case of focussing on the sucrose octasulfate dressing, or to avoid the duplication of work already in existence, such as the abbreviation of the QoL SLR.

6.6 Towards the development of guidelines

The primary aim of this PhD thesis was to evaluate the clinical and economic impact of PMM interventions in DFU and LU, with the intention of developing recommendations for guidance; this being at the heart of the figure shown throughout this thesis (Fig 6.1). This next section begins with an examination of current UK guidelines for DFU and LU and their limitations. Next; a discussion of the recommendations made in this PhD, and how they address the limitations of current practice. Finally, this section discusses the future implications and next steps with regards to guidance for using wound dressings DFU and LU.

6.6.1 Current guidance

A guideline for treatment of DFU was issued by NICE in 2015, focusing on prevention and management, and was last updated in January 2016 (NICE, 2016). The guidance, NG19, advises the use of 1 or more of the following: offloading, control of ischaemia, control of infection, debridement and wound dressings (NICE 2016). Section 1.5.10, is the sole paragraph in this guideline on the use of dressings:

> *When deciding about wound dressings and offloading when treating diabetic foot ulcers, take into account the clinical assessment of the wound and the person's preference, and use devices and dressings with the lowest acquisition cost appropriate to the clinical circumstances*
>
> *(NICE, 2016).*

This is repeated in the Scottish Intercollegiate Guidelines Network (SIGN) guideline for treating venous LUs; published earlier in 2010. Wound dressings are somewhat more prominent in this guideline; being included in the key recommendations, and having a section, 4.3, dedicated to them (SIGN, 2010). However; the SIGN guidance states:

"Simple non-adherent dressings are recommended in the management of venous leg ulcers"

(SIGN, 2010)

This instruction is indicative of the budgetary pressures faced by the NHS; and shows a preference for the lowest cost wound care dressing as at the time of writing there was no robust evidence considered by NICE or SIGN to support the clinical and cost-effectiveness of a more expensive or advanced dressing. There is an abundance of different types of wound dressings used in clinical practice, as shown in the chart extraction in chapter 4. With such a range of products on offer, a cost-containment strategy is useful in reducing acquisition costs in a crowded market, as manufacturers are forced to compete on price to win NHS tenders.

As a health technology assessment body, NICE fits the cost-effectiveness archetype, given the assessment methodology that calculates an incremental cost-effectiveness ratio (ICER), and maps this against a willingness to pay thresholds of £20,000-30,000 per QALY (McCabe et al., 2008). Chapter 5 of this thesis explores both cost-consequence and cost-utility as relevant modelling methods appropriate for NICE.

Despite this guidance appearing to be sensible and pragmatic in reducing upfront acquisition costs, a limitation of this instruction is that it disregards clinical benefits and the associated cost savings offered by efficacious interventions such as the sucrose octasulfate dressing. Dressings that are shown to reduce healing times can provide other savings to the health care system, in the form of reduced contact with health care professionals, overall lower resource use, and lower risk of infection and amputation due to less time with an open wound.

The guidance to choose the dressing with the lowest acquisition cost is in opposition to usual NICE decision-making processes and worryingly, cost-containment could lead to products that offer expedited healing and improved patient outcomes being left on the shelf in favour of cheaper alternatives not offering any significant clinical benefit- and ultimately leading to higher costs and worse outcomes as patients remain ulcerated for longer. This leads to

unnecessary patient suffering, a detriment to society due to the significant costs and high resource use incurred by persistent ulceration.

Another limitation of this strategy is that practitioners in the UK should now be used to the typical assessments of cost-effectiveness or cost-utility issued by NICE over the last 20 years that routinely recommend interventions that are higher cost; but cost-effective given their efficacy. The deviation from this standard procedure in guideline NG19 may lead to confusion about best practice. Clinicians likely understand the benefits of reducing healing times beyond only the clinical benefits, but also the economic benefits; and as such could use interventions that allow them to achieve this. Without a clear direction that needs to be universally applied; the variation that is seen in treatment pathways will continue and optimal outcomes will not be achieved.

6.6.2 Development of guidance

As shown by the results of these studies, the management of chronic wounds such as DFU and LU is a key area that could benefit from updated and refined guidance that provides explicit details regarding dressings. The focus of the studies presented in this thesis is specifically the use of PMM dressings which have not, to date, been addressed by NICE or SIGN.

The evidence presented in this thesis, and the subsequent publication by NICE of guidance for use of the sucrose octasulfate dressing can be presented to clinicians to inform their decision making when choosing a dressing for a patient.

The clinical SLR in chapter 2 supports the superiority of the sucrose octasulfate dressing above other PMM dressings; and demonstrates an improvement in wound healing, both complete closure rates, time to healing, and speed of onset. The patient reported outcome (PRO) study confirms that improved healing will result in an improved QoL for patients with DFU and LU as they are shown to be impacted by their wounds, with more severe wounds causing further suppression of QoL. This heavy burden, and the efficacy of PMM interventions was unanimously supported by the experts consulted in chapter 3, the Delphi study.

The need for guidance is highlighted by the economic SLR which noted the discrepancy in standard care. As only 4 out of 12 included studies were performed within the last 5 years it was important to verify these findings using real-world evidence, as provided in chapter 4;

finding again no universal application of standard of care when looking at wound dressings. This researcher speculates that this is a direct consequence of the lack of guidance, and that without clear direction it will only continue; meaning patient QoL is being reduced and extra NHS funds spent on wound care quite unnecessarily when an efficacious dressing is available.

This thesis has proposed that patients presenting with a DFU or LU be treated with the sucrose octasulfate dressing as part of the main care protocol. This strategy has been tested thoroughly in the economic evaluations carried out in chapter 5 and found to be not only cost-effective but cost-saving in nearly all scenarios included in the robust sensitivity analyses.

This thesis agrees with the published discourse asserting that a focus on healing wounds faster results in better economic outcomes, instead of relying on acquisition cost (Guest et al., 2015). However, this is in stark contrast to the published guidance, which does not recommend a specific dressing (SIGN, 2010; NICE 2016). It is not clear why NICE persists with this instruction despite the cost-effectiveness of more expensive interventions being proven. It can be speculated that this is because of the prior lack of submission to NICE or another body by a wound care dressing.

This thesis has addressed this gap; by proving the high-quality evidence and extensive economic modelling using data relevant to the UK, and in a concurrent project this evidence has been submitted to the NICE MTEP; and guidance recommending the use of the sucrose octasulfate dressing, MTG42 as presented in section 5.7.1 has been approved and published (NICE, 2019).

6.6.3 Beyond treatment guidance

The NICE guideline that recommends the use of the sucrose octasulfate dressing is a key milestone in improving outcomes for patients with DFU and LU. This guidance provides an instruction to clinicians that the sucrose octasulfate dressing provides patients with improved outcomes and is associated with cost savings to the NHS. This is the first time in UK clinical practice that a single type of dressing has been recommended for use above all others. This is an exciting outcome of the work presented here; however, it is not the end of the journey.

Going beyond treatment guidelines; it is important to raise awareness of MTG42 to ensure uptake and optimal access for patients across the UK. As NICE is recognised as a world-leading body it is hoped that this guideline will also enable access to patients outside of the UK.

The implications of these findings are that there should be a shift towards using the sucrose octasulfate dressing, the only wound care dressing proven to be cost effective and recommended by NICE (NICE, 2019). However, there are potential barriers to this. The NHS in England is a large system with defined procurement processes, meaning a change is hard to implement outside of set process cycles (NHS Supply Chain, 2020). However, there is hope for the sucrose-octasulfate dressing to be prioritised at the next review of Advanced Wound Care products at the end of 2020 (NHS Supply Chain, 2020). Further to this, medical technologies guidance has no funding mandate, unlike guidance published for pharmaceutical products. As such, there is no legal obligation for commissioners to follow this guidance, which could have negative implications for patients, clinicians and payers if unproven dressings are used, perhaps due to their lower acquisition price, despite a persistent open wound being burdensome for all stakeholders.

6.7 Chapter summary

The five studies that constitute this research programme have each helped to shed light on areas where research had previously been sparse and have proceeded to fill evidence gaps using secondary research to interrogate the existing literature and collecting new data to supplement where necessary. This evidence was used to drive the development of new economic models for DFU and LU; using data, insights and conclusions that were generated from the previous studies in the thesis. The subsequent acceptance of the economic models by NICE and publication of MTG42 is a testament to the robust nature of this research programme, and the accompanying evidence generation initiatives.

This chapter has discussed the objectives of this thesis in depth, including the strengths and limitations. The final chapter of this thesis includes a brief summary of the thesis, followed by the study's' conclusions and recommendations.

Chapter 7 Summary, recommendations and conclusions

7.1 Introduction

This final part of the thesis draws on the body of evidence that has been discussed in the previous chapters and presents the summary, conclusions and recommendations based on the evidence and insights presented here in this research. Together the studies answer the primary research aim; to evaluate the clinical and economic impact of PMM interventions in DFU and LU to inform the development of treatment guidelines in the United Kingdom. A positive impact would mean reduced healing times for patients, resulting in more time without an ulcer and more life years lived with better quality of life (QoL). Because of reduced time to healing, financial savings to the healthcare system would be experienced; patients would have fewer expensive complications and have less interaction with healthcare professionals.

The following section presents a short summary of the thesis, considers the implications of the studies in relation to clinical, economic and policy themes; and then presents the contribution to knowledge made by the studies, individually and as a collective.

7.2 Summary of thesis

Below, a summary of each of the studies is presented, for further detail please see each of the corresponding chapters. Together, these five studies form the body of work that addresses the primary aim of this PhD thesis.

Study 1 comprised of two systematic literature reviews (SLRs). The clinical SLR found evidence of PMM interventions being effective in improving healing outcomes when compared to standard care. The economic SLR found an abundance and variance of treatment options, presenting multiple applications of 'standard care,' which included a vast array of different protocols. The expert panel in study 2 concluded that that chronic wounds cause significantly reduced health and QoL for patients and this needs to be taken into consideration in patient care with the aim of reducing healing time, and that inhibiting MMPs plays an important role in wound healing. By use of the EQ-5D, study 3 mapped patient QoL against a severity ranking; and showed that patients with DFU or LU had a lower utility score when compared to patients with other chronic conditions, implying that patients with DFU or LU have a worse QoL than patients with epilepsy, heart failure, asthma or COPD. A retrospective chart review of electronic patient records, study 4, found a treatment switch in 79% of eligible visits; with

nearly a quarter of records not providing a reason for the change. This finding reflects the outcome of the economic review in chapter 2; that there is no single application of standard care. This researcher theorised that it is the lack of explicit guidance regarding the use of dressings that has led to this variation in care.

Study 5 carried out a full economic evaluation, comprising two different methods of economic modelling; a static budget-impact model (BIM) and Markov model cost-utility analysis (CUA). The budget-impact analyses showed that by introducing the sucrose octasulfate dressing, the health care system can experience potentially large savings whilst reducing the number of days with ulcers for patients. The results of the cost-utility analysis were in favour of the sucrose octasulfate dressing; driven by the improved rate of healing reported in the clinical evidence. The sucrose octasulfate dressing was proven to be a cost dominant strategy, meaning that it only cost-saving and resulted in health gains. This conclusion was tested extensively using sensitivity analysis and stood resolute in a variety of scenarios.

7.3 Summary of strengths and limitations of the thesis

This thesis enjoys the following strengths:

- Thorough peer review, ISPOR, by NICE and the EAC.
- Resulted in the publication of the first NICE clinical guideline on a specific dressing (https://www.nice.org.uk/guidance/mtg42).
- Multi-method approach using primary and secondary data sources to provide a holistic and well-rounded thesis.
- Diverse range of stakeholders, multi-disciplinary approach reflects the treatment of chronic wounds in practice.
- Alignment with previous research providing external validity to the results.

The following limitations have been identified and, where possible, their impact mitigated:

- Lack of high-quality evidence in wound care; mitigated by the two double-blind RCTs performed on the sucrose octasulfate dressing.
- Variability of diagnosis methods for LU; overcome by including all leg ulcers that are described as chronic due to consistency in treatment protocols.

– Economic modelling takes a payer perspective, that of NICE in England, and thus excludes patient, carer and societal costs. This is the industry standard and what is required for submission into NICE technology appraisal programmes.

7.4 Summary of implications of the thesis

This thesis began with an assessment of the current literature and found no contemporary studies on QoL for patients with DFU and LU; no NHS perspective economic modelling, no analysis of treatment switching and no assessment of the sucrose octasulfate dressing. The body of knowledge that is presented in this thesis has addressed these gaps and drawn conclusions that have several implications for the future. The implications are presented below under the categories of clinical and practice, economic, and policy.

7.4.1 Clinical and practice implications

The research presented in this thesis has demonstrated that there is a dressing available that can improve clinical outcomes for patients; the sucrose octasulfate dressing (Meaume et al., 2012; Edmonds et al., 2018). The implication of this is that, if used, wounds will be more likely to heal, and they will do so at a faster rate. Additionally, patients will benefit from reduced adverse events due to less time with an active ulcer as shown in the economic modelling presented in chapter 5. For DFU patients this equates to fewer amputations, which can be a significant and traumatic surgery; additionally, this will mitigate some of the mortality risk associated with DFU and amputation (Stern et al., 2017). For LU, this would mean fewer infections for patients and less likelihood of a wound becoming long-lasting and thus even more difficult to treat (Margolis et al., 2004).

For a wound care practitioner, the findings presented here should provide evidence to support decision making regarding wound care dressings; as it has been shown that the sucrose octasulfate dressing is the cost-effective choice that offers improved healing. This should provide clarity where previously there has been none; being able to rely on the series of studies presented here using the multi-methods approach should give confidence to decision makers; even in opposition to current NICE guidance NG19 that instructs them to use the dressing with the lowest acquisition cost.

Empowering health care providers (HCPs) to make decisions that are in the best interest of their patients is an important implication of this research; and one that should hopefully cause a step-change in how patients with a DFU or LU are treated.

7.4.2 Economic implications

The clinical outcomes presented in this thesis have subsequent economic implications for the healthcare system in terms of reducing cost and facilitating efficient resource utilisation. Wounds accounted for approximately 5.5% of NHS expenditure in 2016 (Phillips et al., 2016), and this would be expected to reduce if wounds were more likely to heal, and heal faster, with fewer adverse events.

The cost-utility models presented in chapter 5 showed that the highest cost category for both DFU and LU was outpatient treatment such as community nurses or General Practitioner (GP) appointments; and this research shows that this can be reduced by following the treatment regimen including the sucrose octasulfate dressing. In the DFU model, the biggest relative change was seen in the cost of amputation events, which was 47% less in the sucrose octasulfate group than the standard care only group. Amputation is a costly adverse event, and the model shows a nearly 50% drop in the number of amputations carried out in the sucrose octasulfate arm (40/1000 patients vs 21/1000 patients). Key drivers of the cost are the cost of the dressings, the transitions for healing and infection/complication and the resource use with regards to community nursing and hospital visits. The increased likelihood of healing drives the cost savings for the sucrose octasulfate dressing.

These cost savings would enable budgets and resources to be redistributed in the healthcare system to ensure that the maximum health benefit is being obtained from the limited budget and resources available.

7.4.3 Policy implications

The findings of the CUA and BIMs presented here have been ratified by the NICE Medical Technologies Evaluation Process (MTEP) during the assessment of the sucrose octasulfate dressing, as discussed in chapter 5. As a result of this assessment, and as a testament to the robust nature of this research; NICE has subsequently published a new guideline regarding the sucrose octasulfate dressing. Medical Technologies Guidance 42 was published in January 2019 recommending that the sucrose octasulfate dressing, UrgoStart, be used as an option for

people with DFU or (v)LU. This guidance is published and freely available on the NICE website at www.nice.org.uk/guidance/mtg42.

The publication of guidance supporting the sucrose octasulfate dressing is encouraging, however uptake of medical technologies guidance is not mandatory. This is inherently biased against interventions that present as a device, as pharmaceutical products with the same level of evidence and recommendation for use by NICE have a funding mandate from the NHS; and should a patient be clinically indicated to receive the product, then it must be made available to them. However, this does not currently extend to medical devices assessed using the MTEP. To realise the outcomes presented in this thesis, the recommendation to use the sucrose octasulfate dressing should also be in receipt of a funding mandate, to prevent clinicians from avoiding use until later in the treatment pathway due to a bias in favour of dressings with a lower acquisition cost.

Fortunately, this is currently under review and a presentation given at the NICE Annual Conference 2019 in Manchester has explicitly stated that a funding mandate is being developed for medical technologies guidance. This is to address the bias against interventions that are classified as a device. The policy is expected in March 2020 and active from October 2020; it was stated that it will be both prospective and retrospective, thus applicable to the sucrose octasulfate dressing, however the criteria and mechanism for funding is not yet finalised (NICE, 2019).

This is the first guideline of its kind; to recommend the use of one dressing above others and will hopefully lead to an improvement in healing outcomes for patients, which is associated with financial savings for the health system. This thesis has repeatedly pointed out that the use of the dressing with the lowest acquisition cost is not the best strategy to improve outcomes in the categories of clinical, economic, and QoL.

7.5 Contribution to knowledge

This thesis has resulted in a substantial contribution to the knowledge base in this area, drawing on the existing literature, generating new data, and synthesising the two in models to explore proposed changes to practice. This thesis has explored the use of the sucrose octasulfate dressing; a specific type of PMM dressing that is marketed in the UK under the brand name UrgoStart.

The clinical SLR was the first to examine PMM interventions in both DFU and LU patients. Previously, research on dressings has been limited due to the inherent difficulty of performing a randomised, double-blind controlled study; and thus, has been subject to the biases of less robust levels of evidence. The sucrose octasulfate dressing has been tested in multiple double-blind controlled trials and has been found to reduce healing time for patients with a DFU or LU. These studies have for the first time both been included in the SLR presented here; and due to the inclusion of this high-quality evidence; conclusions could be drawn about the efficacy of the sucrose octasulfate dressing, when compared to both a neutral dressing and other PMM interventions.

The economic SLR has built upon previous SLRs in wound care, after the exploratory SLR performed prior to the Delphi panel did not find evidence of strong meta-analyses done in this area. The economic SLR presented in chapter 2 has explored the reasons for this evidence gap and has identified the lack of standardized standard care as a key driver. Now that this relationship has been identified; researchers designing clinical trials should be mindful of these results and focus on using interventions that allow a meta-analysis. The economic SLR also provides evidence that directly counters the assertion in current guidance that practitioners should use the dressing with the lowest acquisition cost; as this SLR has shown that interventions can be cost-effective despite having a higher acquisition cost than a comparator.

The Delphi panel presented in chapter 3 of this thesis took a novel approach to eliciting expert opinion. This study mirrors the real-world treatment of chronic wounds by including a multidisciplinary team of wound care experts; reflecting the varied group of experts that see patients with DFU and LU. The modification of the method to include a literature review using a systematic search strategy to produce the evidence-based statements sets this study apart as distinct and original in its methodology. This study has applied a greater level of academic rigour than is typically found when eliciting expert opinion. The subsequent peer-reviewed publication in the Journal of Wound Care (Russell et al., 2018) will hopefully be the start of a paradigm shift away from the advisory-board style expert panel favoured by the pharmaceutical industry and towards a more systematic, repeatable style.

The PRO study presented here was the first to use EQ-5D-5L in patients with DFU and LU outside of a clinical trial in a real-world setting. The use of the updated EQ-5D-5L instead of the

EQ-5D-3L allows for a greater depth of analysis to accurately detect small changes in patients QoL. In addition to this study being the first use of EQ-5D-5L in these disease areas, it is the first example of reporting utility scores for patients in the UK with DFU and LU in an observational setting; to understand a real-life QoL score, as is experienced by patients day-to-day and not impacted by any clinical trial protocol they could be following. This adds to the body of knowledge by providing utility scores that can be used in economic modelling; and can be assumed generalisable to the UK population.

The chart extraction presented as part of the real-world evidence chapter (chapter 4) has produced new primary data, which has been analysed to produce evidence to inform decision making. The real-world evidence presented here is valuable in understanding current treatment pathways and builds upon previous work by Guest et al., (2018) that reported outcomes and resource use for DFU and LU. This provides additional data to understand the habits of practitioners; which is important when trying to evaluate treatment guidelines, or the lack of, and understand the attitudes towards treatment switching.

The economic evaluation carried out for this study has contributed to knowledge by providing a robust analysis that presents the sucrose octasulfate dressing as cost saving to the NHS when used in patients with DFU and LU. The CUA and BIMs show that an improvement in healing time would be directly responsible for a financial saving to the healthcare system and a QoL gain to patients; should the sucrose octasulfate dressing be used in routine practice when a patient presents with a chronic wound.

These models have been evaluated by NICE and adopted into clinical guidance, MTG42; the first clinical guideline of its kind, for a specific type of wound dressing, recommending its use to improve outcomes for patients. This is a pivotal contribution to knowledge that has tangible consequences in the real-world; patients should be better off, with faster healing wounds that cost the NHS less because of this study.

Together these studies provide an overwhelming body of knowledge using a multi-methods approach. This is a unique attribute of this thesis; the synergy between 5 different methodologies to produce a powerful argument regarding the clinical and cost-effectiveness of PMM interventions.

7.6 Recommendations

The recommendations are presented below.

7.6.1 Healing chronic wounds early needs to be a higher priority

Chronic wound care should be a higher priority area for the NHS. This is because of the substantial burden that is caused by a DFU or a LU. This burden is felt by patients, the healthcare system and the wider society. Ultimately, given the amount of time, money, and resources that is spent on managing wounds, the burden of chronic wounds is felt by other patients in the healthcare system, as they compete for the finite resources available from the NHS. The use of hospital beds when a wound has an exacerbation, or the use of an operating theatre when a DFU requires surgery are both examples of resource use that is incurred by chronic wounds, which could be avoidable if there was a priority focus on implementing the best strategies to improve healing outcomes for patients.

Not only cost, but due to the limited focus on healing wounds, patient QoL is suppressed for longer than is necessary as they suffer with a wound for a long time; evidence also suggests that the longer a wound has existed, the harder it is to heal. This means that healing, and not just managing, a wound should be a priority upon presentation to a health care provider.

7.6.2 The sucrose octasulfate dressing provides a solution

The sucrose octasulfate dressing has been clinically proven to improve healing outcomes for patients with either a DFU or LU. This reduced time to healing has been proven in this thesis to reduce the costs to the healthcare system by avoiding a long continuation of treatment for many weeks whilst wound healing stalls because of using a standard neutral dressing. It is important for clinicians and commissioners to not be myopic about the acquisition cost of a device; the device only accounts for a small fraction of the overall cost of healing a DFU or LU.

The use of the sucrose octasulfate dressing would also alleviate the patient burden felt because of chronic wounds. This is both directly; due to experiencing fewer days with a wound, but also indirectly through the avoidance of adverse events associated with long lasting open wounds. For DFU, the rapid healing offered by the sucrose octasulfate dressing leads to fewer amputations in the economic modelling, and less complications such as critical ischaemia or hospitalisation. For a LU patient, having a healed wound means there is less risk of an infection; which reduces their QoL further due to the associated pain, swelling, itching and potential

exudate or smell. By controlling the number of adverse events through faster healing, the sucrose octasulfate dressing provides a solution to patients with chronic wounds that is non-invasive and recognised by NICE. The recognition by NICE, a world-leading health technology assessment body, is important to ratify the claims made here; both by providing impartial external validity and instilling confidence in clinicians that the sucrose octasulfate dressing improves healing outcomes, and, in turn, economic outcomes.

7.6.3 Treatment guidelines for DFU and LU require updating

Current treatment guidelines for patients with a DFU or LU are out of date and the explicit recommendation in NICE NG19 to use the dressing with the lowest acquisition cost could potentially be causing harm to patients. This recommendation could arguably be a root cause of the divergence in treatment pathways seen throughout the study; coupled with the inconclusive Cochrane reviews on the topic of wound dressings. SIGN guidelines that instruct on the treatment of LU also lack specificity when discussing dressings. The lack of instruction has led to no single intervention being recognised as superior.

The sucrose octasulfate dressing has received a positive recommendation from NICE in January 2019; and the publication of this guidance has automatically rendered NG19 and SIGN 120 out of date. Harm to patients could consequently occur if a clinician is unaware of the new guidance and defers to the NG19 or SIGN guidance; subsequently using a low-cost dressing that does not offer the reduced time to healing and other benefits that are associated with the sucrose octasulfate dressing. It is the strong recommendation of this research that these treatment guidelines are updated to be consistent with the latest guidance supporting the use of the sucrose octasulfate dressing in patients with DFU and LU.

7.6.4 Further research into the sucrose octasulfate dressing

This thesis has presented the sucrose octasulfate dressing as a potential solution to several key issues facing patients with wounds and the clinicians who treat them. Namely, the QoL burden, the clinical difficulty of healing wounds, and the associated expense. Further research into the impact of these recommendations would help to substantiate claims made here; such as a larger real-world study to observe treatment patterns and patient outcomes. This research could focus on outcomes experienced by patients outside of a clinical trial setting; where much of the clinical data has come that supports the sucrose octasulfate dressing. Reducing

uncertainty surrounding the effectiveness of a new intervention should increase the uptake and use of the dressing. It is only with widespread use would the financial and economic implications of this research be fully realised. Studies to address the limitations of this thesis, explored in section 6.4, would help to support the evidence generated here; perhaps to include much larger studies to test the results of the real-world studies presented in chapter 4.

Further economic modelling undertaken from the perspective of either the patient or society, would help to further understand the cost and health implications of having a wound. However; in the UK this type of model is perhaps surplus to requirements as the healthcare budget comes from the government through the NHS, and not from an individual. Therefore, in the UK it is direct medical costs that are of highest importance when assessing the viability of introducing a new intervention. Personal and societal approaches to economic evaluation are important to understand the full burden of disease but are inevitably more complicated, with a broader spectrum of costs included, outside the remit of the NHS.

Given that one of the results of this research is the change in treatment guidance, research that explored the uptake of this guidance and the impact on treatment practice would be useful in assessing the success of this thesis in influencing treatment practice; beyond the development of treatment guidelines.

7.7 Overall Conclusions

The research that has been presented in this thesis has influenced a shift in the understanding and treatment paradigm for DFU and LU. The key finding of this research is that the economic evaluation showed the dominance of the sucrose octasulfate intervention, meaning it is both more effective and cost saving. Clinicians and policy makers should be aware of these findings to facilitate efficient resource allocation to maximise efficiencies when operating in an environment of budgetary pressures. Not only would these financial savings benefit the health care system, but these findings will also improve the health and QoL outcomes of patients with chronic wounds.

More work to educate health care providers on the use of this dressing would help to improve uptake of the guidance that has been produced using work presented in this thesis. Gaining a positive NICE guidance for a product is often only the first hurdle in access; uptake and real-world compliance with MTG42 is the next step. Further to the current guidance, a mandate

that the sucrose octasulfate dressing should be used first line would help to maximise these outcomes as it would reduce the delay for patients receiving an efficacious treatment.

The impact of this guidance and the body of work presented here may raise awareness of the impact of chronic wounds and raise their priority within the NHS; especially as evidence to support the sucrose octasulfate dressing as the solution to the palpable unmet need is now available.

7.8 Closing statement

This thesis has been undertaken with the intention of supporting patients with chronic wounds in achieving optimal outcomes to improve their QoL. By doing this, there will be an opportunity to redistribute funds within the NHS to spend in areas that do not yet have interventions to resolve the unmet need. The findings presented here should help to guide resource allocation to maximise health outcomes for all patients.

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Appendices

Appendix A. Study 1: Systematic literature review (Chapter 2)

A.1.Search string used in electronic databases

"((Wound AND chronic) OR (ulcer AND (pressure OR diabetic foot OR leg))) AND (management OR treatment OR care) AND (dressing*) AND ((resource AND (use OR utilisation)) OR cost) AND (quality of life OR patient outcomes OR burden OR impact) AND (effectiveness OR efficacy)"*

Appendix B. Study 2: Delphi methodology expert panel (Chapter 3)

B.1. Search terms used to identify literature

Search terms	Item
(Wound* and chronic) or (ulcer and (diabetic foot or leg))	Population
Management or treatment or care	Intervention
Dressing*	Intervention
Resource and (use or utilisation) or cost	Outcome
Quality of life or patient outcomes or burden or impact	Outcome
Effectiveness or efficacy	Outcome

B.2. Panel representation

Name	Title	Place of work
David Russell	Consultant Vascular Surgeon and Honorary Clinical Associate Professor	Leeds Teaching Hospitals NHS Trust
Dr Leanne Atkin	Vascular Nurse Specialist	Mid Yorkshire NHS Trust
April Betts	Project Manager/PhD researcher	Manchester Metropolitan University
Dr Caroline Dowsett	Nurse Consultant Tissue Viability	East London NHS Foundation Trust, London
Professor Francis Fatoye	Professor of Health Economics and Outcomes	Manchester Metropolitan University
Sarah Gardner	Clinical Lead, Tissue Viability	Oxford Health NHS Foundation Trust
Dr Julie Green	Senior Lecturer in Nursing, Director of Postgraduate Programmes	Keele University, School of Nursing and Midwifery
Dr Chris Manu	Consultant Diabetologist and Clinical Researcher in Diabetic Foot	Kings College Hospital, London
Tracey McKenzie	Head of Tissue Viability Services	Torbay and Southern Devon NHS Foundation Trust
Helena Meally	Hospital Podiatrist	Leeds Teaching Hospitals NHS Trust
Louise Mitchell	Clinical Lead Podiatrist	Birmingham Community HealthCare
Julie Mullings	Lead Tissue Viability Nurse	University Hospital South Manchester
Professor Isaac Odeyemi	Visiting Professor of Health Technology Assessment and Health Policy	Manchester Metropolitan University
Andrew Sharpe	Advanced Podiatrist and Lecturer Practitioner	West Lancashire Community Service, University of Huddersfield
Dr Gillian Yeowell	Senior lecturer MSK health and wellbeing	Manchester Metropolitan University
Professor Nancy Devlin	Director of Research	Office of Health Economics

B.3. Workbook 1

B.3.1. Introduction to workbook.

Introduction

Objective

Managing chronic wounds is an increasing burden, in 2016 the prevalence of wounds was estimated to be as high as 15/10,000, triple a previous estimate (1). The costs of treating chronic wounds, including Venous Leg Ulcers (VLU), Diabetic Foot Ulcers (DFU), and Pressure Ulcers (PU) are also increasing, with community prescriptions having risen 51% from £122 million to £184 million in the period between 2006 and 2012 (2, 3).

The field of wound management has a number of areas of uncertainty regarding emerging technologies and their place in the treatment pathway. This study aims to address the areas needing expert consensus. Following an extensive review of existing literature (for details please see 'Search Methodology' sheet), evidence-based statements were generated to address identified emerging concepts and areas of controversy; which include the following:

- The definition of chronicity
- The burden of illness
- Reducing healing time
- The role of matrix metalloproteinases (MMPs)
- Impact of early interventions on clinical outcomes
- The use of dressings and treatments

Process Summary: Modified Delphi Method

The Delphi methodology was developed by the RAND Corporation in the 1950's and aims to arrive at an expert consensus using an iterative process. The method consists of a group of experts anonymously replying to a questionnaire; then receiving the group feedback, after which this process repeats itself (4). This is an accepted methodology and there are many examples available (5) (6).

The modified process that we are using includes two rounds of anonymous voting followed by a face-to-face meeting. You are invited to read the list of statements on the Voting Sheet of this workbook and vote yes if you agree or no if you do not. If you vote no; you must fill in comments, if you vote yes; this is not necessary. Your comments should include your reasons for rejecting the statement, and suggestions of how to rephrase the statement based on your assessment of the evidence base of the references provided.

After the first round of voting, all responses will be compiled and moved forwards as follows:

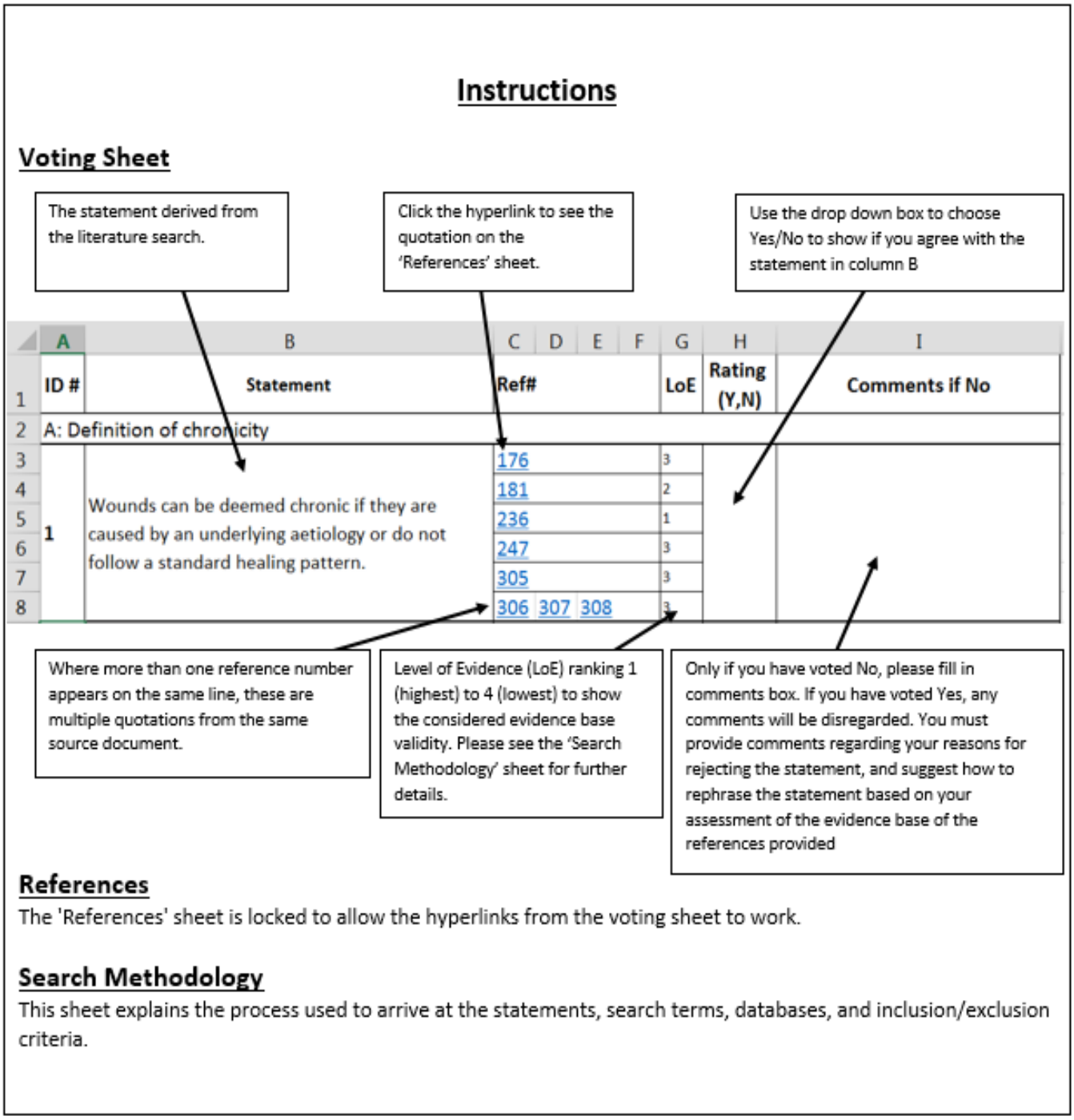
1. Statements with over 80% agreement → Confirmed and removed from the second round
2. Statements with over 80% dissent → Rejected and removed from the second round
3. Statements that did not reach 80% agreement or dissent → Will be modified using the comments and included in the second round of voting.

You will receive a summary of the group's votes in round one, and updated workbook for the second round of voting. Again, you are invited to read the list of statements on the Voting Sheet of this workbook and vote yes if you agree or no if you do not. If you vote no; you must fill in comments, if you vote yes; this is not necessary.

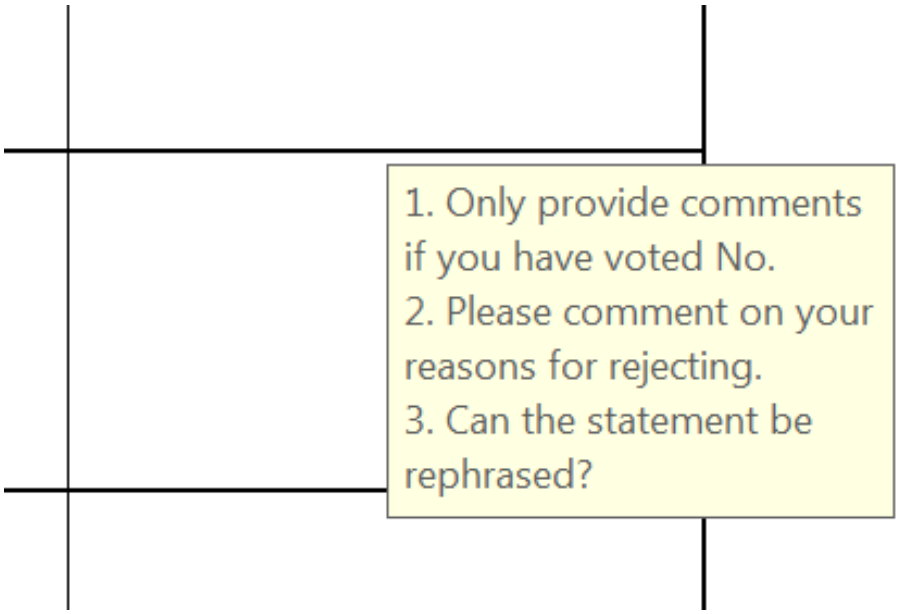
After the second round of voting, all responses will be compiled and moved forwards as follows:

1. Statements with over 80% agreement → Confirmed.
2. Statements with over 80% dissent → Rejected.
3. Statements that did not reach 80% agreement or dissent → Will be modified using the comments and discussed at the meeting.

B.3.2 Instructions for using workbook:



B.3.3 Request for comments if voting 'no':



B.3.4 Workbook 1 voting sheet:

ID #	Statement	Ref#	LoE	Rating (Y, N)	Comments if No
A: Definition of chronicity					
1	Wounds are deemed chronic if they are caused by an underlying aetiology or do not follow a standard healing pattern.	176	3		
		181	2		
		236	1		
		247	3		
		305	3		
		306 307 308	3		
2	Chronic wounds have 30 times the level of matrix metalloproteinases (MMPs) than acute wounds.	156	1		
		197	3		
		198 201	3		

		209	1		
		214	3		
		225	1		
3	Venous Leg Ulcers (VLU), Diabetic Foot Ulcer (DFU), and Pressure Ulcer (PU) patients are shown to have raised levels of MMPs from onset.	233	3		
		294	1		
		295	3		
		296	3		
		297	2		
B: The burden of illness					
4	Chronic wounds significantly impact quality of life because of the pain they cause.	180 268	2		
		271 272 273	3		
		194	1		
		274 275	1		
5	VLU, DFU and PU are a significant workload burden for health care providers.	91	2		
		108	2		
		119	1		
		135	2		
		138	1		
		139	1		
		142	1		
		147	1		

		183	1		
		187	3		
		188	3		
6	Patients with VLU, DFU and PU suffer significantly reduced quality of life across all dimensions, such as: pain, physical limitations, social isolation, depression/anxiety.	114	2		
		237 238	2		
		241 266	1		
		242 267 276	1		
		246	2		
		291	1		
7	The psychological impact of chronic wounds is severe, patients report a loss of self, social isolation, poor self-image, feelings of being a burden and hopelessness for the future.	239 277 278 279	2		
		280 281 282	2		
		283	2		
		284	1		
		285 286	1		
8	The focus of treatment is centred on the physical wound, patients report that this is insufficient, considering the large psychological and social burden.	167	1		
		248 289 290	3		
		287	3		
		292 293	1		
9	Technology-Lipido-Colloid-Nano-OligoSaccharide Factor (TLC-NOSF) has been shown to significantly reduce	263	1		
		270	1		

	pain/discomfort and anxiety/depression for a patient.				
10	Chronic wounds cause a burden to both the patient and to the caregiver.	243 244	2		
11	The cost to the patient and the carer is often excluded or underestimated in cost effectiveness models.	120	3		
		140	2		
		141	2		
		143	1		
		144	1		
		145	1		
12	In addition to a severe quality of life burden, the patient also faces financial costs such as time away from work, early retirement, medications, dressings and transport costs.	121	3		
		123	3		
		125	3		
		189	3		
13	Wounds can take a long time to heal and have a high likelihood of recurrence, leading to a significant quality of life impact.	157	1		
		159	3		
		155	3		
		224	1		
		240	1		
		245	2		

		249	1		
C: Reduce healing time					
14	Ulcers can be slow to heal, with wound size and duration affecting healing.	148	1		
		149	2		
		151	1		
		153	1		
		154	3		
15	More severe ulcers are more expensive.	107	2		
		109	2		
		110 111	2		
		118	2		
		126	1		
16	A large initial wound area reduction is indicative of healing by 24 weeks.	51	1		
		62	1		
		150	2		
17	The standard follows up in clinical trials is 12 weeks to observe wound area reduction.	164	1		
		165	1		
		166	1		
D: The role of matrix metalloproteinases (MMPs)					
18		228	3		
		303	3		

	Inflammation is an early stage of the standard wound healing process.	304	3		
19	MMPs are a part of healthy healing, expressed in the inflammation phase during early wound healing.	210 211	1		
		220	3		
20	When a wound moves to the next phase of healing, levels of MMPs fall.	200 202 203	3		
21	Excess proteases present in VLU, DFU and PU can impair wound healing by preventing progression to the next stage of healing.	57 58	1		
		195	3		
		217	3		
22	The wound is stuck in the inflammation phase leading to the destruction of new tissues.	195	3		
		204	3		
		213	1		
		222	3		
23	Elevated levels of MMPs are predictive of non-healing.	156	1		
		193	1		
		204	3		
		205 206	1		
		223	3		

		226	1		
24	Interventions that modulate the wound environment may enhance healing.	63 65	1		
		68	1		
		203	3		
		215	3		
		218	3		
		230	1		
		232	3		
25	Removing excess MMPs from a wound improves healing.	53	2		
		57 58	1		
		65	1		
		66 68	1		
		73	1		
26	TLC- NOSF technology inhibits MMPs and accelerates healing.	54	2		
		59	1		
		74	1		
		62 64 65	1		
27	Of the 24 known MMPs, MMP-9 has been shown to be detrimental to healing, killing growth factors.	199	3		
		212	1		
		216	3		
		219	3		

		221	3		
28	A specific MMP-9 inhibitor is potentially more effective in stimulating healing.	196	3		
		216	3		
		219	3		
29	TLC- NOSF reduces levels of MMP-9.	301	3		
		302	3		
30	TLC-NOSF has been shown as superior to neutral foam dressings in reducing healing time	62 63 64	1		
		13	2		
E: Early interventions lead to better outcomes					
31	VLU, DFU and PU are associated with increased morbidity and mortality.	78	1		
		122	3		
		177	1		
		178	1		
		179	1		
		190	3		
32	Patients with VLU, DFU and PU are most likely to be elderly and frail, needing minimally invasive treatment options.	168	1		
		170	2		
		185	3		
		186	3		
33		162 265	3		

	Early assessment, diagnosis and treatment of a VLU, DFU and PU can significantly improve quality of life.	264	3		
34	An adjunctive therapy to standard of care can promote faster healing.	4	1		
		6	3		
		8	3		
		43	1		
		44 45	3		
		235	3		
35	Older wounds are harder and more expensive to heal, so early intervention will reduce healing time and cost.	40 41	2		
		127	2		
		130	2		
		131	3		
		169	2		
36	Dressings that are associated with less resource use and shorter treatment periods, lead to fewer adverse events and less disease progression.	87	2		
		90	2		
		92	2		
		95	1		
		97	1		
		134	2		
37		41	2		

	Early investment in treatment provides a reduction in long term costs; prolonged futile conservative treatment is more costly.	128 129 133	2		
		131 132	3		
		152	1		
F: The use of dressings and treatments					
38	Ankle-brachial pressure index (ABPI) measurements help to diagnose VLU and assess patient's suitability for compression.	106	2		
		160 175	3		
		161	3		
		163	3		
39	An adjunctive therapy as well as compression can promote faster healing.	3	2		
		4	1		
		6	3		
		8	3		
		43	1		
		44 45	3		
		235	3		
40	Hosiery has been shown as a cost-effective option and increased use is likely to result in substantial savings for the NHS.	99 100	1		
41		15	1		

	An ideal dressing would be cost effective, accepted by the patient, easy to change, effectively manage exudate, reduce healing time, and be effective on more severe wounds.	16	1		
		17	1		
		19 20	1		
		21	1		
		22	1		
		24	3		
		25	3		
		26 27	3		
		28	3		
		30	1		
		32	1		
		35	1		
		37	1		
		229	1		
		288	2		
42	TLC-NOSF has been shown as superior to Oxidized regenerated cellulose/collagen; especially in non-responsive, older wounds.	60 61 69 70	1		
43	The purchase price of a dressing is not indicative of	85	2		
		86	2		

	cost-effectiveness; there is a need for a long-term view from decision makers.	87	2		
		97	1		
		128	2		
44	Protease inhibitors have been shown to be a cost-effective option.	82	2		
		84	2		
		88 89	2		
		96	1		
		101	3		
45	Nurse visits are a key driver of cost; advanced dressings requiring fewer changes are therefore preferred.	102	3		
		103	3		
		136	2		
		137	2		
		234	3		
46	Dressing changes can be a cause of pain and products and techniques to minimise this are recommended.	140	2		
		258	2		
		259	2		
		262	3		
		288	2		
47	Local management of the wound site considered easy in most cases with the TLC-NOSF dressing.	11	3		
		71 260 261	1		

B.4. Comments on workbook 1

B.4.1 Comments per statement compiled from the returned workbooks.

Please note that statements in green were confirmed as having met or exceeded the 80% consensus threshold. Statements in yellow did not meet the 80% threshold

ID #	Statement	Comments
A: Definition of chronicity		
1	Wounds are deemed chronic if they are caused by an underlying aetiology or do not follow a standard healing pattern.	"Wounds that do not heal in an orderly set of stages or in predictable amount of time. Some patients have underlying aetiologies, but wounds heal in 12 weeks and remain healed. Suggest including long duration or "recurring frequency. "Chronic if not following a standard healing pattern in a defined period but may be acute and heal if an underlying aetiology is managed e.g. offloading for the diabetic foot, compression for VLUs. Would define as chronic only if they do not follow a standard pattern of healing irrespective of the underlying aetiology."
2	Chronic wounds have 30 times the level of matrix metalloproteinases (MMPs) than acute wounds.	"Chronic wounds have a significantly increased level of matrix metalloproteinases (MMPs) when compared to acute wounds, this may be up to 30 times greater. - based on this evidence shown, only one lower evidence level study stipulated 30 times the level"

		"The statement needs rephrasing. A suggestion of up to 30 x … has been reported "
3	Venous Leg Ulcers (VLU), Diabetic Foot Ulcer (DFU), and Pressure Ulcer (PU) patients are shown to have raised levels of MMPs from onset.	"Statement needs rephrasing. Remove onset or define onset further. " "These ulcers may show raised levels of MMPs at initial presentation to a specialist, but this may be delayed from onset of the ulcer. Would change to "at presentation to a specialist"."
B: The burden of illness		
4	Chronic wounds significantly impact quality of life because of the pain they cause.	"DFU's can impact quality of life of a patient without causing pain." "Statement needs rephrasing. Chronic wounds is too generic, what about neuropathic DFU? Pain associated with chronic wounds significantly …. " "Not all chronic wounds cause pain"
5	VLU, DFU and PU are a significant workload burden for health care providers.	"All areas seem to be qualified in the studies my concern is with the term 'significantly' which implies clinical significance, is significantly required in the statement?"
6	Patients with VLU, DFU and PU suffer significantly reduced quality of life across all dimensions, such as: pain, physical	

	limitations, social isolation, depression/anxiety.	
7	The psychological impact of chronic wounds is severe, patients report a loss of self, social isolation, poor self-image, feelings of being a burden and hopelessness for the future.	
8	The focus of treatment is centred on the physical wound, patients report that this is insufficient, considering the large psychological and social burden.	"The focus of treatment is centred on the physical wound, this is insufficient, considering the large perceived and patient reported psychological and social burden"?
		"Sometimes the case but not always. Some patients report …"
		"Do not agree that focus is solely on the wound"
9	Technology-Lipido-Colloid-Nano-OligoSaccharide Factor (TLC-NOSF) has been shown to significantly reduce pain/discomfort and anxiety/depression for a patient.	"For patients with chronic wounds"
10	Chronic wounds cause a burden to both the patient and to the caregiver.	
11	The cost to the patient and the carer is often excluded or underestimated in cost effectiveness models.	

12	In addition to a severe quality of life burden, the patient also faces financial costs such as time away from work, early retirement, medications, dressings and transport costs.	
13	Wounds can take a long time to heal and have a high likelihood of recurrence, leading to a significant quality of life impact.	"Statement needs rephrasing. Wounds have significant impact on QOL due to the duration required for healing & high recurrence rates"
		"Depends on underlying cause"
14	Ulcers can be slow to heal, with wound size and duration affecting healing.	
15	More severe ulcers are more expensive.	"does 'severe ulcer' need qualifying? We are referring to DFU and PU scores, is there a score for VLU or is it based on size?"
		"What is the definition of severe? This statement is too general. Costs increase when patients are admitted to hospital so may want a statement on avoiding complications that result in admission. Also the duration of the wound impacts on cost so this may be a more useful statement."
		"Needs rephrasing. Define severity in terms of ulcers (VLE, DFU, PU). "
		"Done necessarily agree with this as we know that some wounds may not be

		classed as 'severe' but due to poor management/ lack of skills these become expensive."
16	A large initial wound area reduction is indicative of healing by 24 weeks.	"'large initial' needs qualifying and these studies only relate to VLU. "During the first four weeks if a greater than 20% reduction of wound area is seen, healing at 24 weeks is likely in VLU"
		"Although I agree in principle that this is the case, what is the definition of large?? Maybe statement needs to be more specific."
		"We would expect to see wound healing within a four-week period."
17	The standard follows up in clinical trials is 12 weeks to observe wound area reduction.	"Not all trials are designed this way"
C: The role of matrix metalloproteinases (MMPs)		
18	Inflammation is an early stage of the standard wound healing process.	
19	MMPs are a part of healthy healing, expressed in the inflammation phase during early wound healing.	
20	When a wound moves to the next phase of healing, levels of MMPs fall.	"Unsure"

21	Excess proteases present in VLU, DFU and PU can impair wound healing by preventing progression to the next stage of healing.	"No reference to VLU, DFU or PU in quotations. Rephrasing of statement required"
22	The wound is stuck in the inflammation phase leading to the destruction of new tissues.	"This does not make sense as a stand-alone statement. Suggest when MMPs are elevated wounds remain stuck in ……."
		"Does not destruct but prohibits progression"
23	Elevated levels of MMPs are predictive of non-healing.	
24	Interventions that modulate the wound environment may enhance healing.	
25	Removing excess MMPs from a wound improves healing.	"Only helpful once underlying conditions addressed"
		"Removing excess MMPs from a wound may improve healing"
26	TLC- NOSF technology inhibits MMPs and accelerates healing.	"Does it inhibit all types of MMPs? This is not shown in this evidence. "TLC-NOSF technology can inhibit MMPs synthesis, facilitating faster healing"
		"reduces MMP's yes but will not always accelerate healing - again depends on underlying process"

27	Of the 24 known MMPs, MMP-9 has been shown to be detrimental to healing, killing growth factors.	"Whilst MMP-9 is significant other MMPs also impact on wound healing."
28	A specific MMP-9 inhibitor is potentially more effective in stimulating healing.	"Unsure good level of evidence supports this"
29	TLC- NOSF reduces levels of MMP-9.	"In vitro TLC-NOSF has been shown to reduce levels of MMP-9"
		"Can we make this statement without level 1 evidence. Suggest some studies have shown …."
		"Unsure good level of evidence supports this"
30	TLC-NOSF has been shown as superior to neutral foam dressings in reducing healing time	
D: Early interventions lead to better outcomes		
31	VLU, DFU and PU are associated with increased morbidity and mortality.	
32	Patients with VLU, DFU and PU are most likely to be elderly and frail, needing minimally invasive treatment options.	"VLU, DFU and PU is more prevalent in older people and the frail, minimally invasive treatment options may be need in these groups where surgery is not indicated."
		"Age should not be a barrier to invasive treatment options. Not all elderly people are frail."

		"Reference only to VLU in quotations used"
		"Do not agree with whole of statement "
		"Potentially benefiting from minimally invasive options. Most of these patients are higher risk, but not excluded from standard open interventions."
33	Early assessment, diagnosis and treatment of a VLU, DFU and PU can significantly improve quality of life.	"Suggest early diagnosis ……. can lead to improved outcomes"
		"Reference only to VLU in quotations used"
34	An adjunctive therapy to standard of care can promote faster healing.	"Rephrasing needed. Quotations refer to adjunctive therapy in relation to VLU."
		"Not in all cases"
		"Blanket statement and not necessarily applies to all wounds. Should be considered in cases where wound healing may be compromised but not in those that would heal without complications."
35	Older wounds are harder and more expensive to heal, so early intervention will reduce healing time and cost.	"Suggest change to the longer the duration of the wound the harder it is to heal and the more costly. I think you have two separate statements here"
		"No reference to older wounds within quotations. Rephrasing needed."

36	Dressings that are associated with less resource use and shorter treatment periods, lead to fewer adverse events and less disease progression.	"Not enough evidence relating to fewer adverse events or less disease progression from quotations. Rephrasing needed " "No dressing will prevent disease progression" "Unclear statement. Advanced dressings associated with increased initial resource but reduced overall resource because of early healing. "
37	Early investment in treatment provides a reduction in long term costs; prolonged futile conservative treatment is more costly.	
E: The use of dressings and treatments		
38	Ankle-brachial pressure index (ABPI) measurements help to diagnose VLU and assess patient's suitability for compression.	"ABPI assesses suitability for compression but will not help diagnose a VLU - it only assesses for PAD" "ABPI doesn't diagnose venous ulcers it assesses for suitability for compression by assessing arterial status. Statement needs rewording."
39	An adjunctive therapy as well as compression can promote faster healing.	"adjunctive therapy needs to be qualified, i.e. adjunctive therapy, such as dressings that modulate the microenvironment" "Not in all cases"

		"Not in all cases. Uncomplicated ulcers will heal without advanced dressings. Adjunctive therapy is beneficial in those predicted as 'complicated'"
40	Hosiery has been shown as a cost-effective option and increased use is likely to result in substantial savings for the NHS.	
41	An ideal dressing would be cost effective, accepted by the patient, easy to change, effectively manage exudate, reduce healing time, and be effective on more severe wounds.	"Surely an ideal dressing would be effective on all wounds not just severe? "
42	TLC-NOSF has been shown as superior to Oxidized regenerated cellulose/collagen; especially in non-responsive, older wounds.	
43	The purchase price of a dressing is not indicative of cost-effectiveness; there is a need for a long-term view from decision makers.	
44	Protease inhibitors have been shown to be a cost-effective option.	
45	Nurse visits are a key driver of cost; advanced dressings requiring fewer changes are therefore preferred.	"Statement needs rephrasing. Removal of 'preferred' is needed. "

46	Dressing changes can be a cause of pain and products and techniques to minimise this are recommended.	
47	Local management of the wound site considered easy in most cases with the TLC-NOSF dressing.	"I'm not sure what these references or statement are eluding to? Is it that TLC-NOSF is less painful on dressing change? What is meant by local management of the wound site?"
		"Suggest TLC-NOSF is considered easy to use in clinical practice or by clinicians."

B.4.2 Results of iteration 1 voting

Statement	Participant number										Answers		Consensus Level
	1	2	3	4	5	6	7	8	9	10	Yes	No	
1	Y	N	N	Y	Y	Y	Y	Y	Y	Y	8	2	80%
2	N	Y	Y	Y	Y	Y	N	Y	Y	Y	8	2	80%
3	Y	Y	N	Y	Y	Y	N	Y	Y	Y	8	2	80%
4	Y	Y	Y	Y	N	Y	N	N	Y	Y	7	3	70%
5	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	0	100%
6	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	9	1	90%
7	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	0	100%
8	N	N	Y	Y	Y	Y	Y	N	Y	Y	7	3	70%
9	Y	N	Y	N	Y	Y	Y	Y	Y	Y	8	2	80%

10	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	0	100%
11	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	0	100%
12	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	0	100%
13	Y	Y	Y	Y	Y	Y	N	N	Y	Y	8	2	80%
14	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	0	100%
15	N	N	Y	Y	Y	Y	N	Y	N	Y	6	4	60%
16	N	Y	Y	Y	Y	Y	Y	Y	N	N	7	3	70%
17	Y	Y	Y	N	Y	Y	Y	N	Y	Y	8	2	80%
18	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	0	100%
19	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	0	100%
20	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	9	1	90%
21	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	9	1	90%
22	Y	N	Y	Y	Y	Y	Y	N	Y	Y	8	2	80%
23	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	0	100%
24	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	0	100%
25	Y	Y	N	Y	Y	Y	Y	N	Y	Y	8	2	80%
26	N	Y	Y	Y	Y	Y	Y	N	Y	Y	8	2	80%
27	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	9	1	90%
28	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	9	1	90%
29	N	N	Y	Y	Y	Y	Y	N	Y	Y	7	3	70%
30	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	0	100%

31	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	0	100%
32	N	N	N	Y	Y	Y	N	N	Y	Y	5	5	50%
33	Y	N	Y	Y	Y	Y	N	Y	Y	Y	8	2	80%
34	Y	Y	Y	Y	Y	Y	N	N	N	Y	7	3	70%
35	Y	N	Y	Y	Y	Y	N	Y	Y	Y	8	2	80%
36	Y	Y	N	Y	Y	Y	N	N	Y	Y	7	3	70%
37	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	0	100%
38	Y	Y	Y	Y	Y	Y	Y	N	N	Y	8	2	80%
39	N	Y	Y	Y	Y	Y	Y	N	N	Y	7	3	70%
40	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	0	100%
41	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	9	1	90%
42	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	0	100%
43	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	0	100%
44	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	0	100%
45	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	9	1	90%
46	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	0	100%
47	N	N	Y	Y	Y	Y	Y	Y	Y	Y	8	2	80%

B.5. Workbook 2

B.5.1 Voting sheet, workbook 2.

ID #	Statement	Ref#	LoE	Rating (Y, N)	Comments if No
B: The burden of illness					
4	The pain caused by chronic wounds significantly impacts quality of life.	180 268	2		
		271 272 273	3		
		194	1		
		274 275	1		
8	The main focus of treatment on the physical wound, some patients report that this is insufficient, considering the large psychological and social burden.	167	1		
		248 289 290	3		
		287	3		
		292 293	1		
C: Reduce healing time					
15	Larger and older ulcers are more expensive.	107	2		
		109	2		
		110 111	2		
		118	2		
		126	1		
16	The initial wound area reduction is predictive of healing by 24 weeks.	51	1		
		62	1		

		150	2		
D: The role of matrix metalloproteinases (MMPs)					
29	TLC- NOSF have been shown to reduce levels of MMP-9 in vitro.	301	3		
		302	3		
E: Early interventions lead to better outcomes					
32	VLU, DFU and PU are more prevalent in older populations who would potentially benefit from minimally invasive treatment options.	168	1		
		170	2		
		185	3		
		186	3		
34	An adjunctive therapy to standard of care can promote faster healing in wounds where healing is compromised.	4	1		
		6	3		
		8	3		
		43	1		
		44 45	3		
		235	3		
36	Treatments associated with less resource use, shorter treatment periods and fewer adverse events are more cost effective.	87	2		
		90	2		
		92	2		
		95	1		
		97	1		
		134	2		

F: The use of dressings and treatments					
39	An adjunctive therapy such as a dressing that modulates the microenvironment can promote faster healing in complicated wounds.	3	2		
		4	1		
		6	3		
		8	3		
		43	1		
		44 45	3		
		235	3		

B.5.2 Comments on statements from iteration 2

Please note that statements in green were confirmed as having met or exceeded the 80% consensus threshold. Statements in yellow did not meet the 80% threshold

ID #	Statement	Comments
B: The burden of illness		
4	The pain caused by chronic wounds significantly impacts quality of life.	"Not all chronic wounds cause pain. DFUs or other chronic wounds can be present with neuropathy. In which case other factors will be impacting the quality of life"
8	The main focus of treatment on the physical wound, some patients report that this is insufficient, considering	"Not sure this reads correctly as a stand-alone statement? "Clinician focus is on treatment of the wound, which is insufficient as it does not account for the large psychological and social burden experienced by some patients. It is not about the

	the large psychological and social burden.	hole in the patient, it's about the whole of the patient."
		"Current wording within statement does not read correctly. "
		"Needs to read 'The main focus of treatment is on the physical wound. Some patients etc.'"
C: Reduce healing time		
15	Larger and older ulcers are more expensive.	"The final study (126) actual contradicts this point, in some instances pressure ulcer prevention is more expensive than treatment."
		"No reference to size or age of ulceration within references"
		"Based on the evidence in the reference list, the correlation with larger ulcers isn't clear and I would say that it's not always larger ulcers that are expensive, I would however agree to the chronicity being associated with cost."
		"Does this refer to leg ulcers, pressure ulcers or both? Needs to be more specific."
16	The initial wound area reduction is predictive of healing by 24 weeks.	"I would like to think this statement is true but there is only reference to VLU"
		"This is a confusing statement and I'm not sure what is trying to be established."
D: The role of matrix metalloproteinases (MMPs)		

29	TLC- NOSF have been shown to reduce levels of MMP-9 in vitro.	
E: Early interventions lead to better outcomes		
32	VLU, DFU and PU are more prevalent in older populations who would potentially benefit from minimally invasive treatment options.	"Evidence does not suggest that DFU and PU are more prevalent in older populations."
		"Broad statement that just because you are old you would benefit from minimally invasive treatment - treatment options are based on individual risk/benefit analysis - surely everyone would benefit from minimal invasion?"
		"I agree in principle, but the wording needs to be sensitive to avoid it sounding 'ageist'. Wording could maybe be changed to " … older populations who would where possible, benefit from minimally invasive treatment options""
		"older population does not include frailty, there may be younger patients who are more frail that would benefit from minimally invasive treatment options and those who are older but not frail who should be considered for other treatment options"
34	An adjunctive therapy to standard of care can promote faster healing in wounds where healing is compromised.	"Compression therapy is the only consistent adjunct therapy specified, therefore should this state compression therapy rather than adjunctive therapy?"
		"Blanket statement… doesn't necessarily apply to all wounds. Could include something like "… should be

		considered in cases where wound healing may be compromised""
		"Should this read: 'An adjunctive therapy to standard wound care'?"
36	Treatments associated with less resource use, shorter treatment periods and fewer adverse events are more cost effective.	"Treatments associated with improved outcomes are most cost effective - even if this is means more resources etc "
F: The use of dressings and treatments		
39	An adjunctive therapy such as a dressing that modulates the microenvironment can promote faster healing in complicated wounds.	"Adjunctive therapy needs to be specified and there does not seem to be consistent evidence to back this statement"

B.5.3. Voting iteration 2

Statement	Participant number										Answer		Consensus
	1	2	3	4	5	6	7	8	9	10	Yes	No	
4	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	9	1	90%
8	N	Y	Y	Y	N	Y	Y	N	Y	Y	7	3	70%
15	N	Y	Y	Y	N	Y	N	N	Y	Y	6	4	60%
16	Y	Y	Y	Y	N	Y	Y	N	Y	Y	8	2	80%
29	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10	0	100%

32	Y	Y	N	Y	N	N	N	Y	Y	Y	6	4	60%
34	N	Y	Y	Y	Y	Y	N	N	Y	Y	7	3	70%
36	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	9	1	90%
39	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	9	1	90%

B.6 Platform for future dissemination, use cases, KPI measures and future research.

B.6.1. The panel produced the below potential platforms for dissemination:

1. Publications
2. Conferences
3. Nurse forums
4. Hospitals
5. Patient expert groups
6. Partnership with industry
7. Clinical pathways
8. Local nurse champions
9. Academia
10. Local TVN websites
11. CCG platforms

B.6.2. When asked, "How could the dissemination of this consensus document lead to not just creation of awareness, but particularly a change in clinical practice?" the panel provided the following answers:

1. Pre-requirement for nursing standards
2. Local guidelines
3. Training for health care assistants
4. Collect case studies for CCGs showing cost savings
5. Target at 3 levels:
    a) Patient
    b) Clinician
    c) Management

B.6.3 For determining the impact of this consensus statement, the panel proposed:

1. How many times cited, impact factor of journals
2. Audits pre and post implementation
3. Compliance report
4. Number of times used
5. Awareness report
6. A change in healing rates/times
7. If UrgoStart gains NICE approval

B.6.4 When given the opportunity to discuss future areas of research, the panel suggested:

1. Qualitative- clinicians' experience of using the document- did it influence their practice?
2. Risk assessment tool- how do you identify patients who are failing to heal
3. Clinical pathways for VLU, DFU and PU based on the document
4. A practical tool for the Health Care Assistants delivering the wound care
5. Look into the patient experiences and quality of life,
6. Look at caregiver burden- the financial/emotional/social impact
7. Develop tools to measure the impact of the guidelines
8. Look at early adopters vs late adopters and look for barriers to implementation

Appendix C. Study 5: Economic evaluation (Chapter 5)

C.1. Search strategy for targeted literature review

A literature review was undertaken using the PICO (population, intervention, comparator, outcome) methodology to derive search terms, the PICO framework is a well-established tool for developing research questions (Huang et al., 2006). The search string was entered the MMU library search as follows:

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

The MMU library tool searches multiple databases, including PubMed, Medline, Cochrane and Ovid and provides a combined overview of results that can be downloaded and extracted to Microsoft Excel for inclusion and exclusion decision making. The inclusion and exclusion criteria are shown

Inclusion criteria	
Population	Leg Ulcer or Diabetic Foot Ulcer
Interventions	UrgoStart
Outcomes	Economic outcomes, resource use, cost, ICER, cost per patient
Study design	Modelling, economic studies
Language	English
Search dates	No restrictions
Exclusion criteria	
Population	Paediatrics (<18), Acute wounds (including Burns, Trauma, Surgery)
Interventions	Surgical, Novel non-surgical, Infection control measures, Debridement, Bioengineered skin substitutes, Offloading, Compression
Outcomes	No economic outcomes reported

Study design	In vitro studies, review or discussion articles
Language	Non-English Language
Search dates	N/A

C.2 Summary of variables applied in the DFU cost model (Base Case)

Variable	Value	Source
Age	65 years	Explorer
Prior Amputation	50%	Explorer
Major Amputation	24%	NICE Costing Document
Minor Amputation	76%	NICE Costing Document
Proportion with prosthesis after major amputation	86%	NICE Costing Document
Neutral Dressing. Transition probability: open pre -> complicated pre	0.018660468	Explorer (comparator arm). Of 51 patients with open wound& no prior amputation 16 became infected over 20 weeks.
Neutral Dressing. Transition probability: open pre -> closed pre	0.016694216	Explorer (comparator arm). Of 35 patients with open wound& no prior amputation 10 healed by 20 weeks.
Neutral Dressing. Transition probability: open pre -> deceased	0.001934667	National Diabetes Foot Care Audit Third Annual Report, 2018. 520/22653 patients confirmed deceased at 12 weeks.
Neutral Dressing. Transition probability: complicated pre -> closed pre	0.003223928	Explorer (comparator arm). Of 16 patients with infected wound& no prior amputation 1 healed by 20 weeks.

Neutral Dressing. Transition probability: complicated pre -> open post	0.003354487	National Diabetes Foot Care Audit Third Annual Report, 2018. 1469/17514 patient amputations at 6 months
Neutral Dressing. Transition probability: complicated pre -> closed post	0.003354487	
Neutral Dressing. Transition probability: complicated pre -> deceased	0.001934667	National Diabetes Foot Care Audit Third Annual Report, 2018. 520/22653 patients confirmed deceased at 12 weeks.
Neutral Dressing. Transition probability: closed pre -> open pre	0.005460204	Dubsky et al., (2012), of 73 patients, 42 had a DFU recurrence within 3 years.
Neutral Dressing. Transition probability: closed pre -> deceased	0.001934667	National Diabetes Foot Care Audit Third Annual Report, 2018. 520/22653 patients confirmed deceased at 12 weeks.
Neutral Dressing. Transition probability: open post -> complicated post	0.014552464	Explorer (comparator arm). Of 63 patients with open wound with prior amputation, 16 became infected by 20 weeks.
Neutral Dressing. Transition probability: open post -> closed post	0.025581983	Explorer (comparator arm). Of 47 patients with open wound with prior amputation, 19 healed by 20 weeks.
Neutral Dressing. Transition probability: open post -> deceased	0.001934667	National Diabetes Foot Care Audit Third Annual Report, 2018. 520/22653 patients confirmed deceased at 12 weeks.
Neutral Dressing. Transition probability: complicated post -> closed post	0.014290858	Explorer (comparator arm). Of 16 patients with infected wound with prior amputation, 4 healed by 20 weeks.

Neutral Dressing. Transition probability: complicated post -> deceased	0.001934667	National Diabetes Foot Care Audit Third Annual Report, 2018. 520/22653 patients confirmed deceased at 12 weeks.
Neutral Dressing. Transition probability: closed post -> open post	0.005460204	Dubsky et al. 2012, of 73 patients, 42 had a DFU recurrence within 3 years.
Neutral Dressing. Transition probability: closed post -> deceased	0.001934667	National Diabetes Foot Care Audit Third Annual Report, 2018. 520/22653 patients confirmed deceased at 12 weeks.
UrgoStart. Transition probability: open pre -> complicated pre	0.013513855	Explorer (treatment arm). Of 42 patients with open wound& no prior amputation 10 became infected over 20 weeks.
UrgoStart. Transition probability: open pre -> closed pre	0.037200636	Explorer (treatment arm). Of 32 patients with open wound& no prior amputation 17 healed by 20 weeks.
UrgoStart. Transition probability: open pre -> deceased	0.001934667	National Diabetes Foot Care Audit Third Annual Report, 2018. 520/22653 patients confirmed deceased at 12 weeks.
UrgoStart. UrgoStart. Transition probability: complicated pre -> closed pre	0.011102724	Explorer (treatment arm). Of 10 patients with infected wound& no prior amputation 2 healed by 20 weeks.
UrgoStart. Transition probability: complicated pre -> open post	0.003354487	National Diabetes Foot Care Audit Third Annual Report, 2018. 1469/17514 patients' amputations at 6 months
UrgoStart. Transition probability: complicated pre -> closed post	0.003354487	

UrgoStart. Transition probability: complicated pre -> deceased	0.001934667	National Diabetes Foot Care Audit Third Annual Report, 2018. 520/22653 patients confirmed deceased at 12 weeks.
UrgoStart. Transition probability: closed pre -> open pre	0.005460204	Dubsky et al., (2012), of 73 patients, 42 had a DFU recurrence within 3 years.
UrgoStart. Transition probability: closed pre -> deceased	0.001934667	National Diabetes Foot Care Audit Third Annual Report, 2018. 520/22653 patients confirmed deceased at 12 weeks.
UrgoStart. Transition probability: open post -> complicated post	0.009793975	Explorer (treatment arm). Of 84 patients with open wound with prior amputation, 15 became infected by 20 weeks.
UrgoStart. Transition probability: open post -> closed post	0.037715221	Explorer (treatment arm). Of 69 patients with open wound with prior amputation, 37 healed by 20 weeks.
UrgoStart. Transition probability: open post -> deceased	0.001934667	National Diabetes Foot Care Audit Third Annual Report, 2018. 520/22653 patients confirmed deceased at 12 weeks.
UrgoStart. Transition probability: complicated post -> closed post	0.015398578	Explorer (treatment arm). Of 15 patients with infected wound with prior amputation, 4 healed by 20 weeks.
UrgoStart. Transition probability: complicated post -> deceased	0.001934667	National Diabetes Foot Care Audit Third Annual Report, 2018. 520/22653 patients confirmed deceased at 12 weeks.
UrgoStart. Transition probability: closed post -> open post	0.005460204	Dubsky et al., (2012), of 73 patients, 42 had a DFU recurrence within 3 years.

UrgoStart. Transition probability: closed post -> deceased	0.001934667	National Diabetes Foot Care Audit Third Annual Report, 2018. 520/22653 patients confirmed deceased at 12 weeks.
Health State utility scores	0.619 (Open pre) 0.570 (Complicated pre) 0.738 (Closed pre) 0.596 (Open post 0.583 (Complicated post) 0.715 (Closed post)	Explorer
Disutility	-0.28 (Disutility associated with amputation event) 95% CI (– 0.389 to – 0.170)	Clarke, et al., (2002)

Duration of amputation event disutility	4 weeks	Clinical experts

C.3 Summary of variables applied in the LU cost model (Base Case)

Variable	Value	Source
Age	72.6 years SD: 13	Challenge
Duration of infection	2-4 weeks	Expert opinion.
Neutral Dressing: Transition probability: open -> infected	0.0081884	Of 94 patients, 6 became infected over 8 weeks.
Neutral Dressing: Transition probability: open -> closed	0.0474747	Using method described in Cardinal et al., (2008) the 32% RWAR gave a weekly healing rate of 4.75%
Neutral Dressing: Transition probability: infected -> open	0.3333333	1/duration of infection from expert opinion.
Neutral Dressing: Transition probability: closed -> open	0.0033382	Clarke-Moloney et al. 2012, of 100 patients 16 had a recurrence over 1 year.
UrgoStart: Transition probability: open -> infected	0.0097073	Of 93 patients, 7 became infected over 8 weeks
UrgoStart: Transition probability: open -> closed	0.1093336	Using method described in Cardinal et al., (2008) the 58%

		RWAR gave a weekly healing rate of 10.93%
UrgoStart: Transition probability: infected -> open	0.3333333	1/duration of infection from expert opinion.
UrgoStart: Transition probability: closed -> open	0.0033382	Clarke-Moloney et al., (2012), of 100 patients 16 had a recurrence over 1 year.
Health State utility scores	0.52 (Open) 0.52 (Infected) 0.67 (Closed)	Palfreyman (2008). Assessing the impact of venous ulceration on quality of life. Nursing times, 104(41), pp.34-37.

C.4 Variables used in DFU one-way scenario-based DSA

Variable	Base-case value	Minimum value	Maximum value
If a patient has had a prior amputation from a previous wound	50%	0.35	0.65
The proportion of major amputations	0.24	0.17	0.31
The proportion having prosthesis after major amputation	86%	0.60	1.00
The duration of amputation event disutility, in weeks	4.00	2.00	6.00
The cost of one UrgoStart Dressing	4.28	3.00	5.56
The cost of one Neutral Dressing	3.13	2.19	4.07

Hospital inpatient resource use in open pre-state	0.0002	0.0001	0.0003
GP resource use in open pre-state	0.0239	0.0168	0.0311
Hospital outpatient resource use in open pre-state	0.0192	0.0135	0.0250
Podiatrist resource use in open pre-state	0.0032	0.0022	0.0041
Practice Nurse resource use in open pre-state	0.0998	0.0699	0.1298
Community Nurse resource use in open pre-state	0.8103	0.5672	1.0534
Antibiotic prescription resource use in open pre-state	0.0795	0.0557	0.1034
Analgesic prescription resource use in open pre-state	0.3268	0.2288	0.4249
Primary dressing resource use in open pre-state	2.0800	1.4560	2.7040
Secondary Dressing resource use in open pre-state	1.6224	1.1357	2.1091
Bespoke orthosis resource use in open pre-state	0.0192	0.0135	0.0250
Hospital inpatient resource use in complicated pre-state	0.0006	0.0004	0.0008
GP resource use in complicated pre-state	0.0718	0.0503	0.0934
Hospital outpatient resource use in complicated pre-state	0.0577	0.0404	0.0750
Podiatrist resource use in complicated pre-state	0.0095	0.0067	0.0124
Practice Nurse resource use in complicated pre-state	0.2994	0.2096	0.3893
Community Nurse resource use in complicated pre-state	2.4309	1.7016	3.1601
Antibiotic prescription resource use in complicated pre-state	0.2386	0.1670	0.3101

Analgesic prescription resource use in complicated pre-state	0.9805	0.6863	1.2746
Primary dressing resource use in complicated pre-state	6.2400	4.3680	8.1120
Secondary Dressing resource use in complicated pre-state	5.6784	3.9749	7.3819
Bespoke orthosis resource use in complicated pre-state	0.0192	0.0135	0.0250
Hospital inpatient resource use in closed pre-state	0.0000	0.0000	0.0000
GP resource use in closed pre-state	0.0294	0.0206	0.0383
Hospital outpatient resource use in closed pre-state	0.0196	0.0137	0.0255
Podiatrist resource use in closed pre-state	0.0040	0.0028	0.0053
Practice Nurse resource use in closed pre-state	0.0937	0.0656	0.1218
Community Nurse resource use in closed pre-state	0.3788	0.2652	0.4925
Antibiotic prescription resource use in closed pre-state	0.0627	0.0439	0.0815
Analgesic prescription resource use in closed pre-state	0.2410	0.1687	0.3133
Primary dressing resource use in closed pre-state	1.0392	0.7275	1.3510
Secondary Dressing resource use in closed pre-state	0.8106	0.5674	1.0538
Bespoke orthosis resource use in closed pre-state	0.0192	0.0135	0.0250
Hospital inpatient resource use in open post state	0.0144	0.0101	0.0188
GP resource use in open post state	0.0158	0.0110	0.0205

Hospital outpatient resource use in open post state	0.0433	0.0303	0.0563
Podiatrist resource use in open post state	0.0017	0.0012	0.0023
Practice Nurse resource use in open post state	0.0826	0.0578	0.1074
Community Nurse resource use in open post state	0.5869	0.4108	0.7630
Antibiotic prescription resource use in open post state	0.1204	0.0843	0.1565
Analgesic prescription resource use in open post state	0.1324	0.0927	0.1721
Primary dressing resource use in open post state	1.5084	1.0559	1.9609
Secondary Dressing resource use in open post state	1.1765	0.8236	1.5295
Bespoke orthosis resource use in open post state	0.0192	0.0135	0.0250
Hospital inpatient resource use in complicated post state	0.0433	0.0303	0.0563
GP resource use in complicated post state	0.0473	0.0331	0.0615
Hospital outpatient resource use in complicated post state	0.1298	0.0909	0.1688
Podiatrist resource use in complicated post state	0.0052	0.0036	0.0068
Practice Nurse resource use in complicated post state	0.2478	0.1735	0.3221
Community Nurse resource use in complicated post state	1.7608	1.2325	2.2890
Antibiotic prescription resource use in complicated post state	0.3612	0.2528	0.4695

Analgesic prescription resource use in complicated post state	0.3972	0.2780	0.5164
Primary dressing resource use in complicated post state	4.5251	3.1676	5.8826
Secondary Dressing resource use in complicated post state	4.1178	2.8825	5.3532
Bespoke orthosis resource use in complicated post state	0.0192	0.0135	0.0250
Hospital inpatient resource use in closed post state	0.0000	0.0000	0.0000
GP resource use in closed post state	0.0294	0.0206	0.0383
Hospital outpatient resource use in closed post state	0.0196	0.0137	0.0255
Podiatrist resource use in closed post state	0.0040	0.0028	0.0053
Practice Nurse resource use in closed post state	0.0937	0.0656	0.1218
Community Nurse resource use in closed post state	0.3788	0.2652	0.4925
Antibiotic prescription resource use in closed post state	0.0627	0.0439	0.0815
Analgesic prescription resource use in closed post state	0.2410	0.1687	0.3133
Primary dressing resource use in closed post state	1.0392	0.7275	1.3510
Secondary Dressing resource use in closed post state	0.8106	0.5674	1.0538
Bespoke orthosis resource use in closed post state	0.0192	0.0135	0.0250
Quality of life weight for open pre-amputation state	0.6190	0.4333	0.8047

Quality of life weight for complicated pre-amputation state	0.5700	0.3990	0.7410
Quality of life weight for closed pre-amputation state	0.7380	0.5166	0.9594
Quality of life weight for open post-amputation state	0.5960	0.4172	0.7748
Quality of life weight for complicated post-amputation state	0.5830	0.4081	0.7579
Quality of life weight for closed post-amputation state	0.7150	0.5005	0.9295
Disutility associated with amputation event	-0.2800	-0.1960	-0.3640
Neutral Dressing. Transition probability: open pre -> complicated pre	0.0187	0.0131	0.0243
Neutral Dressing. Transition probability: open pre -> closed pre	0.0167	0.0117	0.0217
Neutral Dressing. Transition probability: open pre -> deceased	0.0019	0.0014	0.0025
Neutral Dressing. Transition probability: complicated pre -> closed pre	0.0032	0.0023	0.0042
Neutral Dressing. Transition probability: complicated pre -> open post	0.0034	0.0023	0.0044
Neutral Dressing. Transition probability: complicated pre -> closed post	0.0034	0.0023	0.0044
Neutral Dressing. Transition probability: complicated pre -> deceased	0.0019	0.0014	0.0025

Neutral Dressing. Transition probability: closed pre -> open pre	0.0055	0.0038	0.0071
Neutral Dressing. Transition probability: closed pre -> deceased	0.0019	0.0014	0.0025
Neutral Dressing. Transition probability: open post -> complicated post	0.0146	0.0102	0.0189
Neutral Dressing. Transition probability: open post -> closed post	0.0256	0.0179	0.0333
Neutral Dressing. Transition probability: open post -> deceased	0.0019	0.0014	0.0025
Neutral Dressing. Transition probability: complicated post -> closed post	0.0143	0.0100	0.0186
Neutral Dressing. Transition probability: complicated post -> deceased	0.0019	0.0014	0.0025
Neutral Dressing. Transition probability: closed post -> open post	0.0055	0.0038	0.0071
Neutral Dressing. Transition probability: closed post -> deceased	0.0019	0.0014	0.0025
UrgoStart Transition probability: open pre -> complicated pre	0.0135	0.0095	0.0176
UrgoStart Transition probability: open pre -> closed pre	0.0372	0.0260	0.0484
UrgoStart Transition probability: open pre -> deceased	0.0019	0.0014	0.0025

UrgoStart Transition probability: complicated pre -> closed pre	0.0111	0.0078	0.0144
UrgoStart Transition probability: complicated pre -> open post	0.0034	0.0023	0.0044
UrgoStart Transition probability: complicated pre -> closed post	0.0034	0.0023	0.0044
UrgoStart Transition probability: complicated pre -> deceased	0.0019	0.0014	0.0025
UrgoStart Transition probability: closed pre -> open pre	0.0055	0.0038	0.0071
UrgoStart Transition probability: closed pre -> deceased	0.0019	0.0014	0.0025
UrgoStart Transition probability: open post -> complicated post	0.0098	0.0069	0.0127
UrgoStart Transition probability: open post -> closed post	0.0377	0.0264	0.0490
UrgoStart Transition probability: open post -> deceased	0.0019	0.0014	0.0025
UrgoStart Transition probability: complicated post -> closed post	0.0154	0.0108	0.0200
UrgoStart Transition probability: complicated post -> deceased	0.0019	0.0014	0.0025
UrgoStart Transition probability: closed post -> open post	0.0055	0.0038	0.0071

UrgoStart Transition probability: closed post -> deceased	0.0019	0.0014	0.0025

C.5 Variables used in LU one-way scenario-based DSA

Variable	Base-case value	Minimum value	Maximum value
The cost of one UrgoStart Dressing	4.28	3.00	5.56
The cost of one Neutral Dressing	3.13	2.19	4.07
The duration of infection	3.00	2.10	3.90
Hospital inpatient resource use in open health state	0.02	0.00	0.92
GP resource use in open health state	1.70	0.00	10.52
Hospital outpatient resource use in open health state	1.03	0.00	24.64
Practice Nurse resource use in open health state	16.26	0.00	123.72
Community Nurse resource use in open health state	155.54	0.00	411.52
Antibiotic prescription resource use in open health state	6.14	0.00	32.68
Analgesic prescription resource use in open health state	9.62	0.00	60.60
Primary dressing resource use in open health state	169.74	0.00	1339.32

Secondary Dressing resource use in open health state	169.74	0.00	1339.32
Compression system resource use in open health state	61.36	0.00	230.96
Hosiery resource use in open health state	23.99	0.00	84.80
Hospital inpatient resource use in infected health state	0.02	0.00	0.92
GP resource use in infected health state	1.70	0.00	10.52
Hospital outpatient resource use in infected health state	1.03	0.00	24.64
Practice Nurse resource use in infected health state	16.26	0.00	123.72
Community Nurse resource use in infected health state	155.54	0.00	411.52
Antibiotic prescription resource use in infected health state	6.14	0.00	32.68
Analgesic prescription resource use in infected health state	9.62	0.00	60.60
Primary dressing resource use in infected health state	169.74	0.00	1339.32
Secondary Dressing resource use in infected health state	169.74	0.00	1339.32
Compression system resource use in infected health state	61.36	0.00	230.96
Hosiery resource use in infected health state	23.99	0.00	84.80

Hospital inpatient resource use in closed health state	0.01	0.00	0.68
GP resource use in closed health state	0.70	0.00	4.36
Hospital outpatient resource use in closed health state	0.13	0.00	3.04
Practice Nurse resource use in closed health state	3.70	0.00	26.68
Community Nurse resource use in closed health state	34.62	0.00	80.52
Antibiotic prescription resource use in closed health state	1.69	0.00	9.00
Analgesic prescription resource use in closed health state	2.07	0.00	12.12
Primary dressing resource use in closed health state	26.43	0.00	208.36
Secondary Dressing resource use in closed health state	26.43	0.00	208.36
Compression system resource use in closed health state	18.11	0.00	68.16
Hosiery resource use in closed health state	5.73	0.00	21.76
Quality of life weight for open pre-amputation state	0.52	0.36	0.68
Quality of life weight for infected pre-amputation state	0.52	0.36	0.68

Quality of life weight for closed pre-amputation state	0.67	0.47	0.87
Neutral dressing. Transition probability: open -> infected	0.0082	0.0057	0.0106
Neutral dressing. Transition probability: open -> closed	0.0475	0.0332	0.0617
Neutral dressing. Transition probability: infected -> open	0.3333	0.2333	0.4333
Neutral dressing. Transition probability: closed -> open	0.0033	0.0023	0.0043
UrgoStart. Transition probability: open -> infected	0.0097	0.0068	0.0126
UrgoStart. Transition probability: open -> closed	0.1093	0.0765	0.1421
UrgoStart. Transition probability: infected -> open	0.3333	0.2333	0.4333
UrgoStart. Transition probability: closed -> open	0.0033	0.0023	0.0043

C.6 Variable values used in DFU PSA

Variable	Base-case value	Minimum value	Maximum value
If a patient has had a prior amputation from a previous wound	50%	35%	65%
The cost of one UrgoStart Dressing	£4.28	£3.00	£5.56
The cost of one Neutral Dressing	£3.13	£2.19	£4.07

Community Nurse resource use in complicated pre-state	2.4309	1.7016	3.1601
Bespoke orthosis resource use in closed pre-state	0.0192	0.0135	0.0250
Hospital inpatient resource use in complicated post state	0.0433	0.0303	0.0563
Community Nurse resource use in complicated post state	1.7608	1.2325	2.2890
Transition probability: open pre -> complicated pre	0.0187	0.0131	0.0243
Transition probability: open pre -> closed pre	0.0109	0.0076	0.0141
Transition probability: open pre -> deceased	0.0019	0.0014	0.0025
Transition probability: complicated pre -> open post	0.0034	0.0023	0.0044
Transition probability: complicated pre -> closed post	0.0034	0.0023	0.0044
Transition probability: closed pre -> deceased	0.0019	0.0014	0.0025
Transition probability: open post -> complicated post	0.0146	0.0102	0.0189
Transition probability: open post -> closed post	0.0256	0.0179	0.0333
Transition probability: open post -> deceased	0.0019	0.0014	0.0025
Transition probability: complicated post -> closed post	0.0143	0.0100	0.0186
UrgoStart Transition probability: open pre -> complicated pre	0.0135	0.0095	0.0176

UrgoStart Transition probability: open pre -> closed pre	0.0372	0.0260	0.0484
UrgoStart Transition probability: open pre -> deceased	0.0019	0.0014	0.0025
UrgoStart Transition probability: complicated pre -> closed pre	0.0111	0.0078	0.0144
UrgoStart Transition probability: closed pre -> deceased	0.0019	0.0014	0.0025
UrgoStart Transition probability: open post -> complicated post	0.0098	0.0069	0.0127
UrgoStart Transition probability: open post -> closed post	0.0377	0.0264	0.0490
UrgoStart Transition probability: complicated post -> closed post	0.0154	0.0108	0.0200

C.7 Variable values used in LU PSA

Variable	Base-case value	Minimum value	Maximum value
The cost of one UrgoStart Dressing	£4.28	£3.00	£5.56
The cost of one Neutral Dressing	£3.13	£2.19	£4.07
Hospital inpatient resource use in open health state	0.02	0.00	0.92
GP resource use in open health state	1.70	0.00	10.52

Hospital outpatient resource use in open health state	1.03	0.00	24.64
Practice Nurse resource use in open health state	16.26	0.00	123.72
Community Nurse resource use in open health state	155.54	0.00	411.52
Primary dressing resource use in open health state	169.74	0.00	1339.32
Secondary Dressing resource use in open health state	169.74	0.00	1339.32
Compression system resource use in open health state	61.36	0.00	230.96
Hosiery resource use in open health state	23.99	0.00	84.80
Hospital outpatient resource use in infected health state	1.03	0.00	24.64
Practice Nurse resource use in infected health state	16.26	0.00	123.72
Community Nurse resource use in infected health state	155.54	0.00	411.52
Secondary Dressing resource use in infected health state	169.74	0.00	1339.32
Hospital inpatient resource use in closed health state	0.01	0.00	0.68
GP resource use in closed health state	0.70	0.00	4.36
Hospital outpatient resource use in closed health state	0.13	0.00	3.04

Practice Nurse resource use in closed health state	3.70	0.00	26.68
Community Nurse resource use in closed health state	34.62	0.00	80.52
Primary dressing resource use in closed health state	26.43	0.00	208.36
Secondary Dressing resource use in closed health state	26.43	0.00	208.36
Compression system resource use in closed health state	18.11	0.00	68.16
Hosiery resource use in closed health state	5.73	0.00	21.76
Neutral dressing. Transition probability: open -> infected	0.0082	0.0057	0.0106
Neutral dressing. Transition probability: open -> closed	0.0475	0.0332	0.0617
Neutral dressing. Transition probability: infected -> open	0.3333	0.2333	0.4333
Neutral dressing. Transition probability: closed -> open	0.0033	0.0023	0.0043
UrgoStart. Transition probability: open -> infected	0.0097	0.0068	0.0126
UrgoStart. Transition probability: open -> closed	0.1093	0.0765	0.1421
UrgoStart. Transition probability: infected -> open	0.3333	0.2333	0.4333
UrgoStart. Transition probability: closed -> open	0.0033	0.0023	0.0043

C.8. Results of DFU DSA.

Variable	Min	Max	Variance
Transition probability: open post -> closed post	-£ 804.39	-£ 551.85	-£ 252.53
The cost of one UrgoStart Dressing	-£ 784.06	-£ 549.68	-£ 234.38
UrgoStart Transition probability: open pre -> complicated pre	-£ 782.52	-£ 562.40	-£ 220.12
UrgoStart Transition probability: open post -> complicated post	-£ 771.01	-£ 570.28	-£ 200.72
Transition probability: open pre -> closed pre	-£ 737.89	-£ 603.56	-£ 134.33
Transition probability: complicated post -> closed post	-£ 722.97	-£ 616.90	-£ 106.06
UrgoStart Transition probability: closed pre -> deceased	-£ 707.59	-£ 627.42	-£ 80.16
If a patient has had a prior amputation from a previous wound	-£ 694.78	-£ 639.33	-£ 55.45
UrgoStart Transition probability: open pre -> deceased	-£ 691.58	-£ 643.07	-£ 48.50
Transition probability: open post -> deceased	-£ 684.87	-£ 649.50	-£ 35.37
Bespoke orthosis resource use in closed pre-state	-£ 683.94	-£ 650.17	-£ 33.77

UrgoStart Transition probability: complicated pre -> open post	-£ 683.42	-£ 651.27	-£ 32.15
UrgoStart Transition probability: closed post -> open post	-£ 682.11	-£ 652.47	-£ 29.64
Transition probability: complicated pre -> closed pre	-£ 681.43	-£ 653.03	-£ 28.40
UrgoStart Transition probability: complicated pre -> closed post	-£ 680.88	-£ 653.76	-£ 27.12
Community Nurse resource use in closed pre-state	-£ 679.99	-£ 654.13	-£ 25.86
Primary dressing resource use in closed pre-state	-£ 676.66	-£ 657.27	-£ 19.38
Transition probability: complicated post -> deceased	-£ 676.13	-£ 658.12	-£ 18.01
UrgoStart Transition probability: closed pre -> open pre	-£ 675.74	-£ 658.64	-£ 17.10
Practice Nurse resource use in closed pre-state	-£ 674.80	-£ 659.14	-£ 15.66
Bespoke orthosis resource use in closed post state	-£ 674.79	-£ 659.32	-£ 15.46
Primary dressing resource use in closed post state	-£ 674.03	-£ 659.86	-£ 14.17
UrgoStart Transition probability: complicated pre -> deceased	-£ 673.44	-£ 660.83	-£ 12.62

Community Nurse resource use in closed post state	-£ 672.98	-£ 661.14	-£ 11.84
Hospital outpatient resource use in closed pre-state	-£ 671.57	-£ 662.54	-£ 9.03
Secondary Dressing resource use in closed pre-state	-£ 671.29	-£ 662.82	-£ 8.47
Transition probability: closed post -> deceased	-£ 671.15	-£ 663.03	-£ 8.12
Practice Nurse resource use in closed post state	-£ 670.53	-£ 663.36	-£ 7.17
Primary dressing resource use in open post state	-£ 670.32	-£ 663.69	-£ 6.63
Hospital outpatient resource use in closed post state	-£ 669.12	-£ 664.99	-£ 4.13
Primary dressing resource use in open pre-state	-£ 669.03	-£ 665.09	-£ 3.94
Secondary Dressing resource use in closed post state	-£ 669.00	-£ 665.12	-£ 3.88
GP resource use in closed pre-state	-£ 668.83	-£ 665.10	-£ 3.73
GP resource use in closed post state	-£ 667.80	-£ 666.09	-£ 1.71
Analgesic prescription resource use in closed pre-state	-£ 667.89	-£ 666.22	-£ 1.67
Analgesic prescription resource use in closed post state	-£ 667.44	-£ 666.67	-£ 0.77
Podiatrist resource use in closed pre-state	-£ 667.27	-£ 666.66	-£ 0.61

Antibiotic prescription resource use in closed pre-state	-£ 667.22	-£ 666.89	-£ 0.33
Podiatrist resource use in closed post state	-£ 667.08	-£ 666.80	-£ 0.28
Antibiotic prescription resource use in closed post state	-£ 667.13	-£ 666.98	-£ 0.15
Podiatrist resource use in open post state	-£ 667.03	-£ 666.98	-£ 0.05
The duration of amputation event disutility, in weeks	-£ 667.06	-£ 667.06	£ -
Hospital inpatient resource use in closed pre-state	-£ 667.06	-£ 667.06	£ -
Hospital inpatient resource use in closed post state	-£ 667.06	-£ 667.06	£ -
Quality of life weight for open pre-amputation state	-£ 667.06	-£ 667.06	£ -
Quality of life weight for complicated pre-amputation state	-£ 667.06	-£ 667.06	£ -
Quality of life weight for closed pre-amputation state	-£ 667.06	-£ 667.06	£ -
Quality of life weight for open post-amputation state	-£ 667.06	-£ 667.06	£ -
Quality of life weight for complicated post-amputation state	-£ 667.06	-£ 667.06	£ -
Quality of life weight for closed post-amputation state	-£ 667.06	-£ 667.06	£ -
Disutility associated with amputation event	-£ 667.06	-£ 667.06	£ -

Podiatrist resource use in open pre-state	-£ 666.96	-£ 667.06	£ 0.10
Analgesic prescription resource use in open post state	-£ 666.96	-£ 667.06	£ 0.10
Antibiotic prescription resource use in open pre-state	-£ 666.96	-£ 667.15	£ 0.19
Podiatrist resource use in complicated post state	-£ 666.94	-£ 667.17	£ 0.23
Antibiotic prescription resource use in open post state	-£ 666.88	-£ 667.13	£ 0.25
GP resource use in open post state	-£ 666.83	-£ 667.28	£ 0.44
Hospital inpatient resource use in open pre-state	-£ 666.75	-£ 667.27	£ 0.53
Antibiotic prescription resource use in complicated post state	-£ 666.77	-£ 667.34	£ 0.57
Antibiotic prescription resource use in complicated pre-state	-£ 666.74	-£ 667.34	£ 0.59
Podiatrist resource use in complicated pre-state	-£ 666.69	-£ 667.43	£ 0.74
Analgesic prescription resource use in complicated post state	-£ 666.64	-£ 667.43	£ 0.79
Analgesic prescription resource use in open pre-state	-£ 666.58	-£ 667.44	£ 0.86
GP resource use in open pre-state	-£ 666.41	-£ 667.61	£ 1.19
GP resource use in complicated post state	-£ 666.16	-£ 667.96	£ 1.80

Hospital inpatient resource use in complicated pre-state	-£ 665.86	-£ 668.16	£ 2.30
Transition probability: complicated pre -> deceased	-£ 665.79	-£ 668.49	£ 2.70
Secondary Dressing resource use in open post state	-£ 665.59	-£ 668.32	£ 2.73
Practice Nurse resource use in open post state	-£ 665.52	-£ 668.59	£ 3.06
Analgesic prescription resource use in complicated pre-state	-£ 665.32	-£ 668.79	£ 3.47
Hospital outpatient resource use in open pre-state	-£ 665.06	-£ 668.96	£ 3.90
Hospital outpatient resource use in open post state	-£ 664.84	-£ 669.17	£ 4.33
GP resource use in complicated pre-state	-£ 664.72	-£ 669.39	£ 4.67
The proportion having prosthesis after major amputation	-£ 663.76	-£ 668.85	£ 5.09
Primary dressing resource use in complicated post state	-£ 663.97	-£ 670.14	£ 6.16
Practice Nurse resource use in open pre-state	-£ 663.49	-£ 670.62	£ 7.13
Secondary Dressing resource use in open pre-state	-£ 663.44	-£ 670.58	£ 7.14
Bespoke orthosis resource use in open post state	-£ 663.21	-£ 67.80	£ 7.59

Community Nurse resource use in open post state	-£ 662.51	-£ 671.51	£ 9.00
Bespoke orthosis resource use in complicated post state	-£ 662.01	-£ 672.10	£ 10.09
UrgoStart Transition probability: closed post -> deceased	-£ 661.63	-£ 672.40	£ 10.77
UrgoStart Transition probability: complicated post -> deceased	-£ 661.36	-£ 672.67	£ 11.31
Transition probability: closed pre -> open pre	-£ 660.85	-£ 673.05	£ 12.20
Practice Nurse resource use in complicated post state	-£ 660.86	-£ 673.25	£ 12.39
Secondary Dressing resource use in complicated post state	-£ 660.61	-£ 673.46	£ 12.85
Hospital outpatient resource use in complicated pre-state	-£ 660.26	-£ 673.86	£ 13.60
Bespoke orthosis resource use in open pre-state	-£ 659.85	-£ 674.26	£ 14.41
Bespoke orthosis resource use in complicated pre-state	-£ 658.43	-£ 675.68	£ 17.24
Hospital outpatient resource use in complicated post state	-£ 658.07	-£ 676.00	£ 17.93
Primary dressing resource use in complicated pre-state	-£ 657.33	-£ 676.75	£ 19.41
The proportion of major amputations	-£ 657.32	-£ 676.79	£ 19.47

Community Nurse resource use in open pre-state	-£ 655.15	-£ 678.88	£ 23.73
Hospital inpatient resource use in open post state	-£ 654.60	-£ 679.42	£ 24.81
Practice Nurse resource use in complicated pre-state	-£ 654.22	-£ 679.80	£ 25.58
Transition probability: closed post -> open post	-£ 652.77	-£ 680.88	£ 28.10
UrgoStart Transition probability: open post -> deceased	-£ 652.63	-£ 681.29	£ 28.67
Secondary Dressing resource use in complicated pre-state	-£ 651.89	-£ 682.19	£ 30.30
Community Nurse resource use in complicated post state	-£ 649.05	-£ 685.02	£ 35.98
Transition probability: open pre -> deceased	-£ 647.53	-£ 686.80	£ 39.27
Transition probability: complicated pre -> closed post	-£ 641.05	-£ 692.04	£ 50.99
UrgoStart Transition probability: complicated pre -> closed pre	-£ 639.56	-£ 692.34	£ 52.78
Transition probability: complicated pre -> open post	-£ 635.53	-£ 697.43	£ 61.90
UrgoStart Transition probability: complicated post -> closed post	-£ 629.10	-£ 700.79	£ 71.69

Community Nurse resource use in complicated pre-state	-£ 624.66	-£ 709.46	£ 84.80
Transition probability: closed pre -> deceased	-£ 624.55	-£ 709.60	£ 85.05
Hospital inpatient resource use in complicated post state	-£ 616.64	-£ 717.43	£ 100.78
UrgoStart Transition probability: open pre -> closed pre	-£ 573.43	-£ 741.38	£ 167.95
The cost of one Neutral Dressing	-£ 538.53	-£ 795.15	£ 256.62
UrgoStart Transition probability: open post -> closed post	-£ 517.91	-£ 782.74	£ 264.83
Transition probability: open post -> complicated post	-£ 514.54	-£ 803.07	£ 288.53
Transition probability: open pre -> complicated pre	-£ 476.30	-£ 830.60	£ 354.30

C.9. Results of LU DSA

Variable	Min	Max	Variance
The cost of one UrgoStart Dressing	-£321.52	-£226.90	-£94.62
The cost of one Neutral Dressing	-£223.66	-£324.42	£100.76
The duration of infection	-£274.25	-£274.25	£0.00

Hospital inpatient resource use in open health state	-£273.43	-£312.59	£39.16
GP resource use in open health state	-£268.16	-£305.77	£37.61
Hospital outpatient resource use in open health state	-£260.92	-£580.73	£319.80
Practice Nurse resource use in open health state	-£197.69	-£780.15	£582.46
Community Nurse resource use in open health state	£24.68	-£766.20	£790.88
Antibiotic prescription resource use in open health state	-£273.32	-£278.18	£4.86
Analgesic prescription resource use in open health state	-£272.39	-£284.17	£11.78
Primary dressing resource use in open health state	-£240.36	-£507.00	£266.64
Secondary Dressing resource use in open health state	-£252.76	-£422.32	£169.56
Compression system resource use in open health state	-£234.06	-£385.23	£151.17
Hosiery resource use in open health state	-£247.80	-£341.42	£93.62
Hospital inpatient resource use in infected health state	-£274.20	-£276.64	£2.44

GP resource use in infected health state	-£273.88	-£276.22	£2.34
Hospital outpatient resource use in infected health state	-£273.42	-£293.34	£19.92
Practice Nurse resource use in infected health state	-£269.49	-£305.76	£36.27
Community Nurse resource use in infected health state	-£255.64	-£304.89	£49.25
Antibiotic prescription resource use in infected health state	-£274.20	-£274.50	£0.30
Analgesic prescription resource use in infected health state	-£274.14	-£274.87	£0.74
Primary dressing resource use in infected health state	-£272.80	-£284.25	£11.45
Secondary Dressing resource use in infected health state	-£272.08	-£289.26	£17.19
Compression system resource use in infected health state	-£271.75	-£281.17	£9.42
Hosiery resource use in infected health state	-£272.61	-£278.43	£5.83
Hospital inpatient resource use in closed health state	-£275.20	-£213.16	-£62.04
GP resource use in closed health state	-£279.63	-£246.13	-£33.50

Hospital outpatient resource use in closed health state	-£277.84	-£193.15	-£84.69
Practice Nurse resource use in closed health state	-£311.65	-£42.10	-£269.55
Community Nurse resource use in closed health state	-£417.09	-£84.97	-£332.12
Antibiotic prescription resource use in closed health state	-£274.78	-£271.94	-£2.84
Analgesic prescription resource use in closed health state	-£275.10	-£270.04	-£5.06
Primary dressing resource use in closed health state	-£315.43	£9.57	-£325.00
Secondary Dressing resource use in closed health state	-£281.42	-£224.85	-£56.56
Compression system resource use in closed health state	-£299.74	-£204.00	-£95.75
Hosiery resource use in closed health state	-£287.84	-£236.33	-£51.51
Quality of life weight for open pre-amputation state	-£274.25	-£274.25	£0.00
Quality of life weight for infected pre-amputation state	-£274.25	-£274.25	£0.00
Quality of life weight for closed pre-amputation state	-£274.25	-£274.25	£0.00

Neutral dressing. Transition probability: open -> infected	-£253.92	-£294.49	£40.57
Neutral dressing. Transition probability: open -> closed	-£441.15	-£157.98	-£283.17
Neutral dressing. Transition probability: infected -> open	-£301.94	-£258.95	-£42.99
Neutral dressing. Transition probability: closed -> open	-£263.35	-£284.95	£21.60
UrgoStart. Transition probability: open -> infected	-£287.32	-£261.21	-£26.10
UrgoStart. Transition probability: open -> closed	-£146.51	-£348.01	£201.50
UrgoStart. Transition probability: infected -> open	-£255.98	-£284.21	£28.22
UrgoStart. Transition probability: closed -> open	-£284.14	-£264.50	-£19.64

Appendix D. Publications

D.1 Econ SLR abstract.

A Systematic Review of Economic Outcomes Associated with Use of Topical Interventions for Treatment of Chronic Wounds. Fatoye, F et al. Value in Health, Volume 21, S174

OBJECTIVES: A combination of interventions may be appropriate for a patient with a chronic wound. However, standard care varies by aetiology, geographical location and clinician discipline. A systematic review was undertaken to examine the economic impact of topical interventions for chronic wounds and the variance associated with standard care.

METHODS: A systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Searches of: Science Direct, National Institute for Health and Clinical Excellence Evidence search, Medline (PubMed), Centre of Reviews and Dissemination (University of York), Cochrane Database and discussion with experts and manufacturers identified the literature. Two researchers performed data extraction, with a third consulted where there were disagreements. Economic endpoints including: incremental cost-effectiveness ratio, cost-per Quality Adjusted Life Year and disease related resource use were extracted. A narrative synthesis of results and critical appraisal using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement were performed.

RESULTS: 3422 records identified. After screening, 817 full text articles were judged versus inclusion and exclusion criteria. 15 studies were included: 6 economic analysis along clinical trials, and 9 modelling studies.10 studies focused on VLUs, 3 studies on DFUs and 1 on Pressure Ulcers and 1 on Chronic Wounds. Data tables for methods, results and appraisal using the CHEERS statement were completed. Quality scores ranged from 10 – 15 with a mean of 12.9.

CONCLUSIONS: This review provides some evidence that topical interventions can offer cost-effective solutions for treating chronic wounds compared with standard care. Current evidence predominantly uses the endpoint of wound area reduction; evaluations using complete wound closure as primary endpoint could be more useful. This review informs decision makers and clinicians that more expensive wound care products can be cost-effective in the management of chronic wounds; in opposition to current NICE guidance to use the 'least costly' dressing.

D.2. Econ SLR poster

A SYSTEMATIC REVIEW OF ECONOMIC OUTCOMES ASSOCIATED WITH USE OF TOPICAL INTERVENTIONS FOR TREATMENT OF CHRONIC WOUNDS

Manchester Metropolitan University

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Objective

To examine the economic impact of topical interventions for chronic wounds and the variance associated with standard care.

Background

A chronic wound is burdensome for patients, the healthcare system and wider society. These wounds can last for a long time, often in excess of a year. The prevalence of chronic wounds was estimated to be growing at the rate of 12% per annum in a study looking at 2000 patients in The Health Improvement Network database [1].

With this increasing prevalence, the costs of wound care are also rising, an estimated £1.94 billion spent on Leg Ulcers in 2012/3 and in 2014/5 £1 billion spent on Diabetic Foot Ulcers in the United Kingdom [2,3]. Standard care for wounds varies depending on the type, however they include items such as dressings, debridement, infection control, compression and offloading, delivered by a multidisciplinary team of health care providers [4,5].

Methods

A systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines undertaken.

Searches of: Science Direct, National Institute for Health and Clinical Excellence Evidence search, Medline (PubMed), Centre of Reviews and Dissemination (University of York), Cochrane Database and discussion with experts and manufacturers to identify additional literature. Two researchers performed data extraction, with a third consulted where there were disagreements.

Economic endpoints: incremental cost-effectiveness ratio, cost-per Quality Adjusted Life Year and disease related resource use.

A narrative synthesis of results and critical appraisal using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement were performed.

Table 1: Inclusion /Exclusion criteria

	Inclusion criteria
Population	Chronic wounds
Interventions	Topical dressings or applications
Outcomes	Economic outcomes
Study design	RCT with economic evaluation. Any economic study or modelling
Language	English Language
Search dates	After 1987
	Exclusion criteria
Population	Paediatrics, Acute wounds (including Burns, Trauma, Surgery)
Interventions	Surgical. Novel non-surgical (including electrical stimulation, hyperbaric treatment. Infection control measures. Debridement. Bioengineered skin substitutes. Offloading
Outcomes	Not meeting inclusion criteria
Study design	In vitro studies, review or discussion articles
Language	Non-English language (if the abstract was available in English and enough data was available, this was included in the data extraction).
Search dates	Before 1987

Results

After initial screening of the 3422 titles and abstracts, 2585 were excluded for not being relevant to the research objective. The remaining 817 texts were judged against the inclusion and exclusion criteria. Finally, 15 texts were included as per the PRISMA flow chart.

The studies predominantly examined VLU, with 10 studies focusing on these patients, 3 studies looked at DFU and one each for Chronic Wounds and Pressure Ulcers.

Across the 15 studies, standard care (or good wound care) was used 10 times, including where standard care was provided together with the study treatment.

Seven studies were set in the UK, of these standard care was used in 3, reporting a cost of standard care for DFU outpatient and inpatients, £3330 and £4488 respectively. For VLU, a mean annual cost of £1385·51 – £1795·30 per patient was reported.

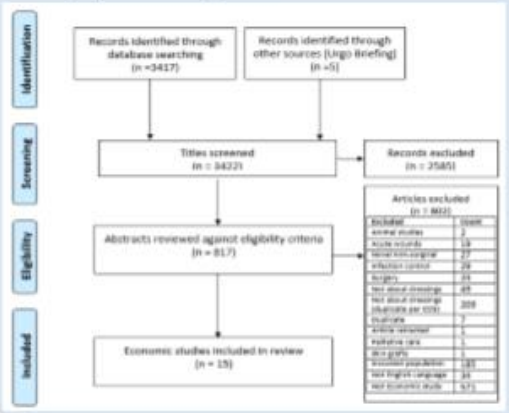

Figure 1. PRISMA flow diagram

Conclusions

The methodological quality of the studies that were included in this review was assessed by use of the CHEERS statement. Of a maximum available 18 points awarded by the checklist a range of scores between 10-15 were awarded, with a mean of 12.9.

The treatment in question was cost-effective or cost-saving in 14 of the 15 studies. The exception; Chuang et al[6], evaluated a randomized controlled trial of ultrasound therapy for hard-to-heal venous leg ulcers found no benefit and more expense associated with the ultrasound therapy.

In an environment of budget cuts and financial pressure on health care systems, cost-effective solutions to health care problems are desirable. Cost-effective interventions for wound care are not necessarily those that are the cheapest at the point of use, the use of the least costly interventions may not lead to the best possible healing outcomes for patients in terms of full closure, time to healing and risk of recurrence.

Improving healing outcomes would alleviate strain on the healthcare system, as long as the uncertainty surrounding evidence supporting new treatments can be balanced with high quality clinical trials supported by accurate economic modelling.

References:
1. Guest, J., Vowden, K. & Vowden, P., 2017. The health economic burden that acute and chronic wounds impose on an average clinical commissioning group/health board in the UK.. Journal of Wound Care, 26(6), pp. 292-303.
2. Guest, J. et al., 2017. Health economic burden that different wound types impose on the UK's National Health Service.. International Wound Journal, 14(2), pp. 322-330.
3. Kerr M. Improving footcare for people with diabetes and saving money: an economic study of England. 2017. [Accessed April 2018].
4. National Institute for Health and Care Excellence (NICE), 2015. NG19 Diabetic foot problems: prevention and management. National Institute for Health and Care Excellence.
5. Scottish Intercollegiate Guidelines Network (SIGN), 2010. Management of chronic venous leg ulcers. Edinburgh: Healthcare Improvement Scotland.
6. Chuang, L. et al., 2011. Economic evaluation of a randomized controlled trial of ultrasound therapy for hard-to-heal venous leg ulcers. British Journal of Surgery, 98(8), pp. 1099-106.

D.3. Clinical SLR abstract

A Systematic Review of Clinical Efficacy Associated with use of Protease-Modulating Interventions with Diabetic Foot Ulcer or Venous Leg Ulcer. Yeowell, G et al. Value in Health, Volume 21, S163

OBJECTIVES: Diabetic foot ulcers (DFUs) or leg ulcers (LUs) of venous, arterial or mixed origin can cause a considerable burden to a patient and healthcare provider, taking a long time to heal and requiring frequent interventions. Dressings are a mainstay of treatment with countless options for a Healthcare Provider. Protease-modulating matrix (PMM) interventions are an alternative to basic or other advanced dressings. A systematic review was undertaken to assess the clinical effectiveness of PMM interventions for DFUs and LUs.

METHODS: A systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines. An online database search, and consultation with experts and manufacturers identified the literature. Databases searched included: Centre Reviews and Dissemination (CRD) York Database, Cochrane Library, Medline (PubMed), National Institute for Health and Clinical Excellence Evidence Search, Science Direct/Scopus. Two researchers performed data extraction with a third consulted in case of any discrepancies. A narrative synthesis of results and critical appraisal of included studies was performed.

RESULTS: A total of 283 records were identified by literature searching. After initial screening of titles and abstracts, 215 full text articles were judged against pre-defined inclusion and exclusion criteria. Six randomised controlled trials and 2 observational studies were included in the review. A total of 1310 patients were included in this study. The three VLU RCTs included a total of 377 patients, and the DFU studies included 933 patients. Healing was the most frequently reported outcome, followed by wound area reduction. A meta-analysis was not possible given the heterogeneity of the included studies.

CONCLUSIONS: This review provides some evidence that PMM interventions have a clinical benefit on wound healing outcomes; however, there were several methodological issues with the studies included. New evidence shows promising results for the treatment of DFUs involving protease modulation by sucrose octasulfate dressings.

D.4. Clinical SLR poster

A Systematic Review of clinical efficacy of Protease-Modulating interventions with Diabetic Foot Ulcer or Venous Leg Ulcer

Manchester Metropolitan University

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Objective

To determine if protease modulating treatments are a clinically effective treatment strategy for Diabetic Foot Ulcers or Leg Ulcers.

Wound dressings

Wound dressings are a mainstay of treatment; being applied to a wound as part of a wider treatment strategy, guidelines include compression, debridement, offloading and infection control to achieve full wound closure [1,2].

Protease-modulating-matrix (PMM) dressings have an effect on the matrix-metalloproteases (MMPs) that are present in chronic wounds. These interventions are intended to rebalance the levels of MMPs in the wound bed, stimulating healing and improving outcomes.

Uncertainty and new evidence

Advice from the National Institute for Health and Care Excellence (NICE) recommends *"the least costly dressing of the type that meets the required characteristics appropriate for the type of wound"* [3].

A prior systematic review of PMM dressings did not find conclusive evidence of clinical benefit for Venous Leg Ulcers[4]. However newer studies have now been published; a pooled analysis[5] and a Double-Blind Randomised Clinical Trial[6] showing superior outcomes for PMM dressings. This has highlighted the need for a review of the evidence.

Methods

A systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines was undertaken. This included a database search, and consultation with experts and manufacturers to identify additional literature.

Databases searched: Centre Reviews and Dissemination (CRD) York Database, Cochrane Library, Medline (PubMed), National Institute for Health and Clinical Excellence Evidence Search, Science Direct/Scopus.

Two researchers performed data extraction with a third consulted in case of discrepancies. A narrative synthesis of results and critical appraisal of included studies as per the NICE submission template for Medical Technologies Evaluation Programme; which has been derived from the Centre for Reviews and Dissemination (CRD) was performed.

Table 1. Inclusion/Exclusion Criteria

Inclusion criteria	
Population	Diabetic Foot Ulcer, Venous Leg Ulcer
Interventions	Protease Matrix Modulating dressings and topical applications
Outcomes	Wound Area Reduction (WAR), Wound Closure,
Study design	Randomised Controlled Trials, Observational studies
Language	English Language
Search dates	Search was carried out December 2017, date unrestricted.
Exclusion criteria	
Population	Paediatrics (<18), Acute wounds
Interventions	Surgical. Novel-non-surgical. Infection control. Debridement. Bioengineered skin substitute. Offloading. Prevention.
Outcomes	Not meeting inclusion criteria
Study design	In vitro studies, review or discussion articles, Treatment pathway/guidelines, Systematic/ Literature Reviews or Meta analyses, Epidemiology Studies, Modelling, Case Studies, Economic studies, Database Studies
Language	Non-English language
Search dates	Unrestricted

Results

From searching the databases 272 results were returned. Discussion with Experts and Manufacturers provided 11 further titles. After initial screening of the 283 titles and abstracts, 68 were excluded for being irrelevant. The remaining 215 texts were judged against the inclusion and exclusion criteria. 202 titles were excluded, with 8 being included as per the PRISMA flow chart.

Of the studies included, 3 had a primary outcome of relative WAR and 5 assessed healing or closure outcomes. Edmonds 2018 demonstrates an odds ratio of 2.6 (p=0.002) of healing at 20 weeks when using a PMM dressing on a DFU [5]. Looking at the total population Munter shows a 30.8% benefit when a treatment regime included the Protease Modulating Dressing, presenting as a 29.8% (CI: 28.8%-30.9%) benefit for LU patients and 37.4% (CI: 34.8%-40.1%) for DFUs [6].

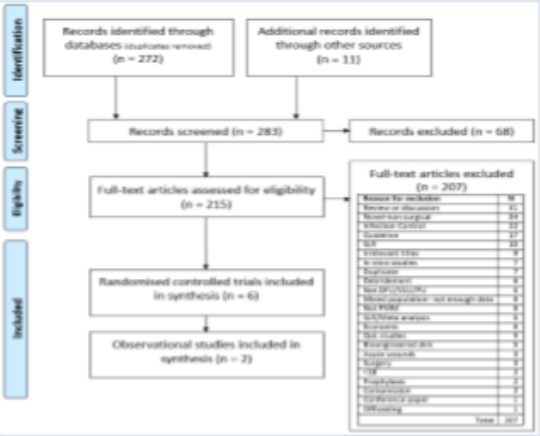

Figure 1. PRISMA flow diagram

Conclusions

This study found evidence of protease-modulating interventions being clinically effective in the management of DFU and VLU. Two studies compare two wound care products by the same manufacturer, achieving double-blinding by producing both the intervention and control dressing with the same material, packaging and colours as one another; with the sole difference being the addition of the PMM agent [5,7].

The critical review of the evidence scored the RCTs as being of an overall moderate quality. The observational studies both scored as being of poor quality. This uncertainty of evidence means that more work is required to produce further evidence. Expert opinion in conjunction with data from clinical studies and literature could inform better treatment practices.

This systematic review highlights the need for further research into the efficacy of protease-modulating treatments. They have been shown to have some efficacy; with the dressing preparation being particularly beneficial to ulcers that are older and larger; which are often the most burdensome ulcers.

The findings of this systematic review could be used to inform clinical decision making with regards to PMM interventions. These interventions are more costly than basic alternatives; however this review has shown that they may improve healing outcomes for to patients; with enhanced potential in patients with DFU and on older and larger wounds.

References:
1. National Institute for Health and Care Excellence (NICE). 2015. *NG19, Diabetic foot problems: prevention and management*, National Institute for Health and Care Excellence.
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4. Westby, M., Noorani, G., Dumville, J., Stubbs, N. and Cullum, N. Protease-modulating matrix treatments for healing venous leg ulcers. Cochrane Database of Systematic Reviews. 2016; 12. Article: CD012013.
5. Munter, K. et al., 2017. The reality of routine practice: a pooled data analysis on chronic wounds treated with TLC-NOSF wound dressings. *Journal of Wound Care*, Volume 26, pp. 4-15.
6. Edmonds, M. et al., 2018. Sucrose octasulfate dressing versus control dressing in patients with neuroischaemic diabetic foot ulcers (Explorer): an international, multicentre, double-blind, randomised, controlled trial. *The Lancet Diabetes & Endocrinology*, Volume 6, pp. 186-96.
7. Mawanne, S. et al., 2012. A randomized, controlled, double-blind prospective trial with a Lipido-Colloid Technology-Nano-OligoSaccharide Factor wound dressing in the local management of venous leg ulcers. *Wound Repair and Regeneration*, 20(4), pp. 508-11.

D.5. Delphi abstract

Addressing Uncertainty in Wound Management Using A Modified Delphi Methodology. Betts, A et al. Value in Health, Volume 20, Issue 9, A794

OBJECTIVES: Increasing prevalence and rising costs of Venous Leg Ulcers (VLU), Diabetic Foot Ulcers (DFU) and Pressure Ulcers (PU), means that a consistent level of care and understanding is needed to improve patient outcomes and maximise cost efficiencies. This study aimed to gain consensus on a set of evidence-based statements from a range of clinical experts.

METHODS: A literature search identified 827 articles, inclusion/exclusion criteria were applied resulting in 145 articles providing 308 quotations in 4 categories: epidemiology, clinical effectiveness, quality of life, and economics. From this, 47 statements were developed. A modified Delphi methodology was used and a consensus threshold of 80% was set. Round I and II: Participants electronically examined and voted yes/no for each statement. If the threshold was not met, comments informed changes. Round III: A meeting to discuss all statements.

RESULTS: Round I: 38/47 statements confirmed, none rejected. 9 statements modified using comments and resubmitted. Round II: 5/9 remaining statements confirmed, none rejected, leaving 4. At the meeting, all 47 were confirmed. During examination of confirmed statements, some modifications were made; agreed by all members of the panel. A consensus document is being developed using the statements.

CONCLUSIONS AND DISCUSSION: The consensus document developed from the statements should help to address areas of uncertainty in the management of chronic wounds by Healthcare Professionals across a range of disciplines resulting in benefits for the patient and healthcare system. The panel enjoyed the Delphi methodology, which was an efficient way of arriving at consensus for a large and varied group. Using a Delphi methodology to gain consensus on evidence-based statements generated from a literature review is an efficient and thorough methodology to resolve uncertainty regarding the management of clinical conditions.

D.6. Delphi poster

Addressing uncertainty in wound management using a modified Delphi methodology

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Objective

To gain consensus surrounding uncertainty in using dressings to improve wound outcomes.

Background

Chronic wounds such as Diabetic Foot Ulcers (DFU) and Leg Ulcers (LU) are increasingly prevalent and are a financial burden on the healthcare system, a 2016 estimate of long lasting ulcers below the knee was 15 out of every 10,0000 people[1]. A 2010-11 estimate calculated that approximately £1 in every £140 of NHS spending is on foot ulcers or amputations each year[2].

Wound dressings are a mainstay of treatment, however, the availability of a wide variety of dressings coupled with a lack of specific guidance presents uncertainty. NICE NG19 states that clinicians are to use "dressings with the lowest acquisition cost appropriate to the clinical circumstances"[3]. Cochrane reviews highlight the lack of robust studies with high levels of evidence surrounding several dressing types [4,5].

To address the uncertainty regarding the use of dressings on chronic wounds, a modified Delphi methodology expert panel, involving two iterations of email questionnaires, and one face to face meeting, was conducted to elicit expertise from a multidisciplinary group of experts.

Methods

- The modified process used for this study is shown below:

- The consensus threshold was 80%, and participants could vote yes or no against the statements, confirming or rejecting them. Unconfirmed statements were modified according to the participants' comments and resubmitted in the next round.

Results

The ten clinical experts on the panel represented Nursing, Tissue Viability, Podiatry, Surgery and Diabetology. Six technical experts representing Qualitative Research, Health Policy and Health Economics, were present to advise on the process, but did not have voting rights on the statements.

Due to the large number of statements confirmed before the final round, as shown in the table to the right, it was considered prudent to revisit comments on statements which had been confirmed with a level of 80-99%, in order to increase the level of consensus and ensure semantic clarity.

The final confirmed statements were used to create a larger consensus statement that had the agreement of the entire panel. This consensus statement is currently awaiting publication.

Round I	
Statements confirmed	38 (81%)
Statements unconfirmed	9 (19%)
Statements rejected	0 (0%)
Round II	
Statements confirmed	5 (56%)
Statements unconfirmed	4 (44%)
Statements rejected	0 (0%)
Face to Face meeting	
Statements confirmed	4 (100%)
Statements unconfirmed	0 (0%)
Statements rejected	0 (0%)

Discussion

The modified Delphi Methodology vs a traditional Expert Panel	
Delphi Methodology	**Expert Panel**
The methodology is structured to place equal weight on the opinion of all panel members.	Unstructured expert panels or advisory boards can be led by dominant or more senior individual.
Iterative; multiple rounds of voting encourages individuals to reflect on their own opinions and knowledge in the context of feedback from others.	Usually a single meeting, individuals are encouraged to put forward their own opinions and not necessarily reach a consensus.
Participants are anonymous when they feed back their opinions.	Participants are not anonymous to one another.
Transparent methodology, the workbook is the basis for all discussions.	Unstructured method without controls on biases. Can allow for more freedom of discussion.

Strengths

- This study aimed to address uncertainties in clinical practice by developing a set of evidence-based statements, validated by experts.
- The systematic literature review reported using PRISMA guidelines and the use of a structured workbook to collect expert opinions allows for repeatability and validation of the results.
- Given the culture of regulatory scrutiny, using a Delphi methodology facilitated by an independent academic institution, protects the legitimacy of scientific exchange between Clinical experts themselves, and between the experts and the sponsoring manufacturers.

Limitations

- The binary voting system did not allow any ranking of the statements.
- As a result of working with opinions, a Delphi panel is subject to low levels of evidence classifications.

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This project was commissioned and funded by Urgo Medical Ltd and designed and executed by Manchester Metropolitan University.

D.7. Delphi manuscript

education

Using a modified Delphi methodology to gain consensus on the use of dressings in chronic wounds management

Objective: Managing chronic wounds is associated with a burden to patients, caregivers, health services and society and there is a lack of clarity regarding the role of dressings in improving outcomes. This study aimed to provide understanding on a range of topics, including: the definition of chronicity in wounds, the burden of illness, clinical outcomes of reducing healing time and the impact of early interventions on clinical and economic outcomes and the role of matrix metalloproteinases (MMPs) in wound healing.

Method: A systematic review of the literature was carried out on the role of dressings in diabetic foot ulcer (DFU), and venous leg ulcer (VLU) management strategies, their effectiveness, associated resource use/cost, and quality of life (QoL) impact on patients. From this evidence-base statements were written regarding chronicity in wounds, burden of illness, healing time, and the role of MMPs, early interventions and dressings. A modified Delphi methodology involving two iterations of email questionnaires followed by a face-to-face meeting was used to validate the statements, in order to arrive at a consensus for each. Clinical experts were selected, representing nurses, surgeons, podiatrists, academics, and policy experts.

Results: In the first round, 38/47 statements reached or exceeded the consensus threshold of 80% and none were rejected. According to the protocol, any statement not confirmed or rejected had to be modified using the comments from participants and resubmitted. In the second round, 5/9 remaining statements were confirmed and none rejected, leaving 4 to discuss at the meeting. All final statements were confirmed with at least 80% consensus.

Conclusion: This modified Delphi panel sought to gain clarity from clinical experts surrounding the use of dressings in the management of chronic wounds. A full consensus statement was developed to help clinicians and policy makers improve the management of patients with these conditions.

Declaration of interest: This study was commissioned and sponsored by Urgo Medical UK as part of a data generation initiative with Manchester Metropolitan University (MMU). The project was funded by Urgo Medical UK and undertaken by an independent academic unit. Study design, protocol development, systematic review and other duties were carried out solely by MMU, where the researchers worked independently from Urgo; not in its offices nor under its direction.

dressings • consensus • Delphi • diabetic foot ulcers • venous leg ulcers • wound care

Diabetic foot ulcers (DFUs) and venous leg ulcers (VLUs) are two of the most common lower limb wounds.[1] A growing global epidemic of chronic wounds not only leaves patients in pain and with a reduced quality of life, but also causes a significant financial burden to health-care providers worldwide.[2,3] In 2016, independent research funded by the National Health Service's (NHS) National Institute of Health Research (NIHR) stated that the prevalence of long-lasting ulcers below the knee that take longer than six weeks to heal is seen in 15 out of every 10,000 people,[4] which is an increase of threefold on a previous estimate. The impact of these wounds is likely to continue to rise, with an ageing population and increasing incidence of diabetes[5] accelerating the growth. The burden of these wounds is felt not only by patients, but also by carers, families, employers, and by the health-care system.

Should a wound remain unhealed and the limb require amputation, this is devastating for the patient, and their subsequent decreased level of independence will place a strain on the family or carers. The financial burden to the health-care system is substantial; Diabetes UK estimated that in 2014–2015 around £1 billion (or approximately £1 in every £140 the NHS spends) is spent on foot ulcers or amputations each year.[6] Prescribing costs are also rising; in 2004, £122 million was spent on wound dressings, eight years later, in 2012, the prescribing costs for wound dressings had risen by 51% to £184 million.[7] The increased demand

David Russell,[1] Consultant Vascular Surgeon and Honorary Clinical Associate Professor; **Leanne Atkin,**[2] Vascular Nurse Specialist, PhD; ***April Betts,**[3] Health Technology Assessment Project Manager; **Caroline Dowsett,**[4] Nurse Consultant Tissue Viability; **Francis Fatoye,**[3] Professor of Health Economics and Outcomes; **Sarah Gardiner,**[5] Clinical Lead, Tissue Viability; **Julie Green,**[6] Senior Lecturer in Nursing, Director of Postgraduate Programmes; **Chris Manu,**[7] Consultant Diabetologist and Clinical Researcher in Diabetic Foot; **Tracey McKenzie,**[8] Head of Tissue Viability Services; **Helena Moally,**[1] Hospital Podiatrist; **Louise Mitchell,**[9] Clinical Lead Podiatrist; **Julie Mullings,**[10] Lead Tissue Viability Nurse; **Isaac Odeyemi,**[3] Visiting Professor of Health Technology Assessment and Health Policy; **Andrew Sharpe,**[11] Advanced Podiatrist and Lecturer Practitioner; **Gillian Yeowell,**[3] MSc Advanced Physiotherapy Programme Leader, PhD; **Nancy Devlin,**[12] Director of Research, Professor

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1 Leeds Teaching Hospitals NHS Trust. **2** Mid Yorkshire Hospitals NHS Trust. **3** Manchester Metropolitan University. **4** East London NHS Foundation Trust, London. **5** Oxford Health NHS Foundation Trust. **6** Keele University, School of Nursing and Midwifery. **7** King's College Hospital, London. **8** Torbay and Southern Devon NHS Foundation Trust. **9** Birmingham Community HealthCare. **10** University Hospital of South Manchester, NHS Foundation Trust. **11** West Lancashire Community Service, Virgin Care and University of Huddersfield. **12** Office of Health Economics, Victoria Street, London.

D.8. PRO abstract

Using EQ-5D to measure quality of life in patients with diabetic foot ulcers and venous leg ulcers. Betts, A. et al. Value in Health, Volume 21, S241

BACKGROUND: Quality of life (QoL) is a subjective phenomenon; meaning it is difficult to assess accurately. There are many instruments to measure QoL; generic tools enable comparisons across interventions and disease areas. The quality of life impact of Diabetic Foot Ulcer (DFU) and Venous Leg Ulcer (VLU) is important to consider, as these wounds can often be long lasting and burdensome for a patient with the need for frequent dressing changes, which can often be painful and cause anxiety.

METHODS: This is a cross-sectional study to determine QoL of patients with DFU and VLU. The study was carried out in multiple treatment centres in the United Kingdom; Patients attending clinics as part of treatment were enrolled sequentially, after obtaining consent. Data was anonymous at collection and entered into a SPSS (version 25) database for analysis. Descriptive statistics of demographic characteristics performed. EQ-5D-5L index scores were calculated using Crosswalk analysis. Subgroup analysis took into account wound severity as judged by the duration of wound and the size of the wound.

RESULTS: Ninety-four patients completed the study, 42 with a DFU and 51 with a VLU. The mean EQ-5D-5L index score for DFU patients was 0.55 and for VLU patients 0.64. Seventeen (42%) DFUs and 19 (38%) VLUs were classified as severe, these wounds had even lower index scores 0.47 and 0.56 for DFU and VLU respectively.

DISCUSSION: These scores indicate that DFU and VLU patients suffer from impaired QoL, with wounds that are older and longer in duration having a worse impact. Interventions and strategies to treat chronic wounds should consider quality of life outcomes for these patients; especially when treating populations with more severe wounds. Interventions that reduce the time to healing for these wounds would help to alleviate the burden on the patient in terms of QoL.

D.9. PRO poster

USING EQ-5D TO MEASURE QUALITY OF LIFE IN PATIENTS WITH DIABETIC FOOT ULCERS AND VENOUS LEG ULCERS.

BETTS, A., FATOYE, F., ODEYEMI, I., YEOWELL, G.

Manchester Metropolitan University

OBJECTIVES

Chronic wounds are associated with significantly reduced health-related Quality of Life (QoL) [1]. These wounds impact multiple dimensions including pain, physical limitation, social isolation, and patients also reported depression, anxiety and low mood [2]. There are many instruments to measure health related QoL; including EQ-5D, preferred by NICE in calculating cost-utility[3,4]. Generic tools such as EQ-5D enable comparisons across interventions and disease areas.

When assessing the burden associated with Diabetic Foot Ulcers (DFUs) and Venous Leg Ulcers (VLUs) QoL is important to consider, as these wounds can often be long lasting with the need for frequent dressing changes, which can often be painful and cause anxiety [5].

METHODS

A cross-sectional study of patients with DFU and VLU in the United Kingdom using EQ-5D-5L to determine QoL. Ethical Approval was granted by the Manchester Metropolitan University. Patients attending clinics as part of treatment were enrolled sequentially, after obtaining consent and data was anonymised at collection. Multiple treatment centres across the UK took part in the study where patients were recruited by healthcare providers when they attended clinics.

Patients provided informed consent and completed a demographic sheet on patient and ulcer characteristics, then they completed EQ-5D-5L to record their QoL at that visit. Descriptive statistics of demographic characteristics was undertaken using SPSS v.24 and EQ-5D-5L index scores calculated using Crosswalk analysis[6].

RESULTS

Ninety-four patients completed the study, 42 with a DFU and 51 with a VLU (1 missing data). Mean age of patients with a DFU was 64 (45-85) whilst for VLU it was 71 (48-93). Eighteen (43%) of the DFU patients had a prior amputation. Thirteen (31%) DFU patients and 36 (71%) VLU patient had multiple wounds.

The mean EQ-5D-5L index score for VLU and DFU patients was 0.64 and 0.55, as shown in Figures 3 & 4 respectively, for patients with different wound severity. 19 (38%) VLUs and 17 (42%) DFUs were classified as severe, these wounds had even lower index scores 0.56 and 0.46 for and VLU and DFU.

These scores, when compared to studies using EQ-5D in other chronic conditions, as shown in Figure 5, demonstrate that patients with DFUs and VLUs show that have among the lowest EQ-5D index scores measured.

Subgroup analysis took into account wound severity as judged by the duration and size of the wound. The requirements for mild/moderate and severe wounds is shown in Figure 1. Figure 2 shows the wounds in each category .

13 months +	Severe	Severe
7-12 months	Moderate	Severe
0-6 months	Mild	Moderate
	≤ 8cm2	> 8cm2

Figure 1: Wound severity matrix. Calculated using a matrix of size vs duration

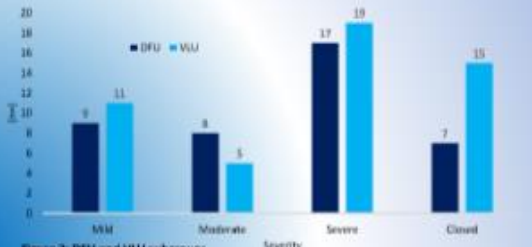

Figure 2: DFU and VLU subgroups

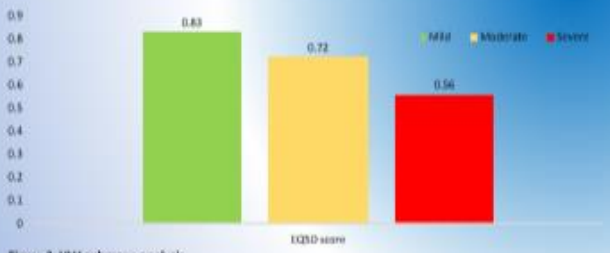

Figure 3. VLU subgroup analysis

Figure 4. DFU subgroup analysis

Figure 4:. EQ-5D utility scores of long-term conditions [7]

RECOMMENDATIONS

These scores indicate that DFU and VLU patients suffer from limited QoL, comparable to other chronic conditions, with wounds that are older and longer in duration scoring even worse. DFUs suppressed the index score more in this sample. The severity criteria used here can be replicated and used easily in clinical practice and subject to further testing could prove useful in identifying patients at high risk of depressed QoL.

Interventions and strategies to treat chronic wounds should consider QoL outcomes for these patients; especially when treating populations with more severe wounds; highlighting the need for treatment strategies to avoid this negative progression. Interventions that reduce the time to healing for these wounds may help to alleviate the impact of wounds on quality of life for these patients.

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D.10. Chart extraction abstract

Real Life Use of Dressings in the Treatment of Leg Ulcers and Diabetic Foot Ulcers. Betts, A et al. Value in Health, Volume 21, S174 - S175

OBJECTIVES: Leg ulcers (LUs) and diabetic foot ulcers (DFUs) can take a long time to heal, with dressings requiring frequent changes. Establishing current treatment pathways and reasoning for changing a care plan, will provide real life understanding regarding the use of dressings and areas providing opportunity to improve patient outcomes and reduce the economic burden of these conditions. The study aimed to establish treatment pathways, incidence of treatment switching, patient outcomes and resource use of patients with a LU or DFU.

METHODS: A multi-centre, retrospective, chart examination performed in multiple care settings. The data extracted included wound characteristics, each visit by the patient, and every intervention. Reasons for a change of treatment plan, and infection and healing rates were captured. Reasons for changing treatment were coded and analysed.

RESULTS: 7 UK centres provided data from 97 patients, totalling 107 wounds and 1050 visits. 90 (9%) wounds were observed for the first time and 42 (4%) healed wounds not requiring dressings were observed, 189 (18%) changes used the same dressing as previously recorded. This left 729 (69%) instances of treatment switching. Reasons for changes to treatment plan were either Clinical (28%), Patient (5%), External (5%) or No reason (62%). External reasons included available stock and guidance from other clinicians.

CONCLUSIONS: 69% of visits resulted in a different type of dressing being applied, with 62% of these changes being made without a reason. The data also suggests superior clinical outcomes are achieved in Randomised Clinical Trials compared to real life. Patients in RCTs receive the same intervention for the trial duration; yet this study finds a switch in nearly 80% of eligible visits. It is theorised therefore that without mandated guidance regarding dressings, current treatment switching practices may continue as observed, with potential adverse outcomes on patient health and quality of life.

D.11. Chart extraction poster

REAL LIFE USE OF DRESSINGS IN THE TREATMENT OF LEG ULCERS AND DIABETIC FOOT ULCERS

BETTS, A. ODEYEMI, I. FATOYE, F. YEOWELL, G. TADEJ, M. LANT, C.
Email: a.betts@mmu.ac.uk

Objective

To establish treatment pathways, incidence of treatment switching, patient outcomes and resource use of patients with a LU or DFU.

Background

Wounds are deemed chronic when they do not follow a normal healing pattern and can be perpetuated by having an underlying aetiology such as diabetes or venous insufficiency[1]. The wounds can take a long time to heal, with dressings requiring frequent changes. This requires resources such as the dressings themselves but also the health care providers (HCP) time, such as community nurse visits which have been seen as key cost drivers in economic studies of DFU and LU [2,3].

Establishing current treatment pathways and the reasons for changing a care plan will provide real life understanding regarding the use of dressings and areas providing opportunity to improve patient outcomes and reduce the economic burden of these wounds.

Methods

A multi-centre, retrospective, chart examination study was performed in multiple care settings. The data was extracted by a nurse at the sites into an iPad data extraction application; after completing appropriate ethics and governance protocols. All data was anonymised at extraction. Approximately 100 patient records from the last 4 years were intended to be included, randomly selected from the participating centres.

The care settings included: at a clinic, at hospital, in their own home or in the practice. The HCPs captured included Community Nurses, Podiatrists and Practice Nurses. The data extracted included wound characteristics, each visit by the patient, and every intervention prescribed to the patient. Treatment notes, where changes to a care plan are meant to be recorded, were also extracted. Using the data, reasons for a change of treatment plan were captured. Using a thematic analysis, the reasons for changing treatment were coded and analysed.

Results

Seven UK centres provided data from 97 patients, totalling 107 wounds and 1050 visits. Treatment switching can be seen below in Figure 1. The reasons for treatment switches were coded into 4 main categories: clinical, patient, external or no reason. These contained several sub-categories as shown in Table 1.

The 107 wounds included 71 LUs and 36 DFUs. In terms of rates of wound closure, 20 LUs (28%) and 9 DFUs (25%) healed in less than 20 weeks. For the wounds that healed, the mean time to healing was 70 days for LUs and 69 days for DFUs.

Dressing related resource use was captured, collecting numbers used of primary and secondary dressings. In open wounds, 57% and 22% less secondary dressings were used for LU and DFU respectively, when considering infected wounds, 9% and 30% less secondary dressings were used for LU and DFU.

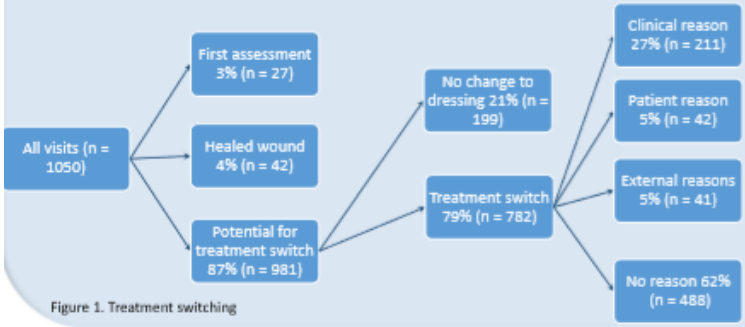

Figure 1. Treatment switching

Table 1. Treatment switching sub-categories

Switch	Sub-categories
Clinical (n = 211)	Wound environment- dry/exudate/sloughy (35%) Infection (19%) Wound deterioration/impaired healing (18%) Wound improvement (17%) Dressing related (6%) Other (6%)
Patient (n = 42)	Lifestyle (36%) Pain (24%) Self-care (10%) Tolerance (31%)
External (n = 41)	Information/direction from other HCPs (66%) Stock availability (34%)
None (n = 488)	Notes, but no reason (19%) Notes left blank (81%)

Conclusions

69% of visits resulted in a different type of dressing being applied, with 62% of these changes being made without a reason.

The data also suggests superior clinical outcomes are achieved in Randomised Clinical Trials compared to real life, a randomised clinical trial of neuro-ischaemic DFU patients found that 30% of patients using a neutral dressing achieved wound closure within 20 weeks [4]. In the active arm of the study, 48% of patients using UrgoStart had confirmed closure of their wound by 20 weeks. This is superior to the outcomes observed here, with only 25% of all DFUs healing by 20 weeks.

Patients in RCTs receive the same intervention for the trial duration; yet this study found a switch in nearly 80% of eligible visits. This lack of consistent care may be responsible for the discrepancy in healing rates observed. The current guidelines for wound dressings are not specific, with clinicians advised to use the 'least costly' dressing that is clinically indicated [5,6]. It is theorised therefore that without mandated guidance regarding dressings, current treatment switching practices may continue as observed, with potential adverse outcomes on patient health and quality of life.

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D.12. DFU BIM abstract

The budget impact and cost-consequence of treating diabetic foot ulcers with UrgoStart.

Betts, A. et al. Value in Health, Volume 21, S249

OBJECTIVES: Diabetic Foot Ulcers are a common complication of diabetes and precede more than 80% of amputations in this population. It is estimated that more than 5 million people in the United Kingdom will have diabetes by 2025; and 10% of this population is expected to have a DFU. Treating ulcers is expensive and investing in interventions that can improve time to healing could reduce current spending by the National Health Service (NHS). UrgoStart is a dressing shown to reduce healing time of DFUs by 20 days when compared to a neutral dressing in a double-blind randomised controlled trial.

METHODS: A budget impact model (BIM) was developed from the perspective of the NHS with a time horizon of 5 years. The BIM identifies patients eligible for treatment with UrgoStart; and considers population growth and new patients diagnosed with diabetes. A 2018 retrospective database analysis of 130 patients examined resource utilization and costs associated with DFU; this was applied to the eligible population.

RESULTS: Over the 5-year period, 1.3 million patients were eligible for treatment with UrgoStart. The cost of treatment per patient using UrgoStart was £1445.90 vs £1638.64 using a neutral dressing. The growing population and newly diagnosed diabetic patients with ulceration accounted for an increase of approximately £25.6 million per year. Over the 5-year period, using UrgoStart instead of a neutral dressing could save £251.7 million for the NHS whilst also avoiding 26.1 million days with ulceration for patients.

CONCLUSIONS: Analysis showed that contrary to current National Institute of Health and Care Excellence (NICE) guidance; using only the “least costly” dressing for chronic wounds such as DFU is not an optimal treatment strategy. UrgoStart, has shown to reduce healing time, which not only improves outcomes for patients but also results in a substantial cost saving to the NHS.

D.13. DFU BIM poster

THE BUDGET IMPACT AND COST-CONSEQUENCE OF TREATING DIABETIC FOOT ULCERS WITH URGOSTART

BETTS, A., YEOWELL, G., ODEYEMI, I., FATOYE, F.

Manchester Metropolitan University

OBJECTIVES

Diabetic Foot Ulcers (DFUs) are a common complication of diabetes, and often precede amputation; a last resort after unsuccessful prior treatment of an infected or gangrenous ulcer. It is estimated that more than 5 million people in the United Kingdom will have diabetes by 2025 [1]; and up to 10% of this population is expected to have a DFU annually [2]. Treating DFUs is time consuming and expensive; investing in interventions with demonstrated improvements time to healing lead to increased efficiencies for the National Health Service (NHS) in England.

Edmonds et al. [3], compared UrgoStart with a neutral dressing in a randomised controlled, double-blind, multi-centre, clinical trial, in a population of patients with a non-infected neuroischaemic DFU. The primary endpoint was full wound closure at 20 weeks and secondary endpoints included a Kaplan-Meier estimate of days to closure. Groups were statistically similar at baseline. Patients using UrgoStart had an adjusted odds ratio of 2.6 of healing at 20 weeks and estimated time to closure of 120 days vs 180 days for the comparator.

METHODS

A budget impact model (BIM) was designed in accordance with the ISPOR Budget Impact- Principles of Good Practice [4]. See Figure 1 for the steps followed.

The BIM was developed from the perspective of the NHS with a time horizon of 5 years; identifying patients eligible for treatment with UrgoStart; taking into account population growth and new diabetes diagnoses. Table 1 outlines included parameters

Table 1: Model parameters

Population: Data from the Office of National Statistics established current and expected population over the next 5 years [6,7]. An estimated 3.4 million people have diabetes, 6% of which will have a foot ulcer annually [2]. Per year, 226,000 patients with DFUs are eligible for treatment with UrgoStart.
Uptake estimation: Predicted at 0% current year, then 30%, 50%, 60% and 75% in years 2-5. Over 5 years, nearly 600,000 people would be treated with UrgoStart.
Resource Utilisation: A retrospective database analysis examined resource use and costs for 130 patients with DFU [8]. These costs were applied to the eligible population.
Treatment Effect: The duration of treatment was assigned according to the calculated values in the Explorer study- 180 days for UrgoStart and 120 days for the neutral dressing [3].

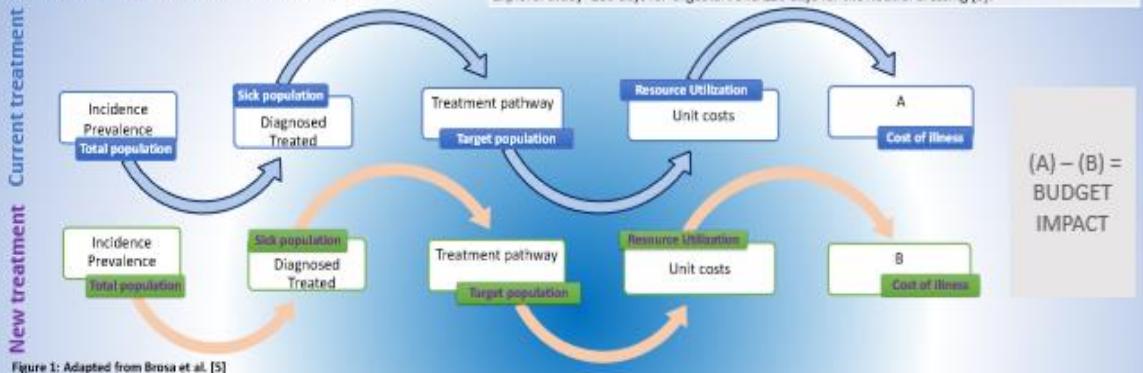

Figure 1: Adapted from Brosa et al. [5]

RESULTS

Budget Impact: Use of UrgoStart was associated with cost savings the annual costs are set out in Figure 2 below. This model estimates a cost per patient treated with a neutral dressing and standard care at £2184.64 and for a patient using UrgoStart and standard care, £1508.77. As a result of improving time to healing, UrgoStart also results in substantially more days without ulceration, as shown in Figure 3.

The cost savings demonstrated by using UrgoStart instead of a Neutral Dressing as first line treatment for Diabetic Foot Ulcers (DFU) is driven entirely by the superior efficacy of UrgoStart with a shorter time to healing as shown in a double blind randomised clinical trial (Explorer).

This model has assumed costs and resource use per week is identical for UrgoStart and a Neutral Dressing; apart from the cost of the dressing.

Figure 2: Total annual costs

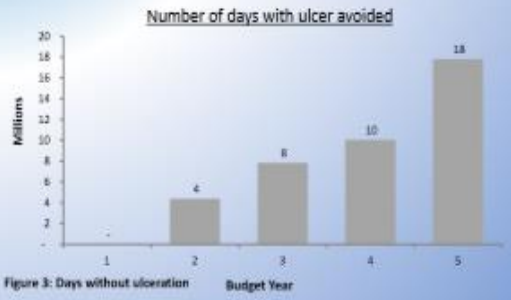

Figure 3: Days without ulceration

RECOMMENDATIONS

This analysis shows UrgoStart to be a cost-saving treatment option, with benefits to the patient and the NHS. Contrary to current National Institute of Health and Care Excellence (NICE) guidance; using only the "least costly" dressing for chronic wounds such as DFU is not an optimal treatment strategy.

UrgoStart should be considered as a first line treatment for all patients with a DFU.

For future research, it is advised to validate this model structure and then evaluate the sources to ensure generalisability.

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References
[1] [illegible]
[2] [illegible]
[3] [illegible]
[4] [illegible]
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[7] [illegible]
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D.14. LU BIM abstract

The budget impact and cost-consequence of treating leg ulcers with UrgoStart. Betts, A. et al. Value in Health, Volume 21, S249

OBJECTIVES: Leg ulcers (LU) can be a complication of vascular or arterial disease, or of mixed or unknown aetiology. In a study of 1000 acute and chronic wounds, LUs accounted for 33% of all wounds. LUs incur a considerable treatment cost; frequent contact with various health care providers for assessment and dressing changes is expensive to the National Health Service (NHS). Reducing healing time could alleviate this burden whilst improving patient outcomes.

METHODS: A budget impact model (BIM) was developed from the perspective of the NHS with a time horizon of 5 years. UrgoStart is a protease-modulating dressing, and mean time to closure for LUs in a large pooled observational study of 6800 patients was 112.5 days, compared to 210 days for a population not using UrgoStart. Population data from the United Kingdom, including population growth, and the incidence of LU the BIM identifies patients eligible for treatment with UrgoStart. A 2018 retrospective database analysis of 505 patients informed resource utilization and costs used in the model.

RESULTS: Over the 5-year period, 3.8 million patients were eligible for treatment with UrgoStart. The cost of treatment per patients using UrgoStart was £1544.23 vs £3114.67 using a neutral dressing. The much-improved time to healing demonstrated by UrgoStart is the driver of these cost savings. Using UrgoStart on all eligible LUs could save on average £1.1 billion per year for the NHS; and reduce the number of days with ulceration by 47%, from 815 million to 435 million days.

CONCLUSIONS: This analysis shows that UrgoStart should be considered as part of a preferred treatment strategy for LUs; there is also evidence to show better healing rates when used as a first line intervention. With current drives towards efficiency in the NHS, UrgoStart provides an opportunity to reduce costs and improve outcomes for patients.

D.15. LU BIM poster

THE BUDGET IMPACT AND COST-CONSEQUENCE OF TREATING LEG ULCERS WITH URGOSTART

BETTS, A., YEOWELL, G., FATOYE, F., ODEYEMI, I.

Manchester Metropolitan University

OBJECTIVES

Leg ulcers (LUs) are a complication of chronic venous disease. Structural changes in the veins and valves controlling blood flow result in deteriorated function of the lower legs [1]. LUs are more common in older individuals, with the annual prevalence for those aged 65- 95 reported at 1.69% [2].

A large pooled data set from real-life observational studies, the Reality study, compared UrgoStart to the use of control treatments in 10,220 patients [3]. The primary outcome of this study was time to wound closure and observed a mean 112 days to closure when using UrgoStart vs 210 days to closure as recorded by studies using standard care and neutral dressings. This model was designed to calculate the budget-impact and cost-consequence of using the UrgoStart technology in the treatment of leg ulcers.

METHODS

A budget impact model (BIM) was designed in accordance with the ISPOR Budget Impact- Principles of Good Practice[4]. See Figure 1 for the steps followed.

The BIM was developed from the perspective of the NHS with a time horizon of 5 years; identifying patients eligible for treatment with UrgoStart; taking into account population growth. Table 1 outlines parameters that were included in the model.

Table 1: Model parameters

Population: Data from the Office of National Statistics established current and expected population over the next 5 years [6,7]. The estimated prevalence of leg ulcer is 1.5% [8]. Per year approximately 775,000 patients with LUs are eligible for treatment with UrgoStart.
Uptake estimation: Predicted at 0% current year, then 30%, 50%, 60% and 75% in years 2-5. Over 5 years, nearly 1.7 million people would be treated with UrgoStart.
Resource Utilisation: A retrospective database analysis examined resource use and costs for 505 patients with LU [9]. These costs were applied to the eligible population.
Treatment Effect: The duration of treatment was assigned according to the values from the Reality study; 112.5 days for UrgoStart and 210 days for the neutral dressing [3].

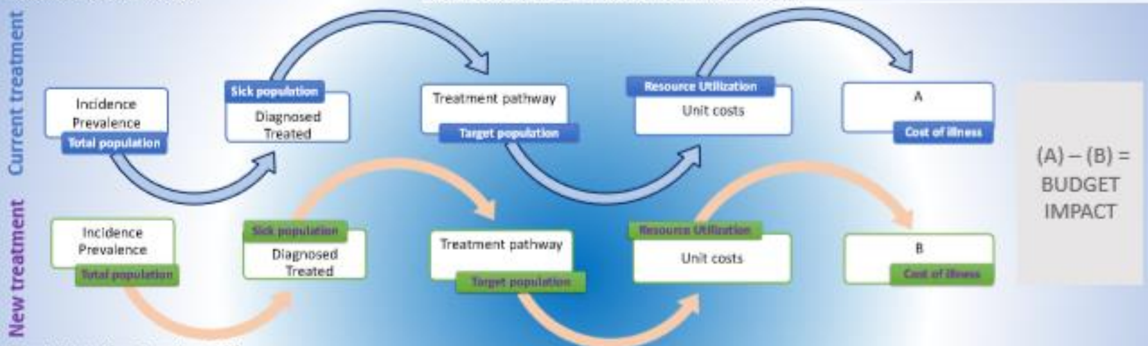

Figure 1: Adapted from Brosa M, et al. [5]

RESULTS

Budget Impact: Use of UrgoStart was associated with cost savings. The annual costs are set out in Figure 2 below. This model estimates a cost per patient treated with a neutral dressing and standard care at £3114.67 and for a patient using UrgoStart and standard care, £1551.13. As a result of improving time to healing, UrgoStart also results in substantially more days without ulceration, as shown in Figure 3.

The cost savings demonstrated by using UrgoStart instead of a neutral Dressing as first line treatment for leg ulcers is driven entirely by the superior efficacy of UrgoStart with a shorter time to healing as observed in a large pooled analysis.

This model has assumed costs and resource use per week is identical for UrgoStart and a Neutral Dressing; apart from the cost of the dressing.

Figure 2: Total annual costs

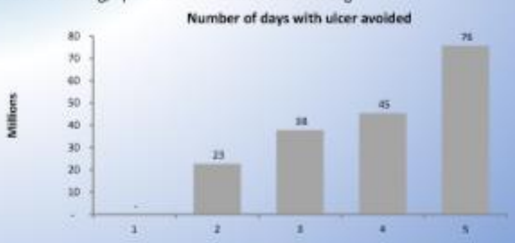

Figure 3: Days without ulceration

RECOMMENDATIONS

This analysis shows that UrgoStart should be part of a preferred treatment strategy for LUs; there is also evidence to show better healing rates when used as a first line intervention. With current drives towards efficiency in the NHS, UrgoStart provides an opportunity to reduce costs and improve outcomes for patients.

UrgoStart should be considered as a first line treatment for all patients with a LU.

The model structure and resource use costs that have been used for this analysis should be validated to ensure generalisability.

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D.16. DFU CUA abstract

Cost-effectiveness and cost-utility analysis of treating diabetic foot ulcers with UrgoStart compared to a neutral dressing. Betts, A. et al. Value in Health, Volume 21, S260

OBJECTIVES: Current National Institute of Health and Care Excellence (NICE) guidance does not indicate a preferred dressing for patients with Diabetic Foot Ulcer (DFU). UrgoStart has recently been shown as superior to a neutral dressing in the double blind randomised controlled Explorer trial. This study examined the cost-effectiveness of UrgoStart compared with a neutral dressing for DFU patients.

METHODS: A Markov-model was designed with seven health states: open, closed, and complicated (pre and post amputation), and deceased. Complicated wounds can cause an amputation event, moving a patient to the post-amputation block. The model took the perspective of the National Health Service (NHS) in the United Kingdom, with a cohort of 1000 patients and base-case time horizon of 1 year. The Explorer trial informed transition probabilities and health-state utility scores; there were no statistically significant differences between the characteristics of the treatment arms at baseline. Both deterministic and probabilistic sensitivity analyses were performed.

RESULTS: UrgoStart was the dominant treatment strategy in terms of cost-effectiveness, with a cost saving of £666.51 and a 0.022 gain in quality-adjusted-life years, per patient. Using UrgoStart leads to more wounds healed at 52 weeks than a neutral dressing, 653 and 473 respectively at a cost of £4879.84 per healed wound for UrgoStart compared with £8136.19 for a neutral dressing. The use of UrgoStart also avoided 19 amputations over a year. Sensitivity analysis showed UrgoStart as cost saving, even when a comparator was set at £0. Across 1000 runs of the model, UrgoStart was dominant every time.

CONCLUSIONS: This analysis showed UrgoStart to be a cost-effective treatment option, with benefits to the patient and the NHS. Primary cost drivers such as community nurse visits and hospital admissions; can be reduced significantly with faster healing. UrgoStart should be considered as a treatment for all patients with a DFU.

D.17. DFU CUA poster

COST-EFFECTIVENESS AND COST-UTILITY ANALYSIS OF TREATING DIABETIC FOOT ULCERS WITH URGOSTART.

BETTS, A., ODEYEMI, I., FATOYE, F., YEOWELL, G., TYE. A.

Manchester Metropolitan University

OBJECTIVES

Current National Institute of Health and Care Excellence (NICE) guidelines do not indicate a preferred dressing for patients with Diabetic Foot Ulcer (DFU); instructing Healthcare Professionals to consider the clinical assessment and patient preference, but to use appropriate devices with the lowest acquisition cost [1]. A NICE Evidence Summary in 2016 identified little good quality evidence to support the use of advanced dressings for chronic wounds [2].

UrgoStart, in a 2018 study, has been shown as superior to a neutral dressing in the double blind randomised controlled Explorer trial (NCT01717183)[3]. The primary endpoint for this study was wound closure at 20 weeks, and patient quality of life was measured using EQ5D-5L. Using information from the Explorer trial, this study examined the cost-utility and cost-effectiveness of UrgoStart compared with a neutral dressing for DFU patients.

METHODS

A Markov-model with seven health states; the model structure is depicted in Figure 1. DFUs have 3 core health states- open, closed and complicated wound. The model makes a distinction for wounds that have not been amputated (pre-amputation), versus patients who have an amputation (post amputation). Complicated wounds can cause an amputation event, moving a patient to the post-amputation block. All-cause mortality was informed by data from The National Diabetes Foot Care Audit [4]. A prospective follow up of 73 DFU patients over a 3 year period, informed the rate of recurrence [5].

The model took the perspective of the National Health Service (NHS) in the United Kingdom, with a cohort of 1000 patients and base-case time horizon of 1 year. The Health Improvement Network (THIN) database was used to inform health state resource from 130 patients with DFU [6]. The NHS Payment by Results tariff and available costing data has been used to calculate resource costs [7].

Explorer informed transition probabilities and utility scores; the patients had a confirmed neuro-ischaemic DFU, with no statistically significant differences between the treatment arms.

Both deterministic and probabilistic sensitivity analyses were performed.

Figure 1: Model Structure

RESULTS

UrgoStart was dominant in terms of cost-effectiveness, with a per patient cost saving of £666.51 and a 0.022 gain in quality-adjusted-life years. UrgoStart leads to more wounds healed at 52 weeks than a neutral dressing, 653 and 473 respectively at a cost of £4879.84 per healed wound for UrgoStart compared with £8136.19 for a neutral dressing.

The use of UrgoStart also avoided 19 amputations over a year as shown in Figure 2. Scenario analysis showed UrgoStart as cost saving, even when a comparator was set at £0. Across 1000 runs of the model, UrgoStart was dominant every time, as shown in Figure 3. The key drivers of this cost saving were community nurse visits and hospital admissions as shown in Figure 4.

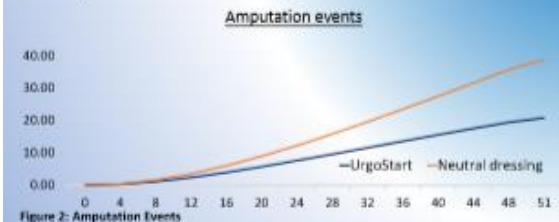

Figure 2: Amputation Events

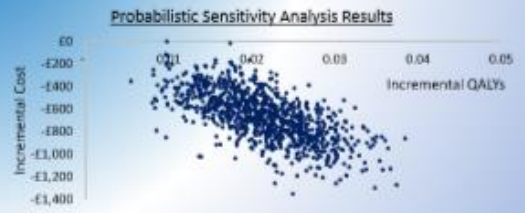

Figure 3: Probabilistic Sensitivity Analysis Results

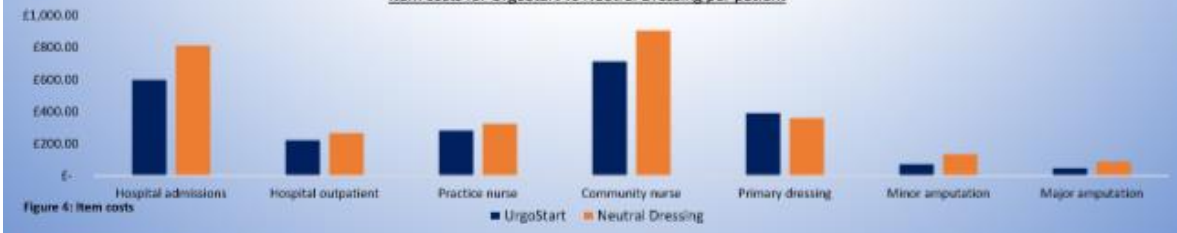

Figure 4: Item costs

RECOMMENDATIONS

This analysis shows UrgoStart to be a cost-effective treatment option, with benefits to the patient and the NHS. Primary cost drivers such as community nurse visits and hospital admissions can be reduced significantly with faster healing.

UrgoStart should be considered as a first line treatment for all patients with a DFU.

It is advisable for future research to validate this model; including the structure and information sources to ensure generalisability.

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D.18. LU CUA abstract

Cost-effectiveness and cost-utility analysis of treating leg ulcers with UrgoStart compared to a neutral dressing. Betts, A. et al. Value in Health, Volume 21, S260

OBJECTIVES: Leg Ulcers (LUs) cause a burden on the patient and National Health Service (NHS); often taking a long time to heal and requiring significant resources to achieve wound closure. UrgoStart has been demonstrated to improve healing outcomes for patients with LUs. This study examined the cost-effectiveness of UrgoStart compared with a neutral dressing for LU patients.

METHODS: A Markov-model with four health states: open, infected, closed and deceased. Infected wounds had to become open wounds in order to close, and closed wounds had a risk of recurrence. The model took the perspective of the NHS in the United Kingdom, with a cohort of 1000 patients and base-case time horizon of 1 year. The Challenge randomised double blind controlled trial informed the patient characteristics and transitions. The study endpoint was relative wound area reduction at 8 weeks; which was used to calculate the transition probability of healing in the model. Both deterministic and probabilistic sensitivity analyses were performed.

RESULTS: UrgoStart was the dominant treatment strategy in terms of cost-effectiveness, with a cost saving of £274.25 and a 0.03 gain in quality-adjusted-life years, per patient. Community nurse visits were the primary cost driver; accounting for 54% and 56% of total costs in the treatment and comparator arm respectively. At 52 weeks 949 wounds had healed using UrgoStart vs 854 wounds using a neutral dressing, at a cost of £1666.80 and £2174.89 per healed wound respectively. Sensitivity analysis showed a cost saving for UrgoStart, even when a comparator was set at £0 cost; over 1000 runs of the model, UrgoStart was dominant in approximately 90% of cases.

CONCLUSIONS: This analysis showed UrgoStart to be a cost-effective treatment option for treating LU; with benefits for the patient and the NHS. UrgoStart should be considered as a treatment for patients with a LU.

D.19. LU CUA poster

COST-EFFECTIVENESS AND COST-UTILITY ANALYSIS OF TREATING LEG ULCERS WITH URGOSTART.

BETTS, A., ODEYEMI, I., YEOWELL, G., FATOYE, F., TYE. A.

Manchester Metropolitan University

OBJECTIVES

In a study of 1000 wounds in the United Kingdom (UK) Venous Leg Ulcers and 'unspecified' leg ulcers accounted for 32% of wounds [1] Leg Ulcers (LUs) cause a burden on the patient and National Health Service (NHS); often taking a long time to heal. A wound dressing will need regular changing and patients are in frequent contact with Healthcare Providers and requiring significant resources to achieve wound closure. Leg Ulcers are the most frequently reported wound in the UK, and are a significant contributor to the $7 billion per year spent on chronic wounds worldwide [2]. Compression is the mainstay of treatment, and current guidelines cite no evidence supporting a single dressing above others, recommending that a simple non-adherent dressing be used [3].

UrgoStart has been demonstrated to improve healing outcomes for patients with LUs [4]. This study examined the cost-effectiveness of UrgoStart compared with a neutral dressing for LU patients.

METHODS

A Markov-model with four health states: open, infected, closed and deceased. Wounds that are infected incur higher costs to the healthcare system. Infected wounds had to become open wounds in order to close, and closed wounds had a risk of recurrence, as informed by literature [5].

The Challenge randomised double blind controlled trial informed the patient characteristics and transitions, these patients had a leg ulcer with no statistically significant differences between the treatment arms. The study endpoint was relative wound area reduction (RWAR) at 8 weeks; which was used to calculate the transition probability of healing in the model. Using a published formula; RWAR has been transformed to provide a weekly healing rate [6]. Transition probabilities do not change over time; and are assumed representative of all wounds, as Challenge included wounds of varied duration.

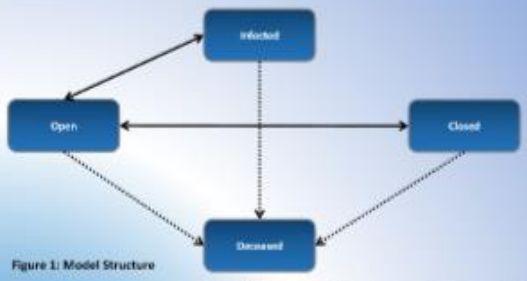

Figure 1: Model Structure

The Health Improvement Network (THIN) database was used to inform health state resource from 505 patients with LU [7]. The NHS Payment by Results tariff and available costing data has been used to calculate resource costs [8].

The model took the perspective of the NHS in the United Kingdom, with a cohort of 1000 patients and base-case time horizon of 1 year. Both deterministic and probabilistic sensitivity analyses were performed.

RESULTS

UrgoStart was dominant in terms of cost-effectiveness, with a per patient cost saving of £274.25 and a 0.03 gain in quality-adjusted-life years. At 52 weeks 949 wounds had healed using UrgoStart vs 854 wounds using a neutral dressing, as shown in Figure 2 , at a cost of £1666.80 and £2174.89 per healed wound respectively. Community nurse visits were the primary cost driver; accounting for 54% & 56% of total costs in the treatment and comparator arm respectively, as shown in Figure 4.

Sensitivity analysis showed a cost saving for UrgoStart, even when a comparator was set at £0 cost; over 1000 runs of the model, UrgoStart was dominant in approximately 90% of cases, as shown in Figure 3.

Figure 2: Closed wounds in year 1

Figure 3: Probabilistic Sensitivity Analysis Results

Figure 4: Item costs

RECOMMENDATIONS

This analysis shows UrgoStart to be a cost-effective treatment option, with benefits to the patient and the NHS. Primary cost drivers included community and practice nurse visits which could both be reduced significantly with faster healing.

UrgoStart should be considered as a first line treatment for patients with a LU.

Validation of this model structure and ensuring generalisability of the data sources and the methods used to extrapolate costs is advised in future research.

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