Leeds Institute of Health Sciences
FACULTY OF MEDICINE AND HEALTH

UNIVERSITY OF LEEDS

WORKING PAPER NUMBER: WP19_1

Economic Evaluation of a Treatment for Non-Healing Wounds with Observational Data – an example of a topical haemoglobin spray for the treatment of Diabetic Foot Ulcers

*Chris Bojke[1], Paul Chadwick[2], Nils Gutacker[3] and Sharon Hunt[4]

AFFILIATIONS

1 University of Leeds
2 The College of Podiatry
3 University of York
4 Wellway Medical Group

*CORRESPONDING AUTHORS CONTACT DETAILS

Chris Bojke – Academic Unit of Health Economics, Leeds Institute of Health Sciences, University of Leeds, Worsley Building, Clarendon Way, Leeds, LS2 9LJ – tel : +44 (0) 113 343 1680 e-mail: c.bojke@leeds.ac.uk

This working paper should cited as: Bojke, C., Chadwick, P., Gutacker, N. and Hunt, S. Economic Evaluation of a Treatment for Non-Healing Wounds with Observational Data – an example of a topical haemoglobin spray for the treatment of Diabetic Foot Ulcers [Internet]. Leeds: University of Leeds, Leeds Institute of Health Science; 2019.

Worsley Building
University of Leeds
Leeds, United Kingdom
LS2 9JT

http://medhealth.leeds.ac.uk/lihs

DISCLAIMER

The series enables staff and student researchers based at or affiliated with the AUHE to make recent work and work in progress available to a wider audience. The work and ideas reported here may not always represent the final position and as such may sometimes need to be treated as work in progress. The material and views expressed in the series are solely those of the authors and should not be quoted without their permission.

Additional information

Funding

This work was funded by InFirst Healthcare, distributors of Granulox haemoglobin spray in the UK

Ethical approval

Ethics Committee approval was not required in line with the NHS Trust's policy at the time on clinical evaluations of CE marked products used within their licensed indications without randomisation

Conflict of interest

CB, PC, NG and SH have received a consultancy fee from InFirst Healthcare for a health economic analysis of the use of Granulox.

Acknowledgements

The views and opinions expressed therein are those of the authors and do not reflect those of the funder, InFirst Healthcare. Thanks are due to Fredrik Elg and Tony Kilbourn formally of InFirst Healthcare for their support throughout the project.

Abstract

Background: Non-healing wounds represent a substantial and growing economic issue to health-care providers. Despite many treatments being available, a large but weak and possibly misleading evidence base has led to simple decision rules being adopted which focus on minimising upfront treatment costs and appear to adopt a conservative and asymmetric approach to assessment of evidence. Methods for the optimal assessment of such uncertainty within economic evaluation have recently been supplemented by the development of a framework which critically embeds uncertainty within a decision-making framework rather than treating it purely as a separate decision for the need for further research. Applying the new framework to wound care treatment decision making may identify whether the current system of decision making is optimal. **Objectives:** To apply an example of an evaluation of a topical haemoglobin spray in the treatment of diabetic foot ulcers to recent methodological developments in health economics which formally incorporate uncertainty into a decision analytical framework and assess the extent to which statistically significantly or otherwise conservative treatment cost-minimising decision rules are optimal. **Methods:** We construct a simple economic evaluation of the haemoglobin spray technology, Granulox, for the treatment of diabetic foot ulcers that have failed to heal within 4 weeks. We apply the results of the economic evaluation including quantitative and qualitative judgements of uncertainty and bias within the recently developed comprehensive algorithm of dealing with uncertainty. **Results:** Available evidence applied within a conservative model find the haemoglobin spray cost-effective. This result is robust to a wide range of sensitivity analyses. Plausible and sceptical interpretation of the evidence is also applied with the result that, within the new evaluation framework, the technology should be either adopted or adopted with evidence development unless there is cause to almost completely discount the evidence. **Conclusions:** Ultra-conservative decision rules in the event of uncertainty are unlikely to lead to optimal decisions in all cases and could preserve persistent unnecessary costs and loss of quality of life. A more nuanced approach which incorporates a number of factors including the extent to which data would have to be biased, should lead to more optimal decisions in wound care. In some cases, even where uncertainty may always remain, the optimal decision may be to adopt the technology rather than reject.

Key words: *Diabetic Foot Ulcers; Decision-making under Uncertainty; Haemoglobin Spray; Chronic Wounds*

JEL classification: *C50 I10*

1 Introduction

Despite representing a major economic issue to health care providers and patients and despite a plethora of treatment options with an ostensibly large evidence base, inherent weaknesses in the evidence base of wound care treatments have left decision makers unsure of optimal treatments. This has led to the adoption of simple, seemingly plausible, decision rules that emphasise minimising upfront costs of treatment. However by requiring new technologies to asymmetrically shoulder the burden of proof, decision makers potentially run the risk of systematically missing out on what may turn out to be cost-effective, even cost-saving, technologies. This may create a situation in which sub-optimal decisions generate persistent avoidable costs and health-related quality of life loss over time. New technologies should not be adopted simply because they are new, but equally they should not automatically be rejected because of uncertainty per se. Optimal evidence based practice requires a more balanced evaluation of the evidence and the consequences of the limitations of the evidence.

Until 2016 the prevailing academic view of the optimal treatment of uncertainty within economic evaluation had been that adoption and uncertainty were essentially two separate issues – that adoption decisions were based on the balance of current evidence and that uncertainty dictates the need for further research [1]. However this separation of expectation and uncertainty has not been fully adopted by health technology assessment agencies like NICE. This left treatment of uncertainty as a somewhat grey area in an otherwise transparent and prescriptive evaluation framework. Recent developments in health economics represent a move from this somewhat controversial viewpoint and argue instead for an approach in which uncertainty is more formally and directly incorporated into an adoption decision-analytic framework. These new developments provide a means of balancing the underlying risks of adoption and rejection given the available evidence and the uncertainty that surrounds it.

We illustrate the argument in wound care within this framework with a conservative economic evaluation of a haemoglobin spray, Granulox, for treatment of non-healing diabetic foot ulcers (DFU). A technology that has not been widely adopted despite demonstrating highly promising effectiveness results in both RCTs and observational studies. In applying the framework for addressing uncertainty we both assess the evidence at face value and also explore the extent to which potential bias may affect results.

2 The health economics of non-healing wound care

Chronic non-healing wounds are estimated to cost $20bn per annum in the United States and £5bn to the NHS in the UK [2, 3]. In Europe the average cost per episode is estimated at €6,650 for leg ulcers and €10,000 for foot ulcers which accounts for 2–5.5% of health-care budgets [4, 5].

Patients are typically managed in the community generating 78% of costs of treatment [6, 7]. 88% of patients with chronic wounds receive care from nurses and it is estimated that wound management takes over 50% of community nurse time in Europe [6, 8]. This represents a non-marginal use of a scarce resource at a time following a 39% reduction in district nurses in the UK over the period 2002-2012 and at a stage where the NHS is facing its worse nurse recruiting crisis [8, 9]. 39% of wounds in the UK remain unhealed after one year and the patient care cost of an unhealed wound is some 135% higher than that of a wound that heals [7].

A key element of the cost drivers and loss of quality of life are the likelihood that unhealed wounds lead to further adverse events such as limb amputation or death. Ulcers are thought to precede 85% of all amputations, diabetic ulcers are the reason for 70% of all lower limb amputations and that globally, every 30 seconds, there is an amputation due to a non-healing diabetic foot ulcer [10]. Quality of life for patients with ulcers and those that have undergone major amputation is argued to be debilitating and lower than patients with other long-term conditions such as chronic obstructive pulmonary disease or renal disease requiring haemodialysis [11, 12].

In addition, around 50% of patients survive for less than two years after major amputation in diabetes; rates similar to that of colon cancer and very much lower than those for breast or prostate cancer [11]. Though it is argued that the high deaths rates are heavily influenced by underlying systemic disease such as diabetes, which may also contribute to the longevity of many wounds [6]. In the UK there thought to be 7,370 diabetes related amputations

per year in England and expert opinion suggests that four out of five of these amputations could be prevented [13]. In total at least £1 in every £140 of NHS expenditure in England is estimated to be spent on care for the diabetic foot [11].

2.1 An Uncertain Evidence Base

Because of the large costs to health care systems and health consequences for patients there is an obvious potential for successful treatments to achieve large health economic gains, either by preventing wounds or improving healing rates and avoiding long-term adverse outcomes. Perhaps as a result, there is an 'overwhelming amount' of wound care treatments available in the market backed up by over 9,500 wound management clinical trials [14].

However despite the proliferation of treatment options and trial data there are no clear optimal treatment choices, a situation attributed to the comparative effectiveness of alternative treatments evidence base being supported by a history of low quality RCTs [6, 14-17]. Inadequate sample sizes, short follow-up periods, non-random allocation to treatment groups, non-blinded assessment of outcomes, and poorly described control groups and concurrent interventions being cited as consistent issues [17]. Cullum et al [6] find that 41% of trials specified no primary outcome, an 'astonishing' 94% of trials finding significant differences were subject to some sort of bias and conclude that the evidence base underpinning optimal treatment choice is surprisingly very poor and that the research agenda is therefore infinite. Madden [18] goes further and paints a picture of an evidence base that has been unduly influenced by 'corporate science' – the production of misleading evidence and investigation designed to look like peer-reviewed academic work. This may have led to a jaded and perhaps cynical view that the existing evidence base is predominantly alienating rather than clarifying: that rather than just uncertain, the evidence base is inherently misleading.

There are broadly two schools of thought that may be addressed to plug this large research gap. The first argues that there is no reason why the standard, more rigorous approach to randomised controlled trials (RCTs) should not be more stringently adopted [19-21]. The other recognises the pressures and costs that have prohibited the generation of a reasonable evidence base in the past and proposes that more pragmatic approaches exploiting the full range of the hierarchy of evidence should be considered [4, 6, 22, 23]. Such pragmatic approaches fits in with the NHS 5 Year Forward View which promotes the capture and use of observational data within routine practice to construct an evidence base [24]. Gotturp et al [4] argue that prospective cohort studies may be particularly helpful when cost and resource use are the main outcomes of interest.

A further issue is the extent to which wound-care health professionals use up-to-date evidence in their decision making. A study in the Netherlands found that nurses in particular were less aware of and less likely to use the Cochrane Library, more likely to use products for which there was compelling evidence it was less effective and only 16% identified as being aware there was evidence on their treatment choice [25].

In conclusion, whilst it is clear that non-healing wounds create substantial costs and utility decrements, the evidence on which are the most clinically effective treatments is characterised by debilitating uncertainty. Under such circumstances it is therefore important that decision rules on adoption of treatments in wound care can rationally accommodate this uncertainty and not adopt overly simple heuristic rules that may perpetuate sub-optimal treatment.

3 Uncertainty, Inertia and Economic Evaluation in the NHS

The NHS Five Year Forward View has identified the rapid adoption of useful or cost-effective health innovations as a potential mechanism in meeting the current financial constraints [24, 26]. However, whilst the NHS has a reputation for invention, it has also been characterised as 'dynamically conservative' and criticised for the slow adoption, diffusion and every-day use of innovative technologies which demonstrate value. Some commentators view inertia as the biggest threat facing the NHS [27, 28].

One major barrier to the diffusion of useful innovations over potentially less effective technologies has been the asymmetric nature of the burden of proof, with new ideas requiring conclusive evidence whereas old ideas are taken on trust [29]. In the context of wound care the National Institute for Health and Care Excellence (NICE) themselves state that in the absence of any robust clinical evidence to guide choice, prescribers should routinely choose the dressing with the lowest acquisition cost amongst appropriate dressings, a simple and seemingly sensible heuristic echoed elsewhere [30, 31]

However whilst this simple conservative heuristic reduces the probability of adopting innovations that are not cost-effective taking hold, they do so at a cost of delaying the adoption of successful innovations whilst a sufficient evidence base is generated. In some cases it may be the case that such evidence is never generated and a cost-effective innovation is never adopted with adverse consequences persisting over time.

To determine whether such approaches are optimal we turn to the economics literature where characterising and quantifying uncertainty has long been a key but rather isolated component of health-economic evaluation. Although the NICE and others have argued methods such as Probabilistic Sensitivity Analysis (PSA) and Cost-Effectiveness Acceptability Curves (CEACs) are essential components of evaluation there has been little guidance on how they should be formally incorporated into any decision making process [32-35]. The orthodox academic position as outlined in Claxton's influential 'Irrelevance of inference' article in 1999 argues that adoption decisions should be made on the basis of available evidence and that uncertainty is a separate issue and drives the need for further research. However NICE technology assessment guidance does not adopt this approach but instead implies some (unspecified) trade-off between expected cost-effectiveness on current evidence and uncertainty as indicated by the implementation of different acceptability thresholds depending on the extent of uncertainty i.e. ICERs above £20,000 per QALY may lead to rejection if the degree of uncertainty is too great, whereas as an ICER of £30,000 may be acceptable so long as there is little uncertainty surrounding that estimate [34]. This unusually vague recommendation may have led to inconsistent approaches to accommodating uncertainty.

Recently health economists have made important strides in incorporating uncertainty more formally into the decision making process which has recently cumulated in a comprehensive algorithm by Claxton and colleagues which brings together many of the considerations together in a formal framework [36-39]. The key insight from these developments is that uncertainty per se is neither a completely separate issue nor sufficient grounds on its own for rejecting technology, instead it needs to be placed in context with respect to other decision components. They list seven sequential considerations which can lead to the four distinct adoption decisions of: adopt; reject; or the coverage with evidence development (CED) options of approval with research (AWR) or only in research (OIR) which represent evidence generated by registry or by RCTs respectively.

1. Based on current evidence is the technology expected to be cost-effective?
2. Are there significant irrecoverable costs?
3. Does more research seem worthwhile?
4. Is the research possible with or without approval?
5. Will other sources of uncertainty resolve over time?
6. Are the benefits of research greater than the costs of research?
7. Are the benefits of approval greater than the expected value of research?

The full sequence of questions need to be considered to arrive at a fully informed decision. Unlike the approach which considers uncertainty purely as a driver for the need for further research, the comprehensive algorithm argues that it can be rational to reject a seemingly cost-effective technology if there are high irrecoverable costs and significant and important uncertainty.

Uncertainty effectively enters the algorithm at question 3 where there is an assessment of the need for further evidence. Although no formal methods are stated, the current convention in health economics is to combine the probability of making an incorrect decision with consequences of making an incorrect decision via a loss function or Value of Information (VOI) approach [40]. This typically involves a quantitative approach to measuring uncertainty (often via PSA) and valuing incorrect decisions in terms of costs and/or QALYs to obtain an Expected Value of Perfect Information (EVPI). Whether formal quantitative methods are used or not, the essential criteria is to establish whether the uncertainty is sufficient to generate the possibility of a costly error based on current evidence.

Having determined whether further research is valuable, the rest of the algorithm explores the likelihood and costs of obtaining that evidence on the basis of any adoption decision made now. For example if approval destroys any incentive or potential of collecting further evidence then coverage with evidence development or even rejection may be the optimal decision.

The Claxton algorithm represents an important and timely step in economic evaluation by more formally incorporating the real consequences of uncertainty within a decision-making framework. Whilst the algorithm

represents a sensible and seemingly pragmatic conceptual decision making tool that can be used at any level of economic evaluation (i.e. not necessarily just NICE appraisals nor those limited to the UK) it currently lacks application. Wound-care would appear to be an ideal environment in which to road test the Claxton algorithm, which we do in the following sections by establishing the cost-effectiveness and uncertainty of a new wound-care device based on a limited evidence base.

4 The Economic Evaluation of a topical haemoglobin spray

Granulox haemoglobin spray is a class III medical device which applied directly to a wound may bypass a compromised circulatory system and supply oxygen from the atmosphere directly to the hypoxic wound bed via a process of 'facilitated diffusion'. Application is direct from a canister costing £125 containing 30 applications. There is no requirement for additional capital outlay.

4.1 Evidence Base

Like many wound care technologies, the evidence base for the spray is limited with a small number of RCTs and observational studies consisting of small patient numbers, limited follow-up and comparison against varying definitions of standard care [41-51]. Though results are consistently positive and statistically significant it is not possible to embed the evidence in a formal network analysis.

The theoretical basis for the mechanism of action for a topical haemoglobin spray is plausible. It is well recognised that wounds cannot heal without adequate oxygen and that healing wounds demand more oxygen than healthy tissue [46]. Chronic or non-healing wounds, defined as wounds which fail to reduce by 40% in area within 4 weeks of standard treatment, are characterised by hypoxia with some 97% of chronic wounds showing low oxygen levels [52]. Gordillo and Sen [53] argue that measurement of wound tissue oxygenation has been shown to be the best predictor of wound healing outcomes when compared to other diagnostic tools.

As haemoglobin is the molecule in the blood that acts as oxygen's transport system then topical haemoglobin applied directly to the wound may bypass a compromised circulatory system and supply oxygen from the atmosphere directly to the hypoxic wound bed via a process of 'facilitated diffusion'. Petri et al [54] find that in a sample of 5 patients with chronic leg ulcers with a mean duration of 63 months, a single application of the topical haemoglobin spray Granulox raised average oxygen saturation in the wound bed from 56.4% to 69% after 5 minutes and 78.8% after 20 minutes. The theoretical basis for the mechanism of action for a topical haemoglobin spray is plausible and straight forward.

In terms of wound healing, in a Mexican RCT with 28 patients with lower leg chronic wounds, Arenberger et al [42] find statistically significant differences in wound closure rates of 7% for standard moist wound treatment versus 93% for standard treatment plus the haemoglobin spray at six month follow-up. Arenbergerova et al [43] detail a Czech RCT in which 72 patients with Venous Leg Ulcers (VLU) with a mean persistence of 2 years were randomised to standard wound and standard wound plus haemoglobin spray therapy. Wound dressings were changed daily. At 13 weeks, 33 of the haemoglobin spray treatment group patients showed healing process with a mean reduction of 53.4% and for the control group there was a mean wound enlargement of 21%. The difference in absolute wound size change was statistically significant.

A number of one-armed observational UK studies exist which support the findings of the RCTs in that patients that were treated with Granulox as an adjunct to standard care show improved rates of healing in chronic wounds relative to their historical rates [44-51].

Hunt and Elg [47] provide a non-randomised retrospective case-controlled study of 20 chronic DFU patients treated in February 2014 in a single UK site with standard treatment and 20 chronic DFU patients treated with standard treatment plus Granulox in February 2015 at the same site. Both cohorts were followed for 28 weeks and provide the basis for a comparative effectiveness measure in a UK setting. Hunt and Elg [47] describe selection of patients in the single treatment centre into cohorts on the basis of consistent exclusion and inclusion criteria which implies no obvious a priori expectation that the cohorts are not comparable. Table 1 shows that there are no statistical differences between the means of patient characteristics such as wound size or duration between cohorts.

Table 1 also shows key outcome measures over time. By week 4 all patients in the haemoglobin spray cohort experienced some wound closure with 25% having had total healing and an overall mean reduction of 63%. In the standard care cohort only 75% of patients had some wound healing with an average reduction in wound area of 26% .

Table 1: Mean patient baseline characteristics

	Standard Care Cohort (N= 20)	Haemoglobin Spray Cohort (N= 20)	Difference	
	Mean (Std Dev)	Mean (Std Dev)	Difference (Std Error)	t-value / Chi-Squared
Baseline Characteristics				
Age, yrs	54.35 (18.74)	55 (21.6)	0.65 (6.4)	0.1
Duration, months	5.35 (2.8)	5.75 (4.09)	0.4 (1.11)	0.36
Wound area, cm^2	6.6 (5.81)	5.08 (6,65)	-1.51 (1.97)	0.77
Haemoglobin A1c, %	6.9 (1.71)	7 (1.45)	0.1 (0.5)	0.2
Neuropathy, %	45	55	10	0.1
Offloading Used, %	55	55	0	0
Outcomes over Time				
Week 4 wound growth %	-26.2 (65.2)	-63.3 (30.9)	-37.1 (16.1)	2.3
Week 16 wound growth %*	-39.2 (70.7)	-87.8 (21.7)	-48.6 (16.5)	2.94
Week 28 wound growth %*	-56.6 (54.6)	-91.5 (20.1)	-34.9 (13.0)	2.68
Week 4 healed %	5	25	20	3.14
Week 16 healed %	10	55	45	9.23
Week 28 healed %	40	75	35	5.01
Died/Amputation %	10	5	-5	0.36
Dressing changes per week	3.34 (1.32)	2.04 (0.13)	-1.29 (0.30)	4.36

After 28 weeks treatment 15 of the 20 patients in the haemoglobin spray cohort had completely healed wounds. Of the remaining 5, one had died and three had stopped using the spray prematurely at the point at which their wounds had healed by 68%, 79% and 91% respectively. The remaining patient was still using the spray and had achieved a 95% wound reduction. For the standard care cohort only 8 patients' wounds had healed. One patient had also died, one patient underwent an amputation and six patients had reduced wound sizes. One patient's wound remained unchanged and 3 had an increase in size (50%, 33% and 33%). At all times the difference between cohorts in terms of growth rates and healed wounds was statistically significant and in favour of the haemoglobin spray, results which are consistent with the results from the two RCTs. There are too few deaths and amputations to draw any inference regarding comparative effectiveness.

The other outcome variable of interest is the number of nurse visits per week for dressing changes for existing wounds. The raw data show that patients treated with the haemoglobin spray required a statistically significant 1.29 fewer dressing changes per week than those on standard care. Potentially this is an outcome of faster healing rates and is indicative of potential cost savings even before complete healing occurs.

In summary, as is common with many wound care products and medical devices in general, the evidence base is limited and difficult to formally synthesise. Nevertheless the evidence base of the short term-effectiveness of Granulox is building with the haemoglobin spray shown to improve healing rates relative to standard care in small scale RCTs and observational studies. A consensus recommendation from a working group of opinion leaders found that although the evidence was sufficient to recommend Granulox as a treatment for patients who had delayed healing or were identified as being at high risk of delayed healing, they also concluded that '*further*

research is needed to determine long-term use and cost-effectiveness' and call for well conducted clinical RCTs to obtain robust evidence, particularly long-term efficacy [52].

4.2 Economic Model Structure

To assess the cost-effectiveness of a haemoglobin spray in the treatment of non-healing Diabetic Foot Ulcers (DFU) we adopt the common markov structure adopted for economic evaluation of wound health technologies which follow the NICE reference case framework [34, 55].

The model is a simple cohort markov model with 4 distinct states: unhealed wounds; healed wounds, reoccurrence of wound and dead. All patients enter the model with unhealed wounds and cycle through the states with evidence based probability measures. Each state has an associated expected cost and health-related utility attached to it. State based utilities and costs are assumed independent of the treatment, with the exception that the haemoglobin spray treatment costs are added to the costs where treatment is still occurring.

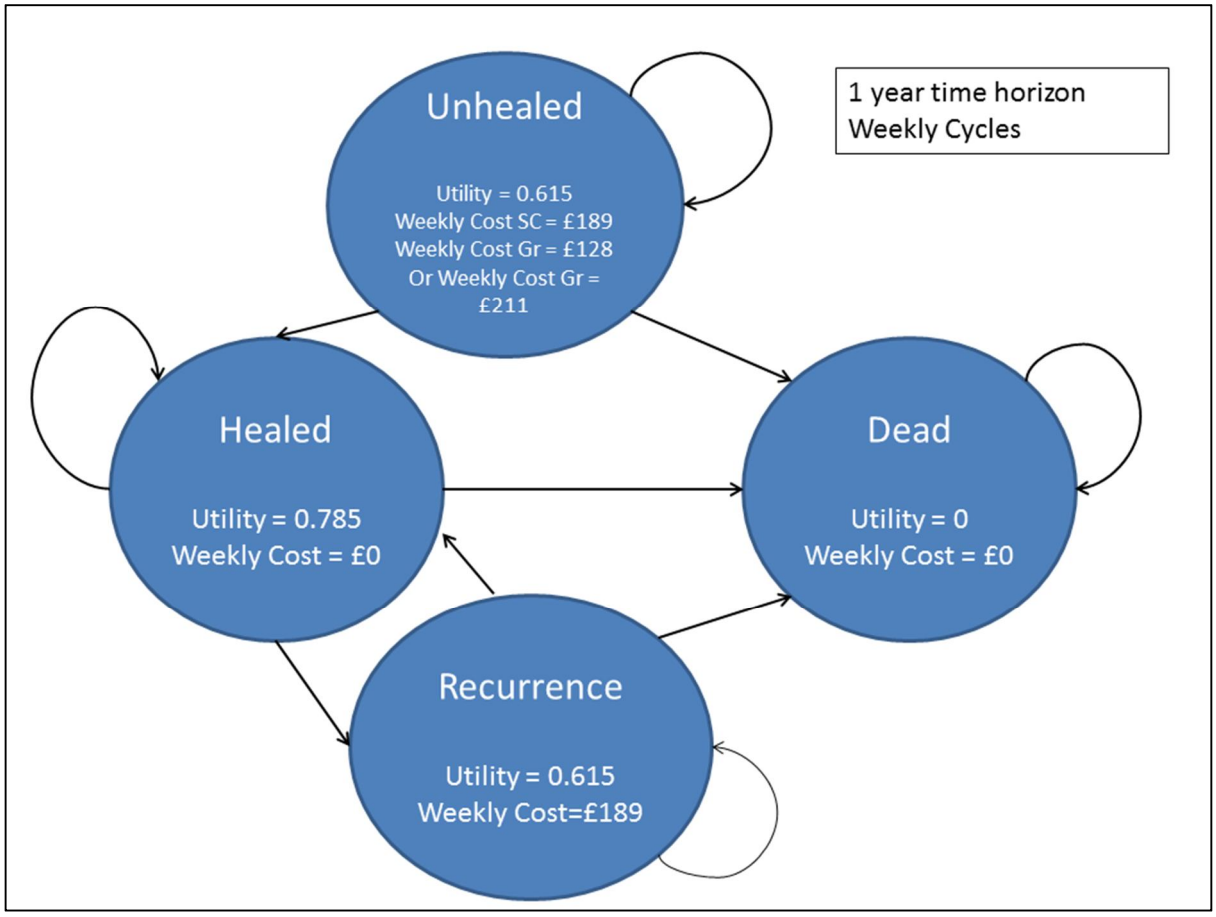

Figure 1 : markov model

We populate the model with parameters relevant for the treatment of non-healing DFUs with utility values, morality and ulcer reoccurrence rates from the wider literature [56-59].The time horizon is 1 year with weekly cycles and at the end of the model duration, costs are summed to obtain total expected costs and utilities converted to Quality Adjusted Life Years (QALYs). Comparators are Granulox as an adjunct therapy versus Standard Care alone.

Of note the model, like many standard wound models, does not contain a state for amputation. Whilst this is clearly a limitation of the model in reflecting reality its omission will need to be understand under the context of whether it is also represents a limitation for decision making – the two are not necessarily the same. We will

return to this element in discussing the results and reflecting on the uncertainty generated by using an observational evidence base.

4.3 Model Parameters

Model parameters are either drawn from the wider literature (morality ; reoccurrence rates ; utility values) or from the Hunt and Elg observational study (unhealed to healed transition probabilities ; frequency of dressing changes ; cost of dressing changes ; cost of haemoglobin spray)

4.3.1 Parameters drawn from the wider literature

Base case utilities for healed ulcers, unhealed/reoccurrence ulcers are 0.785 and 0.615 respectively and drawn from Beaudet, A., et al [56]. The utility of absorbing state death is 0 as is standard.

The probability of mortality is assumed to be the age and gender adjusted mortality rates as estimated by the ONS [60] multiplied by an excess mortality rate for type II diabetic patients [57] further multiplied by a relative rate of 2.48 if the DFU is unhealed [58]

Reoccurrence of wounds is permitted i.e. transition from healed to unhealed and is estimated at a rate of 1% per week [59]. If a reoccurrence of the wound occurs, they are assumed to heal at a population-averaged rate for each treatment group and generate weekly costs as per treatment group.

4.3.2 Parameters drawn from the Observational Study

Unhealed to healed ulcer transition probabilities, dressing change frequencies and dressing cost changes are derived from Hunt and Elg [47].

4.3.2.1 Unhealed to Healed Transition Probabilities

Parametric survival regression models are often used in HTA to extrapolate and predict survival rates beyond the trial/period of observation. This is indeed a requirement in this case as the model runs over a period longer than the 28 weeks of observation. A further indication for regression analysis is that it may accommodate any imbalance in patient characteristics across non-randomised cohorts. In principle if we can understand the relationship between individual characteristics and outcomes then we can address any imbalance in patient populations by constructing modelled counterfactuals for each treatment option applied across the whole population, thus ensuring a completely like-for-like comparison. A second reason that we may wish to use an explicit method for dealing with heterogeneity is that if the observed survival rates are a function of different patients having very different survival expectations then an implicit average which ignores the heterogeneity may miss-specify the hazard function and so make extrapolation problematic. The rational applies to any non-linear regression models that are used to produce parameters which populate models.

In this particular case although t-tests show no statistically significant differences in mean characteristics between the cohorts, it was noticeable that:

a) there was an apparent (and *a priori* predictable) relationship between wound size and healing rates with 89% of wounds which were less than 4cm^2 at baseline healed within 28 weeks whereas only 32% of wounds greater than 4cm^2 at baseline healed. Similarly it was noted that 86% of patients under 30 had wounds that healed as opposed to a rate of 52% if over 30.

b) Although there were no significant differences in mean wound size, the haemoglobin spray cohort had a higher proportion (60%) of wounds that were less than 4cm^2 at baseline, including the only four wounds that were less than 0.5cm^2 at baseline. Similarly, 57% of patients under the age of 30 were in the haemoglobin spray group.

To address the issue of any imbalance in patients across cohorts we include individual characteristics (such as wound size at baseline) in the survival regression models. Survival expectations for each treatment option may then be created for every individual in the population using observed characteristics and estimated parameters. The average patient could be used to produce survival estimates, but as survival models are universally non-linear then the expectation of the average member of the population is not the average of the expectations across the whole population. As we are considering the decision of treatment across a population then it is the average of the expectations and not the expectation of the average which is required. Population-averaged survival curves are therefore created by averaging probabilities of survival across all individuals under each treatment regimen – a process generally known as the corrected group prognosis method the results of which we term explicit population averaging.

All models were estimated using Stata 14 [61] and the results are shown in table 2. Exponential, Weibull and Gompertz proportional hazards (PH) models and Log Normal, Log Logistic and Generalized Gamma accelerated failure time models (AFT) are estimated. In PH models positive coefficients indicate faster healing times and in AFT models negative coefficients indicate faster healing times.

Models include variables that were recorded during the study and were felt by the Specialist Tissue Viability nurse to be likely candidates for significance. The data consist of 40 observations of which 17 observations were censored and a total of 726 time points at risk.

The regression results show a large degree of consistency. All variables are consistent with their a priori expectations in terms of the signs of the coefficient and hence the direction of effect. Younger patients tend to heal quicker and those under 30 heal at a statistically significantly faster rate than those over 30 – a result which holds across every model. Although wound area has the expected sign in all models, it is only statistically significant in the Log Logistic and Generalised Gamma AFT models. This is partly due to a correlation with age under 30. The estimate for the impact of the haemoglobin spray is always statistically significant in all models except Generalized Gamma.

Table 2 : Parametric survival model results for wound survival

	Exponential (PH)	Weibull (PH)	Gompertz (PH)	Log Normal (AFT)	Log Logistic (AFT)	Generalised Gamma (AFT)
Constant Term	-2.465 (1.499)	-5.466 (1.874)	-3.213 (1.637)	2.073 (0.569)	2.223 (0.543)	1.309 (0.660)
Haemoglobin Spray	1.150 (0.503)	2.305 (0.688)	1.987 (0.634)	-0.605 (0.205)	-0.54 (0.209)	-0.356 (0.211)
ln(Wound area)	-0.214 (0.221)	-0.390 (0.256)	-0.331 (0.243)	0.169 (0.090)	0.166 (0.083)	0.141 (0.085)
ln(Wound age)	-0.062 (0.655)	-0.035 (0.720)	-0.019 (0.702)	0.114 (0.264)	0.068 (0.240)	0.188 (0.261)
Age <=30	1.712 (0.852)	2.769 (0.946)	2.487 (0.941)	-1.219 (0.313)	-1.330 (0.333)	-1.081 (0.264)
Age 31-60	0.505 (0.552)	0.397 (0.256)	0.588 (0.563)	-0.100 (0.228)	-0.097 (0.224)	0.005 (0.222)
Neuropathy	0.742 (0.701)	1.002 (0.679)	1.205 (0.724)	-0.359 (0.272)	-0.394 (0.271)	-0.288 (0.231)
HbA1c	-0.295 (0.23)	-0.551 (0.277)	-0.509 (0.266)	0.184 (0.088)	0.161 (0.088)	0.209 (0.074)
Offload	-0.203 (0.613)	-0.325 (0.656)	-0.396 (0.655)	0.023 (0.259)	0.120 (0.235)	-0.010 (0.252)
Ancillary Parameter		2.347 (0.393)	0.112 (0.033)	0.498 (0.078)	0.270 (0.048)	0.439 (0.089)
Kappa						-1.315 (0.810)
AIC	90.37	74.49	80.21	70.81	69.69	69.8
BIC	105.57	91.37	97.1	87.7	86.58	88.38

The AFT models tend to provide a better fit than the PH models with the full Log-logistic model providing the best fit according to AIC and BIC.

The log-logistic regression model is used as our choice for transition probabilities for the base-case model on the basis that it is the best-fitting model, though we note that the generalised gamma model has a very similar statistic of fit. If we average across individual survival curves we estimate a mean (median) healing time of 35 (29) weeks for standard care and 21 (17) weeks for treatment with the haemoglobin spray – an expected difference of 14 (12) weeks. As a sensitivity analysis we conducted the corrected group prognosis method for all estimated models and found that the Log-Logistic model actually gives the smallest incremental difference between treatments with the exception of the Generalised Gamma model. For the Generalised Gamma model the mean (median) healing times

for the population were estimated as 36 (26) weeks for standard care and 26 (18) weeks for the haemoglobin spray – an expected difference of 10 (8) weeks.

Figure 2 shows the modelled log-logistic survival function averaged across all 40 patients compared to the observed Kaplan Meier curves for each cohort. As can be seen, incorporating patient heterogeneity into the modelling of expectations implies a smaller incremental difference between treatment arms than that suggested by the Kaplan Meier method which is unduly influenced by the imbalance in cohorts.

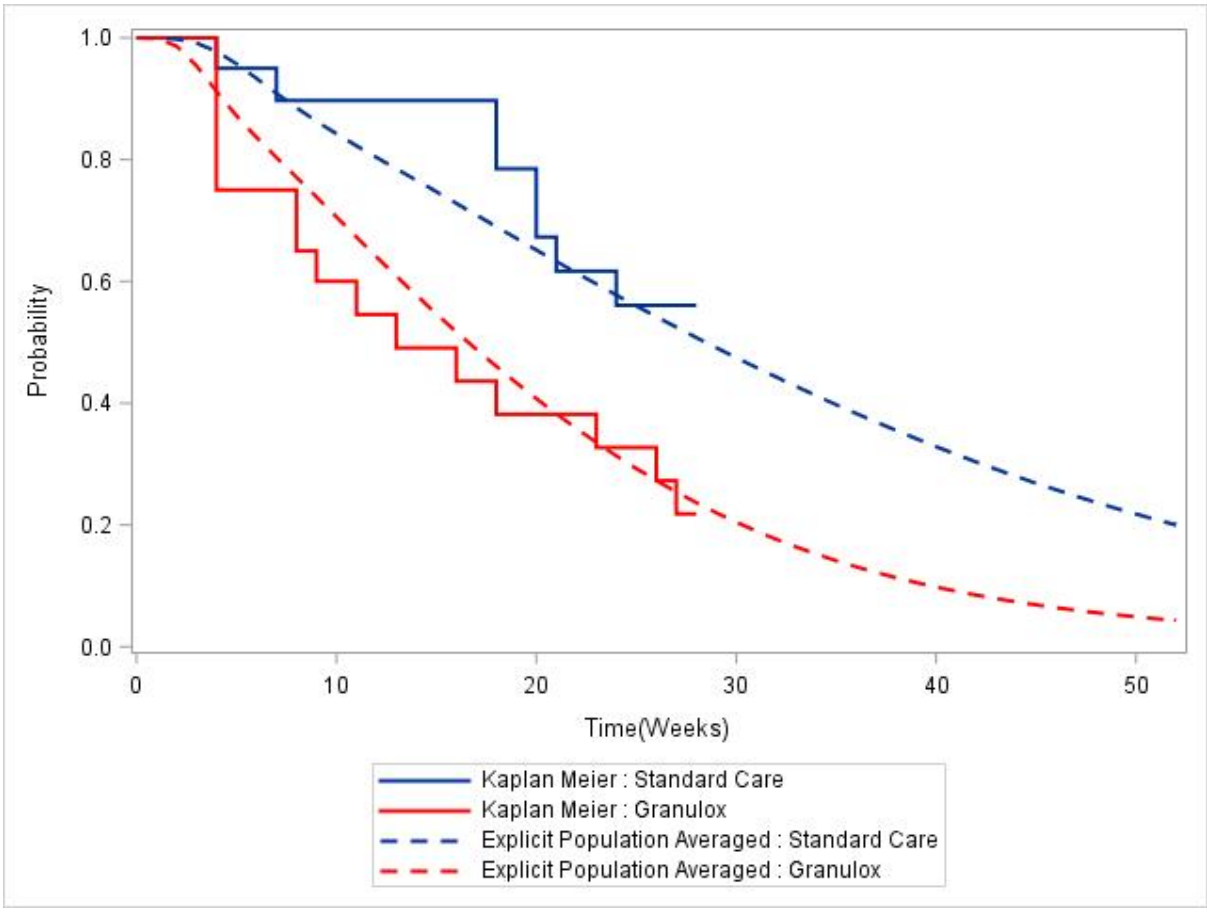

Figure 2 : Kaplan Meier and modelled survival curves for wound survival

Weekly transition probabilities from unhealed-to-healed are directly constructed from the estimated survival curves.

4.3.2.2 Dressing Change Frequency

In a manner similar to that implemented in the estimation of wound healing rates, regression models were used to estimate the weekly dressing change frequency on non-healed wounds under standard care and standard care with the haemoglobin spray treatment.

Although a number of alternatives were tested, the outcomes were very similar and so a simple linear model with robust standard errors to allow for clustering within patients is presented and used and is shown in Table 3.

In total there were 430 observed dressing change frequencies per week for all 40 patients. This represents all weeks were wounds were present and there are no missing values. Though there are few statistically significant explanatory variables, the model is statistically significant and has an R-Squared of 0.226 with a Root Mean Square Error of 1.37.

The haemoglobin spray is found to have a statistically significant impact in reducing the frequency of dressing changes per week conditional on their being an un-healed wound.

Table 3 : OLS estimates of impact on dressing change frequency (weekly)

Parameter	Coefficient	Std Error	t	P>|t|	L95% CI	U95% CI
Constant Term	4.019	1.133	3.550	0.001	1.726	6.311
Haemoglobin Spray	-1.306	0.354	-3.690	0.001	-2.022	-0.590
ln(Wound area)	0.179	0.169	1.060	0.297	-0.163	0.520
ln(Wound age)	-0.091	0.390	-0.230	0.817	-0.880	0.698
Age <=30	-0.492	0.540	-0.910	0.368	-1.584	0.600
Age 31-60	-0.446	0.461	-0.970	0.339	-1.377	0.486
Neuropathy	0.169	0.296	0.570	0.570	-0.429	0.768
HbA1c	-0.070	0.173	-0.400	0.690	-0.421	0.281
Offload	-0.188	0.301	-0.630	0.535	-0.798	0.421

The regression-corrected rates for weekly frequency of dressing changes are therefore estimated at 3.3 visits for the standard treatment and 2 for adjuvant treatment with the haemoglobin spray.

4.3.2.3 Dressing Change Costs

Costs are viewed from an NHS and PSS perspective and are limited to the costs of a per unit dressing of wounds which are estimated using micro costing of resource use from the study and are estimated at £57.15 per dressing change for standard care the majority of which (£54.93) is attributed to nurse time. The cost of a dressing change using the haemoglobin spray is assumed to be the cost of standard care plus the marginal cost of one application of the spray calculated in the base case as the list price cost (£125) divided by the expected number of applications in a canister (30) to give an application cost of £4.17. However for the base case we assume that cans of Granulox may not be shared across patients and in addition there is an arbitrary 25% wastage creating an average application cost of £6.65. The average cost for a dressing change with the adjuvant spray is therefore £63.80. Only patients with unhealed ulcers generate dressing change costs.

4.3.2.4 Weekly Dressing Change Costs

The increased frequency of dressing changes for standard care leads to weekly costs for standard care of £189, exceeding the estimate of weekly costs of £128 as if treated with the haemoglobin spray. For sensitivity analysis we exclude a frequency effect which yields weekly unhealed wound costs of £211.

4.3.2.5 Parameter sources

Table 4 summarises parameter sources and values (where they are time invariant within the model)

Table 4 : Model Parameter Values and Sources

Parameter	Value	Source
Utilities		
Unhealed/Reoccurrence	0.785	Beaudet, A., et al., Review of utility values for economic modeling in type 2 diabetes. Value Health, 2014. 17(4): p. 462-70.
Healed	0.615	Beaudet, A., et al., Review of utility values for economic modeling in type 2 diabetes. Value Health, 2014. 17(4): p. 462-70.
Dead	0	Standard

Transition Probabilities		
Unhealed to Unhealed	Time, patient and treatment dependent	See table 4 - estimated using Hunt, S.D. and F. Elg, Clinical effectiveness of hemoglobin spray (Granulox(®)) as adjunctive therapy in the treatment of chronic diabetic foot ulcers. Diabetic foot & ankle, 2016. 7: p. 33101.
Unhealed to Healed	Time, patient and treatment dependent	See table 4 - estimated using Hunt, S.D. and F. Elg, Clinical effectiveness of hemoglobin spray (Granulox(®)) as adjunctive therapy in the treatment of chronic diabetic foot ulcers. Diabetic foot & ankle, 2016. 7: p. 33101.
Unhealed to Death	Age-Standardised ONS rates * age-related excess mortality for diabetes patients * 2.48 excess risk for unhealed ulcer	ONS National life tables: United Kingdom, 2016; Mulnier, H.E., et al., Mortality in people with type 2 diabetes in the UK. Diabet Med, 2006. 23(5): p. 516-21. And Walsh, J.W., et al., Association of diabetic foot ulcer and death in a population-based cohort from the United Kingdom. Diabet Med, 2016. 33(11): p. 1493-1498.
Healed to Healed	Residual from healed to reoccurrence and healed to death rates	
Healed to Reoccurrence	0.01	Dubsky, M., et al., Risk factors for reoccurrence of diabetic foot ulcers: prospective follow-up analysis in the Eurodiale subgroup. Int Wound J, 2013. 10(5): p. 555-61.
Healed to Death	Age-Standardised ONS rates * age-related excess mortality for diabetes patients	ONS National life tables: United Kingdom, 2016; Mulnier, H.E., et al., Mortality in people with type 2 diabetes in the UK. Diabet Med, 2006. 23(5): p. 516-21.
Reoccurrence to Reoccurrence	Time, patient and treatment dependent	Assumed same as unhealed to unhealed rates as if on Standard Treatment
Reoccurrence to Healed	Time, patient and treatment dependent	Assumed same as unhealed to healed rates as if on Standard Treatment
Reoccurrence to Death	Age-Standardised ONS rates * age-related excess mortality for diabetes patients * 2.48 excess risk for unhealed ulcer	ONS National life tables: United Kingdom, 2016; Mulnier, H.E., et al., Mortality in people with type 2 diabetes in the UK. Diabet Med, 2006. 23(5): p. 516-21. And Walsh, J.W., et al., Association of diabetic foot ulcer and death in a population-based cohort from the United Kingdom. Diabet Med, 2016. 33(11): p. 1493-1498.
Death to Death	1	Assumed absorbing state
Dressing Change Frequency		
Unhealed wounds with Standard Treatment	3.3	See table 5 - estimated using Hunt, S.D. and F. Elg, Clinical effectiveness of hemoglobin spray (Granulox(®)) as adjunctive therapy in the treatment of chronic diabetic foot ulcers. Diabetic foot & ankle, 2016. 7: p. 33101.
Unhealed wounds with adjuvant haemoglobin spray treatment	2	See table 5 - estimated using Hunt, S.D. and F. Elg, Clinical effectiveness of hemoglobin spray (Granulox(®)) as adjunctive therapy in the treatment of chronic diabetic foot ulcers. Diabetic foot & ankle, 2016. 7: p. 33101.
Nursing Costs		
N25AF - Specialist Nursing, Tissue Viability Nursing/Liaison, Adult, Face to face	£ 54.93	National Schedule of Reference Costs - Year 2014-15 - NHS trusts and NHS foundation trusts - Community Health Services
Rinse Costs		
Normasol 25ml (one unit in multi-pack of 25)	£ 0.26	NHS Electronic Drug Tariff, July 2015
Prontosan 40ml (one unit in multipack of 24)	£ 6.35	NHS Electronic Drug Tariff, July 2015
Prontosan Wound Gel 30ml	£ 0.59	NHS Electronic Drug Tariff, July 2015
Weighted Average cost	£ 0.31	Frequencies derived from observational data
Dressing Costs		
Activon Medical Grade Manuka Honey, 25g	£ 1.39	NHS Electronic Drug Tariff, July 2015
Allevyn Adhesive 10cm x 10cm	£ 1.97	NHS Electronic Drug Tariff, July 2016
Allevyn Gentle Border 10 x 10 cm	£ 2.14	NHS Electronic Drug Tariff, July 2016
Allevyn Gentle Border 7.5 x7.5 cm	£ 1.38	NHS Electronic Drug Tariff, July 2015
Aquacel Ag 10cm x 10cm	£ 0.38	NHS Electronic Drug Tariff, July 2015

Aquacel Ag 4cm x 10cm	£ 2.72	NHS Electronic Drug Tariff, July 2015
Aquacel Ag 5cm x 5cm	£ 2.85	NHS Electronic Drug Tariff, July 2016
Aquacel Ag foam adhesive 8cm x 8cm	£ 6.35	NHS Electronic Drug Tariff, July 2015
Aquacel foam adhesive 10cm x 10cm	£ 3.38	NHS Electronic Drug Tariff, July 2015
Aquacel foam adhesive 8cm x 8cm	£ 2.19	NHS Electronic Drug Tariff, July 2016
Inadine 5cm x5cm	£ 1.49	NHS Electronic Drug Tariff, July 2015
Mepilex Border 10cm x 12.5cm	£ 4.69	NHS Electronic Drug Tariff, July 2016
Mepilex Border 15cm x 17.5cm	£ 2.05	NHS Electronic Drug Tariff, July 2015
Mepilex Border 7cm x 7.5cm	£ 0.20	NHS Electronic Drug Tariff, July 2016
Mepilex Border Ag 7cm x 7.5cm	£ 3.41	NHS Electronic Drug Tariff, July 2016
Prontosan Wound Gel 30ml	£ 4.74	NHS Electronic Drug Tariff, July 2016
Softpore 10cm x 15cm	£ 2.18	NHS Electronic Drug Tariff, July 2016
Weighted Average cost	£ 1.91	Frequencies derived from observational data
Average Dressing Change Cost	£ 57.15	

4.4 Economic Evaluation Results

4.4.1 Base Case Results

The base case model reflects the outcomes from the economic model outlined in 4.2 populated by parameters as detailed in table 4.

Figure 3 shows the Markov Trace of patients over states within the model. The impact of the estimated increased healing rates of the haemoglobin spray lead to greater proportions of patients being in the healed state particularly over the early and middle period of the time period. Beyond week 33 the incremental difference between the treatments decreases mainly as a result of a greater proportion of reoccurrence in the spray group due to a greater proportion of healed patients. Of additional note is that death is a very minor driver of HRQoL

Figure 4 shows the improved healing rates translated to reduced dressing changes with an additional direct impact on the frequency of dressing changes (base case) and without the additional impact (healing rate improvement only). As with the markov trace the incremental difference per week after 33 weeks diminishes due to the reoccurrence effect.

Base case model results estimate net present values of 0.651 QALYs for standard care and 0.688 QALYs for the haemoglobin spray indicating an incremental QALY gain of 0.017 QALYs by using the spray as an adjunct to standard care. The costs are £6,813 for standard treatment and £3,945 for the haemoglobin spray indicating an incremental cost of -£2,868 i.e. a cost saving. As the haemoglobin spray treatment has an expectation of higher QALY gains and lower costs, the treatment dominates standard care. The Incremental Net Monetary Benefit (INMB) is estimated at £3,208 where QALYs are valued at £20k per QALY and £3,378 at £30k per QALY. Approximately 90% of the INMB occur through cost-savings.

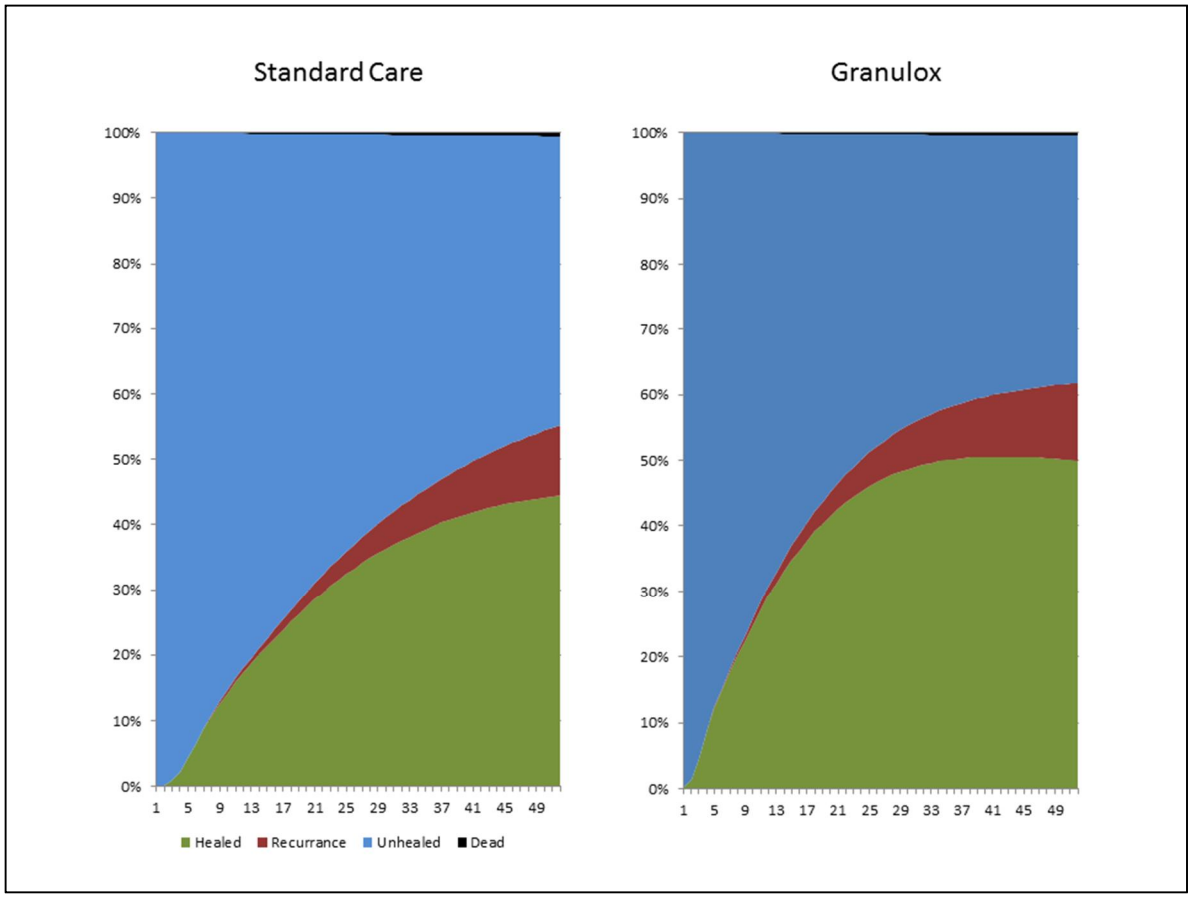

Figure 3 : Markov Trace

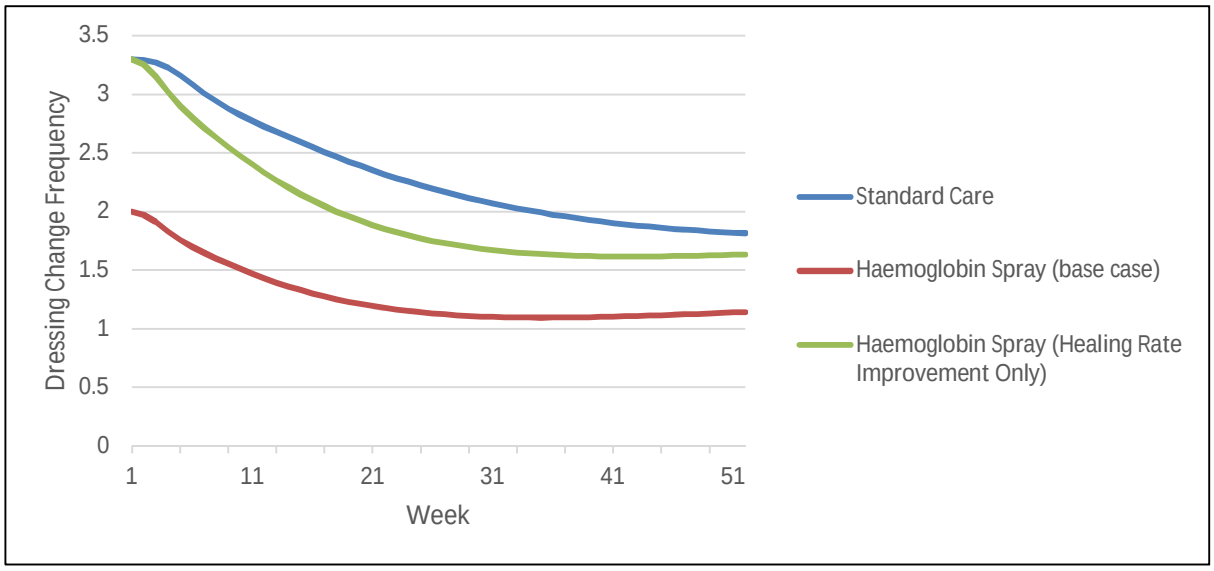

Figure 4 : Expected Weekly Frequency of Dressing Changes

4.4.2 Sensitivity Analysis

Probabilistic Sensitivity Analysis (PSA) is conducted using random draws from the variance/covariance matrices for the wound survival and for the dressing change frequency regression models. For the base case model this estimates that adjuvant treatment with the haemoglobin spray is cost-effective with a probability of approximately 100% with a 99.6% probability that adjuvant treatment with the haemoglobin spray is a dominant treatment option. As a result formal value of information (VOI) calculations show there is no additional benefit for conducting further research.

Table 5 : Base case and sensitivity analyses results

Treatment	QALYs	Cost	Incremental QALYs	Incremental Costs	ICER	PSA Probability CE at £30k per QALY	PSA Probability Granulox dominates
Standard Care	0.651	£6,813					
Haemoglobin spray - Base Case	0.668	£3,945	0.017	-£2,868	Dominates	100%	99.6%
Sensitivity Analyses (all incremental to Standard Care)							
Haemoglobin Spray- No impact on healing rates	0.651	£4,584	0	-£2,229	Cost Minimising	99.7%	0%
Haemoglobin Spray- No impact on dressing change frequency	0.668	£6,476	0.017	-£337	Dominates	92.4%	77.9%
Haemoglobin Spray - 83.5% reduction in estimated impact on healing rate and dressing change frequency	0.654	£6,899	0.003	£87	£29,111	50.7%	23.2%
Exponential survival model			0.016	-£2,069	Dominates		
Weibull survival model			0.029	-£3,486	Dominates		
Gompertz survival model			0.024	-£3,209	Dominates		
Log Normal survival model			0.019	-£2,970	Dominates		
Generalized Gamma survival model			0.018	-£2,548	Dominates		

In addition to the PSA a range of deterministic sensitivity analyses were considered. The analyses presented are those considered most likely to change the conclusion that that adjuvant treatment with the haemoglobin spray is not dominant relative to Standard Care. The analyses covered are:

1. Reducing the effectiveness of the healing rate improvement to 0%
2. Reducing the effectiveness of the reduction in dressing change frequency to 0%
3. A simultaneous reduction in the effectiveness of both healing rate and survival improvements to the point at which the ICER approaches £30k per QALY
4. Changing parametric survival model to alternatives: Exponential, Weibull, Gompertz, Log Normal and Generalized Gamma.

The results are shown in Table 5 and show the results are robust to alternative assumptions with effectiveness of healing rates and frequency changes jointly having to fall by over 82% before the model suggests the technology is not cost-effective at the £30k per QALY threshold.

The sensitivity analyses considered thus far are those most amenable to being expressed in a quantitative fashion and may be implemented by changing parameter values within the model. There are however uncertainties or limitations that are not so easy to express in such a manner and may require some critical appraisal of their likely impact.

For example, although a common element of wound healing models, there is no distinction made between types of unhealed wounds. It is estimated that wounds that are deteriorating are substantially more costly than wounds that are healing but not yet healed [62]. Furthermore the survival modelling approach implicitly assumes that all ulcers are healing and all would be observed to heal if the time period of observation were sufficiently long and there were no other form of censoring (i.e. death). This may well be an unfeasible assumption for both control and haemoglobin spray treatment regimens. However whilst the model is likely to underestimate total costs and overestimate total QALYs in both arms, the data strongly suggest the impact would be greatest in the treatment group which has the only examples of ulcers which are increasing in size. Thus, this model limitation is conservative from the perspective of the new technology and implies a bias against the haemoglobin spray which

therefore has no impact on the conclusion of dominance over standard care alone. It is clearly a limitation of the model in terms of representing reality but the model conclusions regarding cost-effectiveness are likely to be robust to this limitation.

Similarly the model omits the QALY and cost impact of major events such as amputations, which are known to be substantial drivers of the economic argument of diabetes treatment. For example Redekop et al [63] find foot amputations typically yield permanent 0.12 to 0.16 QALY decreases in utility per annum and Kerr [11] reports average tariff costs of £10,688 per major amputation in diabetes with £5,519 post-discharge lifetime costs. This again represents a potentially substantial conservative assumption from the perspective of the haemoglobin spray on the basis that amputations are more likely to occur when ulcers are unhealed.

There is also the element of the reliability of the data. The PSA has covered some of this consideration. For example, one might be concerned by the small number of patients in the study. However this is captured by the standard errors surrounding the parameter estimates which are used in the PSA. We find although estimates of many of the parameters may be considered imprecise in terms of the range of values they may cover, the estimate of the impact of the spray is sufficiently large to be relatively uncertain and in favour of the spray. Although the data are small, they seem to be sufficient to demonstrate improved effectiveness.

Similarly one might be concerned about the non-RCT nature of the data. In general as RCTs randomise allocation of treatment between patients we may expect that the treatment is uncorrelated with other factors that may drive outcomes and therefore we may assume that any observed difference between treatment groups is indeed a function of treatment. Our approach here is not to make that particular assumption for observational data but instead attempt to directly measure the impact of patient characteristics and explicitly accommodate them in the analysis. To this extent we do find some evidence to suggest that the observed improved healing rates, especially in the first few weeks, were indeed a result of a less complex patient case-mix in the spray group as well as that due to treatment, but, importantly, we have also adjusted our analysis to accommodate this impact. This is principally done via the corrected group prognosis method survival curves as shown in figure 2 this and it is clear there is no impact on the qualitative outcomes. This approach does rely on the ability of the regression model to be able to adequately capture the impact of patient characteristics in an unbiased manner and there may be questions regarding this issue. Firstly maximum likelihood (ML) is used to estimate the survival models as is standard, however ML has appealing asymptotic properties i.e. properties of unbiasedness when sample sizes are ‘large’. There is no clear guidance on what could be considered sufficiently large. Perhaps of greater concern is the selection mechanism of patients into the study. If there are unobserved characteristics not captured by the available data which are correlated with the treatment then that could lead to a biased estimate of treatment. Such things are more likely if patients self-select or clinicians select treatment as their treatment decisions may well be based on information we do not observe as analysts. To identify the likelihood of this issue it is important to understand the selection mechanism. As previously discussed in introducing the observational study, the criteria applied by Hunt and Elg of using the first 20 patients within consecutive calendar years does not suggest a selection mechanism that is likely to bias the results, though there is always a possibility that some temporal change between years could have influenced results.

A final issue may regard the choice of comparator group which was standard care in this local setting but may not necessarily be reflective of standard care elsewhere and may exclude other competing technologies which claim similar benefits. Given the nature of the market for wound care products this is perhaps the most pressing limitation as there is little we can say about the expectation on results.

In conclusion, the result of dominance does indeed appear robust to a number of sensitivity analyses including parametric as well as those posed a result of critical assessment of other model/data limitations, though it is difficult to compare against other potential technologies.

5 Application of Claxton Algorithm and Discussion

In order to establish an optimal decision via the Claxton algorithm then either definitive answers are required for each of the seven sequential questions or the uncertainty is such that alternative paths lead to the same outcome.

To this purpose identifying which questions can be definitely answered is useful as it may limit the range of possible conclusions. For example in this case it seems clear that adoption of this technology generates no significant irrecoverable costs.[1] In addition the quantitative evidence from the economic model may be directly used to inform answers such as use of INMB for establishing cost-effectiveness or EVPI to determine whether future research is worthwhile. For other questions other information may be required.

Other uncertainties may exist for which it is not possible to make such definitive statements. For example there may be concerns regarding the use of observational data even after regression-correction has been applied to address any imbalance in cohorts. In which case a sensible approach might be to adopt different perspectives and understand the implications of adopting that approach. When these consequences are clear one can make a decision on which perspectives appear reasonable.

For example, for the case in hand, one could perhaps adopt positions of being:

a) Accepting: the data and/or model are reasonable and sufficient or are conservative from the perspective of the haemoglobin spray;
b) Sceptical: data and/or model are uncertain and perhaps over-optimistic from the perspective of the spray treatment to some degree
c) Dismissive: data and/or model are potentially biased to the extent of being misleading in terms of predicted cost-effectiveness
d) Completely Dismissive : data and/or model are potentially biased to the point that there is no useful information provided

Each of these positions has important consequences for the use of the Claxton algorithm. For example, given our results and the robustness to the sensitivity analyses, the first two positions would imply a belief that current evidence does suggest the technology is cost-effective whereas with the latter two positions, one may be unwilling to form any opinion on the cost-effectiveness of the technology and in the last case perhaps even on the potential value of the product.

When it comes to the third question which asks whether there is any value in further research, if one adopts position a) then the univariate sensitivity analysis, the PSA and EVPI find no uncertainty and hence no value in further research. Similarly d) implies the same conclusion but on very different grounds. Positions b) and c) require some further ad-hoc analysis to address.

In order to explore the value of the uncertainty it is worthwhile exploring the wider context of treatment and the volume and expected costs of potential patients. Diabetes UK estimate a UK population of 2.6 million patients with type II diabetes of which one in twenty will develop a chronic foot ulcer in any given year [12]. If, as estimated, 15% of these DFUs develop into chronic wounds then there are approximately 26,000 chronic DFUs eligible for treatment with the haemoglobin spray each year. Suppose that adjuvant treatment with the haemoglobin spray has no effect, in which case the impact of incorrectly approving the spray will be to add an incremental cost of £22 per week for an unhealed ulcer. Applying this cost to our modelled markov trace of healed, unhealed and dead for standard care in our model implies a waste of £805 per patient per year which if applied to the whole DFU population aggregates up to approximately £21m per annum. If, on the other hand that adjuvant treatment with the haemoglobin spray is as effective as estimated and is not used, then the unnecessary costs generated are estimated at £2,868 per patient per year aggregated up to a population level of £74.5m per annum. If we additionally factor in expected QALY loss valued at £30k then the (conservative) Net Monetary consequence of rejecting the spray is £88m per annum on dressing costs alone. The difference between these end points is approximately £110m per annum. Because of these annual values (which ignore amputation costs) then even difficulty in assigning probability weights to each eventuality may well lead to the conclusion that further research is not only highly valuable but also likely to exceed the costs of research. The sheer volume of potential patients per annum being the main driver of the results.

[1] If no significant irrecoverable costs is accepted this also conveniently limits discussion of this example to just figure one of Claxton et al.

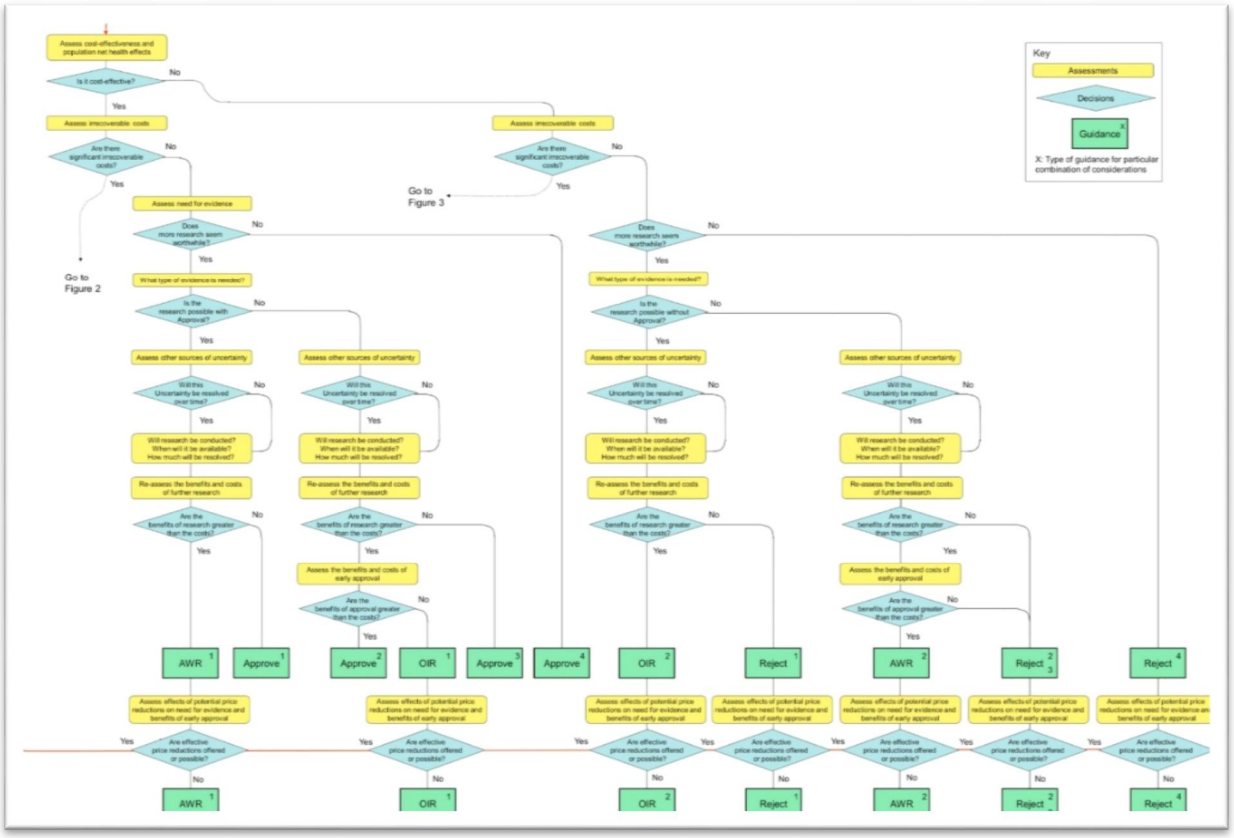

Figure 5: Claxton complex algorithm reproduced from Value in Healh Claxton, K., et al., A Comprehensive Algorithm for Approval of Health Technologies With, Without, or Only in Research: The Key Principles for Informing Coverage Decisions. Value Health, 2016. 19(6): p. 885-891.

Prior to this point in the algorithm positions a) and d) lead to definitive but opposite optimal decisions of approve and reject respectively. With an expectation that future research would be worthwhile then for b) reject is ruled out and for c) approve is ruled out, but further information is required to narrow the choice further. This hinges on whether future research is more likely to occur with approval or without. In most circumstances such a question addresses the possible different incentives each option provides to the producer of the technology with a specific concern that sometime incentives to generate research may be eliminated. However on the basis of current evidence development in a situation where incentives to produce evidence are maximised, it may be rational to rule out industry-sponsored trials [64]. Instead we may consider research council funded RCTs or registry-based observational studies.

Whichever evaluation technique is used given the potentially wide range of plausibly cost-effective treatments any method of evidence generation may need to be innovative in incorporating as many technologies as needed. For example adaptive multi-arm multi-stage (MAMS) which eliminate less-effective options over defined stages should be considered [65]. For the observational studies then designs such as stepped wedge, cluster-controlled non-randomised trials would appear a plausible, pragmatic and cost-effective means of generating robust evidence purged of systematic bias [66]. Indeed incorporating service providers in generating the evidence may well be one means of increasing the likelihood that providers of care, such as community care nurses are more receptive to adopting current evidence in their treatment decisions. It has been argued that the responsibility for developing a body of evidence should actually lie with nurses [64]. A limiting factor with the AWR approach is that it may require an infrastructure be constructed at an initially prohibitively high fixed cost [6].

Table 6 : Perspectives on Evidence and Algorithm conclusions

Perspective	Summary	Optimal Decision if Evidence Development is viable	Optimal Decision if Evidence Development is not viable
a) Accepting of data and model	Technology is likely to be cost-effective ; no irrecoverable costs; no uncertainty	Approve	Approve
b) Sceptical of data and model	Technology is likely to be cost-effective; no irrecoverable costs; high value of uncertainty	AWR or OIR	Approve
c) Dismissive of data and model	Technology is not likely to be cost-effective; no irrecoverable costs; high value of uncertainty	AWR or OIR	Reject
d) Completely dismissive of data and model	Technology is not likely to be cost-effective; no irrecoverable costs; no or low value of uncertainty	Reject	Reject

Returning to our example, having assessed the expected cost-effectiveness, identified a lack of large upfront irrecoverable costs and assessed the value of further research we can now identify optimal adoption strategies under each perspective of the evidence and whether evidence development is possible or not. Our conclusions are shown in table 6.

The key issue is to resolve the position(s) on the data and in particular whether it is defendable to be dismissive or completely dismissive of the evidence? On balance we would argue not. The mechanism of action is plausible, the results of trials and observational studies are positive and consistent and although there are limitations in the trials, there are no obvious signs of systematic bias. Gottrup et al [67] classify the evidence on Granulox as Grade 1B, the second highest score on the GRADE approach to treatment recommendation and a consensus recommendation from a working group of key UK opinion leaders found that the evidence was sufficient to recommend the spray as a treatment [52].

If, as a result, we can rule out the dismissive positions on the evidence then the other factors point to either adoption or AWR. Note, that in the event that the costs of setting up registries are too high or it is otherwise not possible and the technology will not feature in any trials then the optimal decision is to adopt and not to reject.

6 Conclusion

Treatment of non-healing wounds is a major challenge to health-care providers with substantial costs and loss of health related quality of life. And despite a saturated market of treatment choices a weak and potentially misleading evidence base has led to use of a simple de facto conservative rule of adoption – minimise treatment cost per dressing change unless there is definitive evidence of clinical and cost-effectiveness. We apply recent developments in the treatment of uncertainty in optimal decision-making to an example technology and identify the potential limitations of the simpler decision heuristic.

We find that on the balance of evidence for an example new technology, the haemoglobin spray Granulox, the current recommended decision process may lead to a situation in which the NHS is persistently generating unnecessary costs as well as quality of life decrements. We conservatively estimate these to be approximately £90 million every year.

Given the state of the wound care market, with many products supported by weak evidence bases, the story developed around the spray may apply to many products and a further issue may be one of prioritising which products to assess first. Nevertheless such additional issues should not be used as an excuse for maintain the current inertia. We argue that decision makers should take a more nuanced approach to prioritising and incorporating uncertainty into their decision making process and understand the full consequences of rejecting treatments that appear to be cost-effective. In wound care it would seem that key to making better decisions requires a method of assessing the nature of bias within the evidence base. Where implementation costs are low,

like our example, consideration should be given to generating evidence through adoption with research. This may well lead to a situation where technologies which turn out to be not cost-effective are adopted for the evaluation period, but this is balanced against the risk that truly cost-effective technologies are never adopted. If evidence cannot be generated, then even with uncertainty, the optimal solution in some cases may be to adopt the technology.

7 References

1. Claxton K. The irrelevance of inference: a decision-making approach to the stochastic evaluation of health care technologies. Journal of health economics. 1999 Jun;18(3):341-64.

2. Frykberg, R.G. and J. Banks, *Challenges in the Treatment of Chronic Wounds.* Adv Wound Care (New Rochelle), 2015. **4**(9): p. 560-582.

3. Guest, J.F., et al., *Health economic burden that wounds impose on the National Health Service in the UK.* Bmj Open, 2015. **5**(12): p. 8.

4. Gottrup, F., J. Apelqvist, and P. Price, *Outcomes in controlled and comparative studies on non-healing wounds: recommendations to improve the quality of evidence in wound management.* J Wound Care, 2010. **19**(6): p. 237-68.

5. Phillips, C.J., et al., *Estimating the costs associated with the management of patients with chronic wounds using linked routine data.* Int Wound J, 2016. **13**(6): p. 1193-1197.

6. Cullum, N., et al., *Programme Grants for Applied Research*, in *Wounds research for patient benefit: a 5-year programme of research*. 2016, NIHR Journals Library: Southampton (UK).

7. Guest, J.F., K. Vowden, and P. Vowden, *The health economic burden that acute and chronic wounds impose on an average clinical commissioning group/health board in the UK.* J Wound Care, 2017. **26**(6): p. 292-303.

8. Lindholm, C. and R. Searle, *Wound management for the 21st century: combining effectiveness and efficiency.* International Wound Journal, 2016. **13**: p. 5-15.

9. Helm, T. *Recruitment crisis hits NHS with one in nine posts currently vacant*. The Observer, 2017.

10. Jarbrink, K., et al., *The humanistic and economic burden of chronic wounds: a protocol for a systematic review.* Syst Rev, 2017. **6**(1): p. 15.

11. Kerr, M., *Diabetic Foot Care in England: An Economic Study*. 2017 Insight Health Economics.

12. Snyder, R.J. and J.R. Hanft, *Diabetic foot ulcers--effects on QOL, costs, and mortality and the role of standard wound care and advanced-care therapies.* Ostomy Wound Manage, 2009. **55**(11): p. 28-38.

13. Diabetes UK *Twenty devastating amputations every day*. 2016 13/01/2017]; Available from: https://www.diabetes.org.uk/About_us/News/Twenty-devastating-amputations-every-day/.

14. Sood, A., M.S. Granick, and N.L. Tomaselli, *Wound Dressings and Comparative Effectiveness Data*, in *Adv Wound Care (New Rochelle)*. 2014: 140 Huguenot Street, 3rd FloorNew Rochelle, NY 10801USA. p. 511-29.

15. Bell-Syer, S.E., *Review: little evidence exists for type of dressing or support surface or for nutritional supplements for pressure ulcers.* Evid Based Nurs, 2009. **12**(4): p. 118.

16. Carter, M.J., *Health Economics Information in Wound Care: The Elephant in the Room*, in *Adv Wound Care (New Rochelle)*. 2013: 140 Huguenot Street, 3rd FloorNew Rochelle, NY 10801USA. p. 563-70.

17. Bolton, L.L., *Quality Randomized Clinical Trials of Topical Diabetic Foot Ulcer Healing Agents.* Adv Wound Care (New Rochelle), 2016. **5**(3): p. 137-147.

18. Madden, M., *Alienating evidence based medicine vs. innovative medical device marketing: a report on the evidence debate at a Wounds conference.* Soc Sci Med, 2012. **74**(12): p. 2046-52.

19. Bell-Syer, S., et al., *Letter: evidence-based wound care in the UK: a response to David Leaper's editorial in International Wound Journal April 2009 6 (2).* Int Wound J, 2009. **6**(4): p. 306-9; author reply 309-10.

20. Weller, C. and J. McNeil, *CONSORT 2010 statement: updated guidelines can improve wound care.* J Wound Care, 2010. **19**(8): p. 347-53.

21. Carter, M.J. and R.A. Warriner, 3rd, *Evidence-based medicine in wound care: time for a new paradigm.* Adv Skin Wound Care, 2009. **22**(1): p. 12-6.

22. Leaper, D., *Evidence-based wound care in the UK.* Int Wound J, 2009. **6**(2): p. 89-91.

23. Gottrup, F. and J. Apelqvist, *The challenge of using randomized trials in wound healing.* Br J Surg, 2010. **97**(3): p. 303-4.

24. NHS England, Public Health England, Health Education England, Monitor, Care Quality Comission, NHS Trust Development Authority. *Five Year Forward View*. 2014.

25. Eskes, A.M., et al., *Do stakeholders in wound care prefer evidence-based wound care products? A survey in the Netherlands.* Int Wound J, 2012. **9**(6): p. 624-32.

26. Department of Health, Innovation Policy Branch *Innovation Health and Wealth, Accelerating Adoption and Diffusion in the NHS*. 2011.

27. Ham, C., *Inertia rather than privatisation is the biggest threat facing the NHS*, in *BMJ Blogs*. 2016.

28. Coles, L.C.o., *Operational productivity and performance in English NHS acute hospitals: Unwarranted variations*. 2016, Department of Health: London (UK).

29. Coulthard, J., *NHS England Lesson 8 – Getting things done – the bias to inertia*. 2015 [24 June 2015]; Available from: https://johncoulthard.co.uk/2015/06/24/nhs-england-lesson-8-getting-things-done-the-bias-to-inertia/.

30. Al-Benna, S., *A discourse on the contributions of evidence-based medicine to wound care.* Ostomy Wound Manage, 2010. **56**(6): p. 48-54.

31. NICE, *Wound Care Products (update)*, in *Key Therapeutic Topics*. 2017.

32. Claxton, K., et al., *Probabilistic sensitivity analysis for NICE technology assessment: not an optional extra.* Health Econ, 2005. **14**(4): p. 339-47.

33. Fenwick, E. and S. Byford, *A guide to cost-effectiveness acceptability curves.* Br J Psychiatry, 2005. **187**: p. 106-8.

34. NICE, *Guide to the methods of technology appraisal 2013*, in *Process and methods guides*, 2013, http://publications.nice.org.uk/pmg9: London.

35. Barnsley, P., et al., *Uncertainty and Risk in HTA Decision Making*, in *OHE Research Papers*. 2016, Office of Health Economics.

36. Claxton, K., et al., *A Comprehensive Algorithm for Approval of Health Technologies With, Without, or Only in Research: The Key Principles for Informing Coverage Decisions.* Value Health, 2016. **19**(6): p. 885-891.

37. Forster, M. and P. Pertile, *OPTIMAL DECISION RULES FOR HTA UNDER UNCERTAINTY: A WIDER, DYNAMIC PERSPECTIVE.* Health Economics, 2013. **22**(12): p. 1507-1514.

38. Sculpher, M. and K. Claxton, *Establishing the cost-effectiveness of new pharmaceuticals under conditions of uncertainty - When is there sufficient evidence?* Value in Health, 2005. **8**(4): p. 433-446.

39. Rothery, C., et al., *Characterising Uncertainty in the Assessment of Medical Devices and Determining Future Research Needs.* Health Econ, 2017. **26 Suppl 1**: p. 109-123.

40. Claxton, K.P. and M.J. Sculpher, *Using value of information analysis to prioritise health research: some lessons from recent UK experience.* Pharmacoeconomics, 2006. **24**(11): p. 1055-68.

41. Arenberger, P., et al., *Expected outcomes from topical haemoglobin spray in non-healing and worsening venous leg ulcers.* Journal of Wound Care, 2015. **24**(5): p. 228-236.

42. Arenberger, P., et al., *Clinical results of the application of a hemoglobin spray to promote healing of chronic wounds.* GMS Krankenhhyg Interdiszip, 2011. **6**(1): p. Doc05.

43. Arenbergerova, M., et al., *Effect of topical haemoglobin on venous leg ulcer healing.* EWMA Journal, 2013. **13**(2): p. 25-30.

44. Bateman, S., *Topical haemoglobin spray for diabetic foot ulceration.* British Journal of Nursing, 2015. **24**(12): p. S24.

45. Bateman, S.D., *Use of topical haemoglobin on sloughy wounds in the community setting.* Br J Community Nurs, 2015. **Suppl Wound Care**: p. S32, s34-9.

46. Chadwick, P., *Pilot Study: haemoglobin spray in the treatment of chronic diabetic foot ulcers.* Wounds Uk, 2014. **10**(4): p. 76-80.

47. Hunt, S.D. and F. Elg, *Clinical effectiveness of hemoglobin spray (Granulox(®)) as adjunctive therapy in the treatment of chronic diabetic foot ulcers.* Diabetic foot & ankle, 2016. **7**: p. 33101.

48. Norris, R., *A topical haemoglobin spray for oxygenating chronic venous leg ulcers: a pilot study.* British Journal of Nursing, 2014. **23**(20): p. S48.

49. Tickle, J., *A topical haemoglobin spray for oxygenating pressure ulcers: a pilot study.* British journal of community nursing, 2015. **Suppl Wound Care**: p. S12, S14.

50. Tickle, J. and S.D. Bateman, *Use of a topical haemoglobin spray for oxygenating pressure ulcers: healing outcomes.* British journal of community nursing, 2015. **20 Suppl 12**: p. S14.

51. Dawn Hunt, S., et al., *Evaluating the effect of a haemoglobin spray on size reduction in chronic DFUs: clinical outcomes at 12 weeks.* Br J Nurs, 2016. **25**(12): p. S59-64.

52. Chadwick, P., et al., *Appropriate use of topical haemoglobin in chronic wound management: consensus recommendations.* Wounds U K, 2015: p. 30-35.

53. Gordillo, G.M. and C.K. Sen, *Evidence-Based Recommendations for the Use of Topical Oxygen Therapy in the Treatment of Lower Extremity Wounds.* International Journal of Lower Extremity Wounds, 2009. **8**(2): p. 105-111.

54. Petri, M., et al., *Photoacoustic imaging of real-time oxygen changes in chronic leg ulcers after topical application of a haemoglobin spray: a pilot study.* Journal of wound care, 2016. **25**(2): p. 87, 89.

55. Ashby, R.L., et al., *VenUS IV (Venous leg Ulcer Study IV) - compression hosiery compared with compression bandaging in the treatment of venous leg ulcers: a randomised controlled trial, mixed-treatment comparison and decision-analytic model.* Health Technol Assess, 2014. **18**(57): p. 1-293, v-vi.

56. Beaudet, A., et al., *Review of utility values for economic modeling in type 2 diabetes.* Value Health, 2014. **17**(4): p. 462-70.

57. Walsh, J.W., et al., *Association of diabetic foot ulcer and death in a population-based cohort from the United Kingdom.* Diabet Med, 2016. **33**(11): p. 1493-1498.

58. Mulnier, H.E., et al., *Mortality in people with type 2 diabetes in the UK.* Diabet Med, 2006. **23**(5): p. 516-21.

59. Dubsky, M., et al., *Risk factors for reoccurrence of diabetic foot ulcers: prospective follow-up analysis in the Eurodiale subgroup.* Int Wound J, 2013. **10**(5): p. 555-61.

60. ONS *National life tables: United Kingdom*, 2016.

61. Statacorp. 2015. *Stata Statistical Software: Release 14.* College Station, TX: StataCorp LP.

62. Harding K, Posnett J, Vowden K. A new methodology for costing wound care. International wound journal. 2013 Dec;10(6):623-9.

63. Redekop WK, Stolk EA, Kok E, Lovas K, Kalo Z, Busschbach JJ. Diabetic foot ulcers and amputations: estimates of health utility for use in cost-effectiveness analyses of new treatments. Diabetes & metabolism. 2004 Dec;30(6):549-56.

64. Pagnamenta, F., *Evidence generation for wound care dressing selection: reviewing the issues.* J Wound Care, 2017. **26**(9): p. 545-550.

65. NHS Health Research Authority *Multiple Interventions of Diabetic Foot Ulcer Treatment Trial*. 2017 20 September 2017]; Available from: http://www.hra.nhs.uk/news/research-summaries/midfut/.

66. Pannick, S., et al., *Translating staff experience into organisational improvement: the HEADS-UP stepped wedge, cluster controlled, non-randomised trial.* BMJ Open, 2017. **7**(7): p. e014333.

67. Gottrup, F., et al., *Use of Oxygen Therapies in Wound Healing.* J Wound Care, 2017. **26**(Sup5): p. S1-s43.