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Medical technology consultation: MT539 3C Patch System for treating diabetic foot ulcers

Supporting documentation – Committee papers

The enclosed documents were considered by the NICE medical technologies advisory committee (MTAC) when making their draft recommendations:

1. **EAC assessment report** – an independent report produced by an external assessment centre who have reviewed and critiqued the available evidence.
2. **EAC assessment report addendum –** an addendum to the assessment report produce by external assessment centre who have reviewed and critiqued the available evidence.
3. **Assessment report overview** – an overview produced by the NICE technical lead which highlights the key issues and uncertainties in the company's submission and assessment report.
4. **Scope of evaluation** – the framework for assessing the technology, taking into account how it works, its comparator(s), the relevant patient population(s), and its effect on clinical and system outcomes. The scope is based on the sponsor's case for adoption.
5. **Adoption scoping report** – produced by the adoption team at NICE to provide a summary of levers and barriers to adoption of the technology within the NHS in England.
6. **Sponsor submission of evidence** – the evidence submitted to NICE by the notifying company.
7. **Expert questionnaires** – expert commentary gathered by the NICE team on the technology.
8. **Patient questionnaires –** patient commentary gathered by the NICE team on the technology.
9. **EAC correspondence log** – a log of all correspondence between the external assessment centre (EAC) and the company and/or experts during the course of the development of the assessment report.

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

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

Assessment report: MT539 3C Patch

Document cover sheet

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Version number	Brief description of changes	Author/Reviewer (e.g. J. Smith)	Date (DD/MM/YY)	Date sent to NICE (if applicable)
V1.0	Baseline draft report to NICE	All	13/05/2021	13/05/2021
V2.0	Draft post NICE comments for QA	All	24/05/2021	
V3.0	Update for NICE comments and QA	All	26/05/2021	26/05/2021
V4.0	Update for fact check	R Malcolm, M Green and J Craig	3/6/2021	3/6/2021

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical Technologies Guidance

MT539 3C Patch System for Treating Diabetic Foot Ulcers

External Assessment Centre Report

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Contains confidential information	Yes
Number of attached appendices	6

Purpose of the assessment report

The purpose of this External Assessment Centre (EAC) report is to review and critically evaluate the company's clinical and economic evidence presented in the submission to support their case for adoption in the NHS. The report may also include additional analysis of the submitted evidence or new clinical and/or economic evidence. NICE has commissioned this work and provided the template for the report. The report forms part of the papers considered by the Medical Technologies Advisory Committee when it is making decisions about the guidance

Declared interests of the authors

Description of any declared interests with related companies, and the matter under consideration. Please refer to NICE's Policy on managing interests for board members and employees.

None

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- Prof Frances Game, Consultant Diabetologist and Director of R&D, Royal Derby Hospital, University Hospitals of Derby and Burton NHS FT. Non-financial professional: Chief Investigator and first author of the largest randomised controlled trial of this technology (Game et al. 2018; from 2012 until 2018).
- Elaine Ricci, Clinical Specialist, South Tyneside and Sunderland NHS Trust. No conflict of interest declared.
- David Russell, Associate Professor and Honorary Consultant Vascular Surgeon, University of Leeds. Non-financial professional: Local principal investigator for Leucopatch trial and named collaborator on trial publication (February 2016 to September 2018).
- Rachel Berrington, Senior Diabetes Nurse Specialist, University Hospitals of Leicester NHS Trust. Non-financial professional: she has given advise to the 3C Patch team about their pathway but she has not

received any payment for the work and it was purely from a clinical perspective her opinion of the process in the real world.
- Dr Paul Chadwick, Podiatrist, Salford Royal Infirmary, Salford Royal NHS Foundation Trust, Clinical Director Royal College of Podiatry, and Visiting Professor Birmingham City University. No conflict of interest declared.

Rider on responsibility for report

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

Contents

Abbreviations	
Term	**Definition**
AE	Adverse event
AHSN	Academic Health Science Network
BNF	British National Formulary
CDSR	Cochrane Database of Systematic Reviews
CMS	Centers for Medicare & Medicaid Services
CI	Confidence interval
CPCI-S	Conference Proceedings Citation Index-Science
CRN	Clinical Research Network
DFU	Diabetic foot ulcer
DHSC	Department of Health & Social Care
DFSG	Diabetic Foot Study Group
DSA	Deterministic sensitivity analysis
EAC	External Assessment Centre
EQ-5D	EuroQol 5 dimensions
EWMA	European Wound Management Association
FDA	Food and Drug Administration
FDAMA	Food and Drug Administration Modernization Act
Hb	Haemoglobin
HbA1c	Glycated haemoglobin
HPV	Human papillomavirus
HRG	Healthcare Resource Group
HRQoL	Health related quality of life
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
ICTRP	International Clinical Trials Registry Portal
IFU	Instructions for use
IQR	Interquartile range
ISDF	International Symposium on the Diabetic Foot
ITT	Intention-to-treat
IWGDF	International Working Group on the Diabetic Foot
MAUDE	Manufacturer and User Facility Device Experience
MDFT	Multidisciplinary specialist diabetes foot clinic
MHRA	Medicines & Healthcare products Regulatory Agency
mmHg	millimetres of mercury
NA	Not applicable
NDFA	National Diabetes Footcare Audit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NR	Not reported
NRES	National Research Ethics Service

NWCSP	National Wound Care Strategy Programme
OR	Odds ratio
PICO	Population, intervention, comparator, outcomes
PP	Per protocol
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
RCT	Randomised Controlled Trial
RES	Research Ethics Service
RNS	Regulatory News Service
SAE	Severe adverse event
SD	Standard deviation
SE	Standard error
TcPO2	Transcutaneous oxygen pressure
TTO	Time trade off
UK	United Kingdom
VAS	Visual Analogue Scale
Vs	Versus

Executive Summary

The company identified 6 clinical studies (5 published and 1 unpublished) reported in 4 papers and 2 abstracts. One abstract (Hogh et al. 2019) was excluded because no outcomes were reported for people with diabetes. The unpublished study, (Zink et al. 2021), described a German clinical pathway was also excluded. The EAC did not identify any further evidence. All 4 studies met the evaluation scope in the Decision Problem.

The pivotal study was a multicentre, international, randomised controlled trial (RCT) by Game et al. (2018a) of people with diabetes and hard-to-heal foot ulcers. Patients (n=269) were randomised to standard care or standard care plus adjunctive treatment with 3C Patch for 20 weeks or complete healing. At 20 week follow-up, 34% of ulcers were healed in the 3C Patch group versus 22% in standard care (p=0.0235). Time to healing was shorter with 3C Patch compared with standard care (p=0.025).

Two pilot studies (Löndahl et al. 2015 and Jørgensen et al. 2011) reported that 3C Patch was effective to treat hard-to-heal ulcers, including some of a long duration.

The EAC judged that the RCT, which was funded by the company, was subject to a low risk of bias and the comparative benefits were mainly attributable to the 3C Patch System.

Evidence is insufficient to support the other claimed benefits (for example, reduced infections, amputations, resource use, improved quality of life). However, the RCT was not powered to detect differences in these parameters.

The main concerns relate to the generalisability of the results to clinical practice. These relate to differences in:

- Eligible populations: NHS services are expected to use UrgoStart before 3C Patch; 1% of patients in the control arm of Game et al. (2018a) used this dressing for at least 1 week. Inclusion criteria in this RCT were more restrictive than the indicated population described in the Instructions for Use (IFU). The latter is more consistent with expected clinical practice.

- NHS clinicians will review healing progress after 4 to 6 weeks of using 3C Patch and regularly thereafter, and decide whether the patch is improving healing rates relative to standard care. This will be more flexible than the rule proposed in the company's clinical pathway and

used in its economic model but will still result in some discontinuations, unlike in all the clinical studies.

There are no published economic evaluations of 3C Patch. The company submitted a cost analysis, using a Markov model, comparing 3C Patch with standard care in people with hard-to-heal DFUs. Following advice from experts that people with moderate to severe infections would not receive a 3C Patch until the infection had resolved, the EAC incorporated a separate infection health state into the model.

The company derived efficacy data from an unplanned, post hoc analysis of patient level data from Game et al. (2018a). It included weekly healing rates obtained from 42% of patients who had a 50% or greater improvement in ulcer area at 5 weeks. The remaining 58% of the 3C Patch cohort were assumed to move on to standard care, with a weekly healing rate of about half the rate reported for patients in standard care in the RCT (0.7% versus 1.5%).

The EAC disagreed with the company on the discontinuation rates and the related healing rates in the 3C Patch arm. It adopted the healing rates observed in the RCT for both arms. The EAC also changed various cost parameters, particularly for inpatient and outpatient costs

The company's model results showed that over 2 years, 3C Patch was cost saving compared with standard care (saving £191 per patient). Probabilistic sensitivity analysis (PSA) reported similar values. After applying the EAC's updated clinical and cost parameters, 3C Patch was cost increasing (higher cost of around £1,600 to £2,000 per patient). Changes to the unit costs accounted for about £800 of the these, with a further cost increase of about £370 arising from the different discontinuation and healing rates. The PSA estimated that there was a 31% probability that 3C Patch was cost saving. However, the results were clustered around the intersection of the axes, indicating there is a lot of uncertainty in the model.

These uncertainties with the economic model mirror the uncertainties with the clinical evidence. These relate to which patients will continue with the 3C Patch after 5 weeks and their subsequent probability of healing. Neither the results from the trial, nor the post hoc analysis provide values which can inform an economic model of the expected impact of 3CP on clinical practice. The impact of the uncertainty is shown in a two-way analysis of healing rates and discontinuation rates. These suggest that, if clinicians continue with 3C Patch when weekly healing rates are under 4.5%, then 3C Patch will be cost increasing. This is thrice the rate observed with standard care (1.5%). Some clinicians have indicated they will continue with 3C Patch if *any* improvement on standard care rates is observed.

The results of the EAC's analyses, particularly its PSA, suggest that there is considerable uncertainty around the economic case and, therefore, the economic analysis does not support the case for adopting 3C Patch.

1 Decision problem

The EAC has completed Table 1.1 to critique the company's definition of the decision problem.

Table 1.1: Critique of the decision problem

Decision problem	Scope	Proposed variation in company submission	EAC comment
Population	People with diabetic foot ulcers (DFUs) that are not healing despite standard wound care	People with DFUs that are not healing despite standard wound care including the use of advanced dressings where appropriate.	Variation is reasonable as the patient population with hard-to-heal ulcers could have an advanced dressing in the pathway prior to using 3C Patch. The company submission stated that 85% of patients had an advanced dressing in the run-in period in the Game et al. (2018a) RCT. The clinical experts stated that the dressings used in the 4-week run-in period were not particularly advanced (most were iodine or foam, and none were UrgoStart [an advanced dressing with proven efficacy]) (EAC correspondence log 2021). The EAC notes that about 1% of patients in the control arm of Game et al. (2018a) used this dressing for at least 1 week. The experts confirmed that UrgoStart was not part of standard care when recruitment for the Game et al. (2018a) RCT was undertaken. The company defined hard-to-heal ulcers as those with less than 50% progress towards healing during a 4-week run-in period in which best standard of care is provided.

Decision problem	Scope	Proposed variation in company submission	EAC comment
			The experts advised that in clinical practice there would be no equivalent to the 4-week run in and they would not apply a 50% rule on change in ulcer size from baseline to determine which patients might benefit from a 3C Patch. Rather, the clinician would be able to tell from the patient's history that their wound had not progressed with previous treatment.
Intervention	3C Patch as an adjunctive treatment in addition to standard of care	None	The clinical studies used 3C Patch with standard care and the experts advised this is how it would be used in practice (EAC correspondence log 2021). The EAC notes that the 3C Patch was known as "Leucopatch" prior to 2017 (the patch was prepared using a manual procedure and standard laboratory centrifuge). In 2017, the LeucoPatch System was launched (including the same intervention but with a fully automated centrifuge added to the system). The name of the device was changed to the 3C Patch System in 2020.
Comparator(s)	Standard conventional and advanced wound dressings for DFUs, including UrgoStart. Standard care is likely to vary depending on the characteristics of the wound (size, depth, and position) and stage of healing.	None	The EAC notes that "standard wound care" is variable across locations and that there is limited evidence for "advanced dressings". However, standard care treatment according to the NICE clinical guideline (NG19, 2015a) has several components including: • offloading • control of foot infection • control of ischaemia (for example, surgery to bypass blocked blood vessels to restore blood circulation to the affected area) • wound debridement

Decision problem	Scope	Proposed variation in company submission	EAC comment
			• wound dressings. No specific dressings are recommended. Rather the guideline advises use of devices and dressings with 'the lowest acquisition cost appropriate to the clinical circumstances.' The experts agreed that the components outlined above are the core components of standard care, with or without advanced dressings such as UrgoStart (EAC correspondence log 2021). The EAC notes that the inclusion of UrgoStart as a comparator in the scope does not align with anticipated clinical practice. The experts positioned 3C Patch as a treatment option for those in whom other advanced dressings (including UrgoStart) have failed. They stated that UrgoStart would be used before 3C Patch in patients with hard-to-heal ulcers, being easier to use (EAC correspondence log 2021). It is also much cheaper (£[redacted] per dressing versus £150 per 3C Patch. The Game et al. (2017) RCT protocol stated that the comparator was: Usual wound care provided in a multidisciplinary foot care clinic, in accordance with international guidelines. The company advised that patients failing on 3C Patch would still be treated and the ulcer dressed. The mix of components may however change after failing 3C Patch (EAC correspondence log 2021).

Decision problem	Scope	Proposed variation in company submission	EAC comment
Outcomes	The outcome measures to consider include: • measures of treatment effectiveness and wound healing, for example: o proportion of people with complete epithelialisation or healing o time to complete epithelialisation or healing o change in ulcer area • complications related to non-healing wounds, for example: o incidence of wound-related complications (including new infection) o number of new amputations o pain at ulcer location o frequency and amounts of antibiotic or pain medication requirements • device-related AEs • patient-reported outcomes, for example: o patient tolerance and acceptability o health related quality of life	None	Game et al. (2018a) reported on complete would healing, time to complete healing, infection rates, days on antibiotics, pain, amputations, revascularisation and AEs. The company submission reported mean treatment duration (17.1 weeks) and mean number of patches per patient (14.3). The clinical experts advised that time to complete healing is the most important outcome. It is associated with fewer clinic visits and dressing changes, a lower risk of infection and amputation, and it reduces the loss in quality of life (EAC correspondence log 2021). The RCT defined complete healing as complete epithelialisation without that is maintained for 4 weeks. This is consistent with clinical practice. The experts noted standard care can be effective if used consistently but that many patients struggle with adherence to effective interventions such as offloading (EAC correspondence log 2021). Some outcomes have not been evidenced in the company's clinical evidence submission including patient tolerance and acceptability, and demand for NHS foot care resources.

Decision problem	Scope	Proposed variation in company submission	EAC comment
	• measures of resource use of total number of 3C Patch treatments needed o frequency and total number of secondary dressing changes o demand for NHS DFU care – outpatient, community, primary care and inpatient care		Limited evidence on quality of life was provided from Game et al. (2018a) for a subset of patients who were ulcer free at 20 weeks (n=20).
Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be long enough to reflect differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.	None	The cost analysis submitted by the company matches the cost analysis specified in the final scope. The time horizon is appropriate to capture the costs and consequences of the technology compared with the specified comparator.
Subgroups	None identified.	None	NA
Abbreviations: AE – adverse event; DFU – diabetic foot ulcer; EAC – External Assessment Centre; NA – not applicable; NHS – National Health service; NICE – National Institute for Health and Care Excellence; RCT – randomised controlled trial			

2 Overview of the technology

As described in section 2 of the company submission, 3C Patch is a single-use autologous biological patch made on site from a patient's blood sample which is used to treat foot ulcers in people with diabetes. The IFU states that the 3C Patch System used to produce the 3C Patch consists of a 3C Patch kit, 3CP counterbalance, 3CP centrifuge and 4 centrifuge cups. The 3C Patch kit is individually packed and comprises 1 3C Patch device, 1 3C Patch needle holder, 1 winged blood collection set (G_{21}) with protector, 1 alcohol swab, 1 post-sampling adhesive bandage, 1 primary wound cover dressing (Tricotex), and 1 ruler with adhesive. These kit components are for single use only. The 3CP counterbalance is a non-sterile accessory component used with the 3CP table-top centrifuge. The company supplies the 3CP centrifuges on loan to the NHS as part of the 3C Patch System (EAC correspondence log 2021).

To produce a 3C Patch, an 18 ml blood sample is drawn directly into the 3C Patch device, a specialised blood collection and processing tube. This device is placed into the 3CP centrifuge and spun for 20 minutes resulting in a layered matrix of fibrin, leukocytes and platelets which form the 3C Patch. The IFU states that 3C Patch processing should commence within 5 minutes following blood collection, and if drawing blood takes longer than this, poor patch preparation could result. The disc-shaped patch is applied directly on the wound leukocyte-side down and is covered with a primary non-adhesive dressing (supplied in the 3C Patch kit). The IFU states that the primary dressing must be fixed with tape to keep in place, with an appropriate secondary dressing usually required to control wound exudate. The 3C Patch should be applied to the wound within 60 minutes of preparation (IFU).

The number of patches required can be estimated from the wound area, with wounds of areas between 5 cm^2 and 10 cm^2 requiring 2 3C Patches, those between 10 cm^2 and 15 cm^2 requiring 3 patches, and those between 15 cm^2 and 20 cm^2 requiring 4 patches (IFU). The clinical experts were asked to comment on the proportion of patients in clinical practice who might have a large ulcer requiring more than 1 dressing (EAC correspondence log 2021). The answers given varied from very few patients to 15% of patients. One expert noted that most of the ulcers are less than 1 cm^2 (EAC correspondence log 2021). Another expert advised that it is unusual to get DFUs of this size. This expert also noted that surgical wounds may be this size, but these have often reduced to below this size before becoming static (EAC correspondence log 2021). The EAC notes the RCT did not include DFUs above 10 cm^2 (2 patches). There is also some uncertainty regarding the logistics of treating such large ulcers in practice (such as the ability to draw

blood to fill 4 3C Patch devices, additional appointment time, and other logistical aspects).

The company submission described that treatment with the patch lasts 7 days with any remaining patch material that has not integrated or been absorbed into the wound or primary dressing removed after this. Following this, the treatment can be repeated. The company recommends initial treatment with the patch for between 4 and 6 weeks with treatment continuing for patients who demonstrate improvement (see section 3).

The IFU states that 3C Patch is used weekly. The EAC notes that no information is provided in the IFU regarding the maximum number of treatment weeks for which 3C Patch can be continued.

The company submission described that the 3C Patch acts as a concentrated form of cells, growth factor and signalling molecules which actively promotes wound healing. Innovative aspects also include that no additional reagents are used and that the 3CP centrifuge uses a fully automated programme to create the patch. The IFU states that the 3CP centrifuge includes optical sensors that allow for complete automation of the procedure. These sensors detect coagulation by measuring the light transmission through the 3C Patch device with transmission decreasing as the fibrin is polymerised (IFU).

3C Patch Device was classified as a CE marked Class IIa medical device under the Medical Device Directive on the 20 December 2019 and is valid until 27 May 2024. The 3CP centrifuge was certified to conform with 2014/35/EU electrical equipment on the 28 December 2020. Both certificates were included in the company submission.

The company outlined previous versions of the device in the submission. Leucopatch was launched in 2011 as the first device which involved a manual procedure using a third-party centrifuge. In 2013, LeucoPatch was launched with a new device lid design. The company submission stated that the outcome was identical to the first Leucopatch device. The LeucoPatch System was launched in 2017 including the same device but with a fully automated centrifuge added to the system. The name of the System was changed to the 3C Patch System in 2020 (identical to the LeucoPatch System).

The company submission stated that although the 3C Patch System includes an automated procedure with the 3CP centrifuge, most of the clinical studies have been conducted using a manual procedure to develop the 3C Patch. The company confirmed that the automated procedure is being used throughout the NHS and will continue to be used in the future (EAC correspondence log 2021).

The company confirmed that the automated procedure produces the same outcomes as the manual procedure but does not require any manual checking for coagulation (EAC correspondence log 2021). It provided the EAC with its internal technical report [redacted]) which concluded that [redacted] Hence, the evidence generated using the earlier Eppendorf 5702 Centrifuge is assumed to generalise to the current system.

The EAC notes that the company submission referred to the US version of the IFU. The EAC has referred to the current UK version of the IFU throughout this report. The EAC confirms that there are differences between these IFU documents.

The EAC notes that contraindications are absent in the UK IFU. Rather, the IFU states that 3C Patch has not been tested on:

- actively infected wounds
- malignant wounds
- patients with sepsis
- patients with haemophilia, sickle cell anaemia, thrombocytopenia, leukaemia, or other blood dyscrasia
- patients being treated for malignant or neoplastic diseases or collagen vascular diseases.

The IFU also states that:

- Manufacturing the 3C Patch may increase risks of decompensation in patients with the following conditions and disorders: patients receiving blood thinning medication or patients under treatment for malignant diseases or connective tissue diseases; moderate to severe cardiovascular and pulmonary disorders; haematological or lymphoproliferative disorder; systemic infection; moderate to severe malnourishment; immunocompromised conditions; liver and renal failure; active GI bleeding or patients on dialysis.
- Osteomyelitis is a common complication of DFUs. Rule out osteomyelitis prior to treatment with the 3C Patch. Discontinue the 3C

Patch and treat osteomyelitis if it is diagnosed during management of the wound.
- Patients must be able to donate the required amount of blood.

The company confirmed that use of 3C Patch is not contraindicated for actively infected wounds. However, the company also stated that because 3C Patch has not been widely tested on actively infected wounds, clinical judgement is needed when deciding whether to use 3C Patch in the presence of infection (EAC correspondence log 2021). The company noted that it is possible to continue treatment with 3C Patch if a mild diabetic foot infection develops during treatment and the clinician feels the treatment is under control (EAC correspondence log 2021). However, if the wound shows signs of a moderate/severe infection prior to starting 3C Patch treatment, the company recommends treating the infection first (EAC correspondence log 2021). If a moderate/severe infection occurs during treatment, the company recommends prioritising this before continuing treatment with 3C Patch (EAC correspondence log 2021).

In the RCT, treatment with 3C Patch was continued for patients contracting new infections. The EAC asked the clinical experts if they would continue treatment with 3C Patch when a DFU became infected while using the patch. Four experts advised that they would discontinue treatment until the infection has cleared. One expert stated they would continue with treatment, another expert would continue unless the patient was going for surgery on the area, with the final expert advising they would discontinue treatment if the infection was moderate or severe but might continue with 3C Patch if the infection was mild (EAC correspondence log 2021).

The EAC also asked the experts about how they would define an active infection. One expert advised that an active infection is one requiring systemic antibiotics. A second advised that there would be redness/inflammation or purulence around the ulcer. A final expert advised that typical signs of wound infection include increased purulent drainage, increased heat, increased swelling, increasing redness, and loss of function. This expert also noted that the wound would be checked for new onset of discolouration to the wound bed, increasing wound size, friable breakdown, tunnelling, increased exudate and increasing odour (EAC correspondence log 2021).

The company stated that actively infected refers to a wound showing clear signs of acute severe infection (EAC correspondence log 2021).

The IFU states the 3C Patch System is intended to be used as wound management for recalcitrant wounds in conjunction with standard of care procedures tailored to the specific cause of the wounds (such as diabetic,

venous, surgical). However, the scope of this assessment is limited to wound care for DFUs.

3 Clinical context

A description of the clinical context and proposed pathway for treating hard-to-heal diabetic foot ulcers (DFUs) with 3C Patch is provided in section 3 of the company submission. This identified the NICE (2015a) guideline on diabetic foot problems: prevention and management (NG19) as the relevant pathway and that the NICE recommendation on UrgoStart (UrgoStart for treating diabetic foot ulcers and leg ulcers) is also relevant. The submission advised that the International Working Group on the Diabetic Foot (IWGDF) Guideline on interventions to enhance healing of foot ulcers in persons with diabetes (Rayman et al. 2020) recommends considering autologous combined leucocyte, platelet and fibrin patch (3C Patch) for use in non-infected DFUs that are difficult to heal. The company also submitted [redacted] (Zink et al. 2021).

The EAC agrees the most relevant pathway is the 2015 NICE Guideline (NG19, 2015a). This recommends that people with DFUs should be offered one or more of the following as standard care:

- offloading (interventions to reduce the amount of weight placed on the foot)
- control of foot infection
- control of ischaemia (for example, surgery to bypass the blocked blood vessels to restore blood circulation to the affected area)
- wound debridement (removal of dead or infected tissue or foreign objects from the wound)
- wound dressings.

The NG19 guideline also states that:

- People with diabetic foot problems should be managed by a foot protection service, with people with problems being referred to a multidisciplinary foot care service.
- The clinical assessment of the wound and the person's preference should be considered when deciding about wound dressings and offloading for treating DFUs, and devices and dressings with the lowest acquisition cost appropriate to the clinical circumstances should be used (recommendation 1.5.10).
- The overall health of the person with diabetes, how healing has progressed, and any deterioration should be considered when deciding

the frequency of follow-up as part of the treatment plan (recommendation 1.5.13).

The guideline development group felt it was inappropriate to recommend specific types of dressing.

Other relevant NICE documents include:

- The 2019 medical technologies guidance on UrgoStart for treating diabetic foot ulcers and leg ulcers (MTG42) which recommends that UrgoStart should be considered for treatment in patients with non-infected diabetic foot ulcers or venous leg ulcers.
- The 2015 advice on wound care products (KTT14).
- The 2016 evidence summary on chronic wounds: advanced wound dressings and antimicrobial dressings (ESMPB2).
- The 2020 advice on NATROX oxygen wound therapy for managing diabetic foot ulcers and complex or chronic non-healing wounds (MIB208), a portable oxygen delivery device for managing chronic, non-healing and complex wounds, including diabetic foot ulcers.
- The 2016 advice on Woundchek Protease Status for assessing elevated protease status in chronic wounds (MIB83), a point-of-care diagnostic test to assess protease activity in chronic wounds.

The EAC notes the IWGDF recommendation supporting the use of the 3C Patch. The EAC asked the experts whether a clinical pathway developed by clinicians in Germany would be relevant to the decision problem in the UK. The experts advised they could not comment on this without seeing the document, noting that there are differences in the healthcare system in Germany (for example more private medicine, insurance claims, and no podiatry; EAC correspondence log 2021).

The EAC also notes that the National Wound Care Strategy Programme (NWCSP) (AHSN Network 2019) commissioned by NHS England has issued recommendations for the care of lower limb ulcers (National Wound Care Strategy Programme 2020) and surgical wounds (National Wound Care Strategy Programme 2021). The lower limb recommendations include those for both leg ulcers and foot ulcers. For DFUs, the NWCSP states that care should be provided as recommended by NICE (NG19, 2015a).

Disease context

Foot problems are common in people with diabetes and can be caused by diabetic neuropathy, peripheral arterial disease, insufficiently well controlled diabetes, poor fitting footwear and walking barefoot (NICE 2015a; Diabetes UK, 2019). It is estimated that 10% of people with diabetes will experience a

DFU at some point in their lives (Diabetes.co.uk 2019). DFUs are associated with long healing durations, a high risk of amputation, and increased mortality (Jeffcoate et al. 2018). DFUs are often hard-to-heal and can become complicated by infection (McIntosh et al. 2019). One study reported that 35% of DFUs healed within 12 months (with an average healing rate of 4.4 months), 48% remained unhealed, and 17% resulted in amputation (Guest et al. 2018). For people with DFUs, optimal wound management is vital to facilitate wound healing and minimise the risk of further complications.

Advanced wound dressings

The company provided an analysis of the advanced and microbial dressings used in the run-in period and in the control arm of the RCT. Protease modulating dressings were classified using BNF categories and the Journal of Wound Care classification system which differ. The analysis reported that 85% of patients received at least one week of treatment in the run-in period with any advanced or antimicrobial dressing, rising to 94% in the control arm of the RCT (EAC correspondence log 2021). The experts noted that, from their perspectives, many of the dressings classified as 'advanced' were not 'advanced' and none were UrgoStart but agreed their use was unlikely to have influenced outcomes (EAC correspondence log 2021).

Proposed pathway

The company defined hard-to-heal ulcers as those with less than 50% progress towards healing during a 4-week run-in period in which best standard of care, as recommended by NICE (NG19, 2015a), has failed to promote ulcer healing. The proposed pathway is presented in appendix F.

The company's pathway stated that treatment with best standard of care should be tried for at least 6 weeks. If the ulcer area has not reduced by 50% or more over a 4-week period (that is the DFU is hard-to-heal), the clinician should consider using 3C Patch.

The company noted that 3C Patch should be used alongside other elements of best standard of care as recommended by NICE (NG19, 2015a) during these 4 to 6 weeks. The company confirmed that 3C Patch is not used in combination with any other advanced dressings (EAC correspondence log 2021).

After 4 to 6 weeks of treatment with 3C Patch, the clinician should review if adequate progress in healing has occurred over the period, for example by measuring if there has been a reduction of 50% or more in ulcer area (Company pathway and EAC correspondence log 2021).

If adequate progress in healing has not occurred, for example a reduction in ulcer area of 50% or more has not been achieved since the baseline measure from about 6 weeks ago, the pathway states that treatment should be discontinued and that other treatment options should be considered.

The company noted that best standard of care as recommended by NICE, including advanced dressings where appropriate, would continue when 3C Patch is discontinued until healing is achieved, or the patient has an amputation or dies (EAC correspondence log 2021).

If adequate progress has occurred since baseline, then clinicians should judge:

a) Is healing likely to be achieved without further use of the 3C Patch? If yes, stop using the Patch
b) Is continuing the 3C Patch necessary to achieve healing? If yes, continue using the Patch.

Thereafter, the clinician should continue to monitor and review progress towards healing and should stop using 3C Patch based on when they judge:

- healing is likely without further use of the 3C Patch
- healing has stalled and other treatment options should be considered

In cases where good progress has been made and treatment with 3C Patch stopped, if healing stalls then the clinician should consider resuming treatment with the patch.

Comments on the proposed pathway

The clinical experts agreed with the proposed overall structure of the clinical pathway and the positioning of 3C Patch as a treatment option when other advanced dressings had failed. They added these seemed reasonable according to NICE and other international guidelines (EAC correspondence log 2021). The experts said that the treatment options recommended in the NICE clinical guideline (NG19, 2015a) represent the core components of standard care, with or without advanced dressings such as UrgoStart (EAC correspondence log 2021). They also endorsed the need for careful monitoring, judgement of the wound and progress at every stage during 3C Patch treatment.

When asked about the company's eligible population, defined using the 50% change in area rule over a 4-week period, the clinical experts advised that there would be no equivalent to either a 4-week run-in period, or a requirement to fail to achieve a 50% or more reduction in wound size over

these weeks. Rather, the clinician would be able to tell from the patient's history that healing of their wound had not progressed with previous treatment (EAC correspondence log 2021).

The clinical experts explained that measuring a '50% reduction in ulcer area', as used by the company to define hard-to-heal DFUs and measure adequate progress to support continuing with the 3C Patch, could be difficult and would require specialist equipment to measure the wound accurately. The experts also raised other issues about adopting the 50% decision rule in clinical practice including that:

- The 50% threshold may be too high and any improvement/progression (for example, a 30% reduction in ulcer area) with the 3C Patch could be beneficial in this population and could warrant continuation with the patch provided a greater improvement was seen with the patch compared with previous treatments.
- The 50% threshold could be 'too hard and fast' and that a patient orientated approach could be used as some patients respond better to treatment than others. One expert stated that each wound and patient is different, and the circumstances of individuals need to be taken into consideration.
- From a patient perspective, it might be difficult to stop using the 3C Patch if there was some improvement in ulcer healing (but not reaching the 50% threshold).
- The patient's willingness to continue treatment, including providing blood weekly, will also inform the clinical judgement.
- Reduction in ulcer area is not the best measure of healing, rather the reduction in volume/depth of the ulcer should also be considered.

One of the experts also suggested that this 50% threshold may have been led by the evidence. The Game et al. (2018a) trial excluded patients from randomisation if a reduction in ulcer area of more than 50% was observed during the 4-week run-in period.

As detailed in the EAC correspondence log (2021), 2 experts advised that they would only discontinue 3C Patch treatment if the healing trajectory was no better than prior to using this intervention. One expert noted that even if there was only a small reduction in ulcer size over a 5-week period with 3C Patch, they would continue treatment. The other expert also stated that absolute wound healing is predicted on a 4-week (not 5-week) wound area reduction. Another expert advised that treatment would be evaluated on an ongoing basis and, if 3C Patch was having no effect at week 4, then the treatment plan for the DFU would be reviewed. This expert also stated that treatment with 3C Patch would continue until the wound reached a point

where 3C Patch was having no therapeutic effect when evaluated over a 2-week period. One expert advised that in their clinics, a 50% reduction in ulcer area at 4 weeks is used as a standard measure of efficacy for all interventions. Another expert noted that the 50% threshold seemed reasonable, but some clinical judgement needed to be used alongside this threshold. This expert suggested that if there was a 48% reduction in ulcer area, they would continue with 3C Patch treatment. Another expert advised that they would also consider pain reduction, patient perception, and compliance alongside reduction in ulcer size. Finally, one expert advised that they would be guided by the manufacturer as to the expected response to treatment and noted that the guidance on the manufacturer's website states to stop or pause treatment at 6 weeks "if there is no effect". This expert also suggested that whilst 50% wound healing at 4 weeks is a good predictor of wounds that go on to heal in a timely fashion with a low incidence of complications, this is an ambitious target for a change in wound biology with the dressing to occur.

The EAC concludes that the experts have a different definition of the eligible population to the company. The experts use clinical judgement, informed by the patient's history and their presentation, to determine who might be suitable for 3C Patch. This is probably more consistent with the indicated population in the IFU, being those with recalcitrant wounds. However, as discussed in the next section, the evidence is for patients who meet the company's decision rule. Hence, there are issues of generalisability of the clinical evidence to the likely NHS eligible population.

The experts have advised that objectively measuring wound progress in hard-to-heal wounds is challenging. Moreover, other factors such as improvement in granulation tissue formation, reduction in the depth, and changes in the edges and margins are all likely to influence decision making, together with patient preferences. Therefore, once 3C Patch treatment has commenced, a single rule such as a 50% reduction in ulcer area is unlikely to be workable in practice. The company has applied this rule in its economic model, although it was not adopted in the clinical studies. Hence, there are there are further issues of generalisability of the economic evidence to the likely NHS eligible population.

The EAC has summarised key differences between the IFU, proposed company pathway and clinical experts' advice in Table 3.1.

Table 3.1: Comparison between the IFU, company pathway, and clinical experts' advice

	IFU	Company pathway and consistency with evidence	Clinical experts' advice
Population eligible for 3C Patch	3C Patch is intended to be used as wound management for recalcitrant wounds in conjunction with standard of care procedures tailored to the specific cause of the wounds (such as diabetic, venous, surgical).	3C Patch should only be considered for hard-to-heal ulcers, defined as those in which ulcer area has not reduced by 50% or more over a 4-week run-in period with best standard of care. Consistent with clinical evidence.	The clinical experts advised that: • There would be no equivalent to the 4-week run-in period; rather the clinician would be able to tell from the patient's history that healing of their wound had not progressed with previous treatment. • Accurately measuring a '50% reduction in ulcer area' is difficult in practice. • Reduction in ulcer area is not the best measure of healing, rather the reduction in volume/depth of the ulcer, alongside other factors should also be considered.
When to review use of 3C Patch	3C Patch is applied weekly. It should be used in conjunction with standard of care procedures tailored to the specific cause of the wounds (such as diabetic, venous, surgical). No detail is provided regarding the maximum number of treatment weeks for which 3C Patch can be continued. No detail is provided regarding when ulcer healing should be	3C Patch should be used alongside other elements of best standard of care as recommended by NICE (NG19, 2015a) for 4 to 6 weeks. After 4 to 6 weeks of treatment with 3C Patch, the clinician should review if adequate progress in healing has occurred over the period, for example by measuring if there has been a reduction of 50% or more in ulcer area.	The clinical experts advised that: • Accurately measuring a '50% reduction in ulcer area' is difficult in practice. • Reduction in ulcer area is not the best measure of healing, rather the reduction in volume/depth of the ulcer should also be considered. One expert advised their clinic uses a 50% reduction in ulcer area at 4 weeks as a standard measure of efficacy for all interventions. A second thought that the rule was reasonable but should be interpreted flexibly with some clinical judgement.

	IFU	Company pathway and consistency with evidence	Clinical experts' advice
	reviewed, how this should be assessed, or when 3C Patch treatment should be discontinued. Note the Company submission describes the USA IFU not the UK IFU.	Not consistent with RCT clinical evidence but adopted in economic model.	The 4 other experts advised they would continue with 3C Patch if it was having a therapeutic effect compared with healing rate before starting 3C Patch. One expert noted that they would assess ulcer healing at week 5; 2 experts would assess ulcer healing at week 4. One expert would also consider pain reduction, patient perception, and compliance alongside reduction in ulcer size. Another expert stated that each wound and patient is different and that individual circumstances need to be taken into consideration. One expert advised that whilst 50% wound healing at 4 weeks is a good predictor of wounds that go on to heal in a timely fashion with a low incidence of complications, this is an ambitious target for a change in wound biology with the dressing to occur.
Abbreviations: IFU – Instructions for Use; NICE – National Institute for Health and Care Excellence; RCT – randomised controlled trial.			

The EAC notes [redacted](Zink et al. 2021)[redacted]

The clinical experts confirmed that UrgoStart would be used before 3C Patch in patients with hard-to-heal ulcers, being easier to use than 3C Patch, with 3C Patch only used if the ulcer was not healing using UrgoStart (EAC correspondence log 2021). The EAC agrees with this view.

The experts also noted that clinical practice varies between different centres and individual wounds, with some centres adopting weekly visits and others fortnightly visits or longer for patients with DFUs (EAC correspondence log 2021). One expert advised that due to the prevalence of DFUs in their service, it is only possible to see most patients every 3 to 4 weeks (EAC correspondence log 2021). Another expert noted that it would be rare for patients to attend weekly for the whole of their ulcer treatment (EAC correspondence log 2021). Two experts advised that visits every 2 weeks for 3C Patch would be preferable, with one of these experts suggesting that this is especially important for those that are failing to meet a healing trajectory (EAC correspondence log 2021).

Generally, the experts agreed that adopting weekly visits for 3C Patch should be possible for services (EAC correspondence log 2021). Two experts noted that the impact on services would be minimal given the low number of patients likely to be treated with 3C Patch at any one time (EAC correspondence log 2021). One expert suggested that weekly visits may be difficult for clinics initially, but if more DFUs healed quickly then this would release capacity in the long term (EAC correspondence log 2021). In contrast, one expert advised that moving to weekly visits would severely stretch the service. However, this expert also accepted that if patients heal more quickly than the number of active patients will reduce resulting in some improvement in capacity with time, depending on the overall increase in healing rates (EAC correspondence log 2021). None of the experts were aware of any services which have used 3C Patch but only offered an appointment once every 2 weeks (EAC correspondence log 2021).

Most experts agreed that the use of 3C Patch is likely to increase appointment time due to the need for phlebotomy and processing of the patch (EAC correspondence log 2021). One expert advised that drawing 18 ml of blood (or more for larger ulcers) into the device can be a slow process (EAC correspondence log 2021). Five experts agreed that the centrifuge element of making the 3C Patch takes around 20 minutes and that this may increase the nurse time per appointment by approximately 10 minutes (EAC correspondence log 2021). One of these experts suggested that this could be

longer depending how efficiently the nurse and podiatrist are working together and if it is difficult to draw blood from the patient (EAC correspondence log 2021). Another expert advised, that if patients are taking anticoagulation medication, the appointment will take longer and this needs to be considered (EAC correspondence log 2021). The EAC notes that this is also stated in the IFU. Finally, one expert advised that taking blood takes a minimum of 10 minutes to set up and perform, and whilst it is possible to do some standard care during this process, this will add additional time (EAC correspondence log 2021). This expert suggested that the process may take more than 40 minutes and suggested that additional time will be needed if the centrifuge is not kept in the treatment room (EAC correspondence log 2021).

One expert also suggested that the use of 3C Patch does not need to increase the appointment time if patient flow is well managed, and a second expert advised that although the use of 3C Patch is likely to increase appointment time in the short term, the process does become less time consuming with experience (EAC correspondence log 2021). This expert also noted that as this technology is not used on a high volume of patients, this does not create a lot of excess appointment time (EAC correspondence log 2021).

The NICE guidance recommends all people with hard-to-heal foot ulcers are managed by a multidisciplinary foot care service but does not define whether this service should be in primary or secondary care. Using 3C Patch would seem to require all patients to attend a secondary care setting to access the device and practitioners able to do venepuncture. Currently, many services do not have this skill set and would need to expand their interdisciplinary working.

The EAC notes that the company submission states that 3C Patch can be used once per week for up to 20 weeks at the discretion of the treating healthcare practitioner. The company's submission also states that initial treatment with 3C Patch is recommended for between 4 and 6 weeks, with treatment continuing for patients who demonstrate adequate improvement. The EAC asked the company representatives about this inconsistency. They stated that expert opinion indicated that, in routine practice, treatment with 3C Patch would not continue for 20 weeks or indeed the mean treatment period of 17.1 weeks observed in the pivotal study (Game et al. 2018a) (EAC correspondence log 2021). The EAC also confirms that the IFU does not specify the maximum number of treatment weeks for which 3C Patch can be continued. The company has advised that 3C Patch has been used in Germany, with an average of 6.4 treatments per patient (not weeks) in a normal clinical setting.

This gives rise to concerns about generalisability of the RCT to clinical practice.

The company provided a rationale for selecting 4 to 6 weeks to review healing progress based on the Game et al. (2018a) trial, where patients were treated with the 3C Patch for 20 weeks or until healing occurred. The company stated that most ulcers which healed by week 20 demonstrated a significant reduction in ulcer area by weeks 4 to 6, and that 78% of ulcers which healed by week 20 had a 50% reduction in ulcer area by week 5 (EAC correspondence log 2021). The company submission also stated that 61% of patients who met the 50% reduction in ulcer area at week 5 healed by week 20 compared with only 14% of those who had not reached the 50% threshold at week 5.

Special considerations, including issues related to equality

The Scope (NICE 2021) reported the following special considerations relating to equality: “3C Patch requires blood to be taken weekly and may not be suitable for people who are unable to provide blood samples, including people with trypanophobia (fear of needles). 3C Patch is intended for people with diabetes. In some cases, diabetes can be considered a disability. People of South Asian, African and African Caribbean family origin are more at risk of diabetes. However, there is no evidence that the prevalence of diabetic foot ulceration and amputation is higher in these subgroups than in the general population of people with diabetes in the UK. Disability and race are protected characteristics under the 2010 Equalities Act.”

No additional equality issues were identified in the company submission.

The EAC notes the experts advised it would be difficult to deliver 3C Patch in community settings due to the training and resource needs (for example, the process requires phlebotomy, a podiatrist to apply the patch and a centrifuge). The experts agreed that that this could present an inequitable service for housebound patients (EAC correspondence log 2021).

4 Clinical evidence selection

4.1 Evidence search strategy and study selection

Appendix A of the company submission contains a description of the search methodology used to retrieve relevant clinical evidence. The extent to which the EAC could assess the appropriateness of the search methodology was restricted due to lack of detail in the search reporting, though there appeared to be some limitations that could potentially impact on search sensitivity and the identification of relevant evidence. Details of the EAC critique of the company search strategy are provided in appendix A.

Due to the limitations in search reporting, the company's search methods were not reproducible. Being unable to replicate and re-run the searches conducted by the company, the EAC conducted a de novo literature search to identify evidence.

The EAC search was conducted in a range of resources containing details of published, unpublished and ongoing research. The EAC search retrieved 2,103 records. After deduplication 1,578 records remained for assessment. Full details of the EAC's de novo search methods are provided in appendix A.

The company's inclusion criteria specified Leucopatch, 3C Patch, DFU, and recalcitrant or hard-to-heal wounds. The company's exclusion criteria specified use of platelet-rich plasma products or non-3C Patch products.

The EAC's inclusion and exclusion criteria are shown in Table 4.1:

Table 4.1: EAC Inclusion and exclusion criteria

	Inclusion criteria	**Exclusion criteria**
Population	People with DFUs that are not healing despite standard wound care	Patients with other wound types (for example, malleoli ulcers) or not having received standard wound care
Intervention	3C Patch	None
Comparators	Standard conventional and advanced wound dressings for DFUs, including UrgoStart. Standard care is likely to vary depending on the characteristics of the wound (size, depth, and position) and stage of healing.	None
Outcomes	The outcome measures to consider include: • measures of treatment effectiveness and wound healing, for example: o proportion of people with complete epithelialisation or healing o time to complete epithelialisation or healing o change in ulcer area • complications related to non-healing wounds, for example: o incidence of wound-related	None

	Inclusion criteria	Exclusion criteria
	complications (including new infection) ○ number of new amputations ○ pain at ulcer location ○ frequency and amounts of antibiotic or pain medication requirements • device-related AEs • patient-reported outcomes, for example: ○ patient tolerance and acceptability ○ health related quality of life • measures of resource use ○ total number of 3C Patch treatments needed ○ frequency and total number of secondary dressing changes ○ o demand for NHS DFU care – outpatient, community, primary care and inpatient care	
Study design	RCTs of any size and duration. Prospective and retrospective non-randomised comparative studies will be eligible for inclusion if they report relevant clinical effectiveness or safety data for the relevant intervention and comparator. Non comparative or single arm studies will be eligible for inclusion if they report relevant clinical effectiveness or safety data for the relevant intervention and comparator. Systematic reviews will be included for reference checking purposes only.	News articles, non-systematic reviews, single case reports
Limits	Restricted to English language A date limit of 2009 was applied to the search	Studies published before 2009
Abbreviations: AE – adverse event; DFU – diabetic foot ulcer; NHS – National Health Service; RCT – randomised controlled trial		

4.2 Included and excluded studies

The Submission included 6 studies overall: 3 fully published studies (Game et al. 2018a, Löndahl et al. 2015, Jørgensen et al. 2011), one unpublished study (Zink et al. 2021), and 2 abstracts (Hogh et al. 2019 and Katzman et al. 2014).

The EAC's search and selection process included the same 3 fully published studies (Game et al. 2018a, Löndahl et al. 2015, Jørgensen et al. 2011) and the Katzman et al. (2014) abstract. The Hogh et al. (2019) abstract was excluded by the EAC. The intervention is Leucopatch, but the abstract describes a mixed population and outcomes were not reported separately for the patients with diabetes (n=4 out of 26 patients). The unpublished study was provided by the company. It did not meet the inclusion criteria but has been used to inform the proposed pathway (see Table 4.2).

Table 4.2: Studies included by the company and/or the EAC with reasons for disagreement

Study	Company inclusion	EAC inclusion	Reason for disagreement
Game et al. (2018a)	Yes	Yes	NA
Löndahl et al. (2015)	Yes	Yes	NA
Jørgensen et al. (2011)	Yes	Yes	NA
Zink et al. (2021)	Yes	No	[redacted]
Hogh et al. (2019)	Yes	No	Excluded; mixed population and outcomes were not reported separately for the patients with diabetes (n=4 out of 26 patients).
Katzman et al. (2014)	Yes	Yes	NA
Abbreviations: NA – not applicable; NR – not reported			

Four studies were therefore included by the EAC as relevant to the decision problem.

Multiple publications were found for these four included studies. Correspondence with the company confirmed the groupings of the papers into the four studies. The main and supplementary publications for each of the studies are:

Main paper: Game et al. (2018)

Supplementary publications:

- Game et al. (2017), (2018b) and (2018c), Nottingham University Hospitals NHS Trust (2014) and (2013), Löndahl et al. (2019) and (2017) and Löndahl and Lundquirst (2018).

Main paper: Löndahl et al. (2015)

Supplementary publications:

- Reapplix (2010), Löndahl et al. (2012a) and (2012b), Jørgensen et al. (2013) and (2011)

Main paper: Katzman et al. (2014)

Supplementary publications:

- Löndahl et al. (2013) and Fagher et al. (2015).

RCT

Game et al. 2018a; ISRCTN 27665670 and NCT02224742.

This observer-masked RCT compared 3C Patch (LeucoPatch) applied weekly in addition to standard care with standard care only in 269 adult patients who had diabetes (as defined by WHO criteria) complicated by one or more foot ulcers, and a baseline glycated haemoglobin (HbA1c) of no more than 12% (108 mmol/mol). All ulcers were hard-to-heal, meaning that the cross-sectional area decreased by less than 50%, and the cross-sectional area of the index ulcer was 50–1000 mm², at the end of the 4-week run-in period. Patients, randomised 1:1, were followed for 20 weeks during the intervention stage and subsequently for a 6-week observation period, in 32 centres with specialist diabetic foot clinics in the UK (22 centres), Denmark (7 centres) and Sweden (3 centres). New patches were applied on a weekly basis until healing or the end of the study. Patients receiving standard care also attended weekly for the 20 week intervention stage.

The primary outcome was the proportion of ulcers in the intention-to-treat (ITT) population that healed within 20 weeks after randomisation. There were no differences between the groups at baseline. A total of 132 patients were treated with 3C Patch and 137 with standard care. In the 3C Patch group, 45 (34%) of 132 ulcers healed within 20 weeks versus 29 (22%) of 134 ulcers in the standard care group (odds ratio (OR) 1.58, 95% confidence interval (CI) 1.04–2.40; p=0.0235) by ITT analysis. Time to healing was shorter in the 3C Patch group (p=0.0246) than in the standard care group. Adverse events (AEs) were not significantly different between the groups.

Case series

The first included case series (Löndahl et al. 2015) used 3C Patch (LeucoPatch) once a week for up to 19 treatments or until the target ulcer was completely epithelised. It included 44 adult patients with diabetes and non-ischaemic Wagner grade 1 or 2 DFUs with a duration of > 6 weeks and a maximal area of 10cm^2, with ≤ 40% change in ulcer area during the 2-week run-in period, treated at secondary or tertiary multidisciplinary diabetic foot clinics in Denmark or Sweden. The primary endpoint was healing within 20 weeks. Complete epithelisation was achieved in 15 (34%) of the 44 patients at 12 weeks and 23 (52%) at 20 weeks. None of the AEs during the study were judged to be related to the LeucoPatch treatment.

The second included case series (Jørgensen et al. 2011) was described as a pilot study; patients were treated weekly with Leucopatch for 6 weeks, or until healing was complete. It included adult patients attending a Danish outpatients centre, with chronic cutaneous ulcers on the lower extremities, chronic DFUs (grade I-II according to the Wagner scale) or amputation wounds, that had been present for at least 2 months and had failed to heal by conventional means (including n=5 patients with DFUs). The primary efficacy outcome was the proportional change in wound area during the 6-week treatment period. The percentage reduction in wound area was reported for 3 of the 5 patients (4.5%, 38.9% and 82.9% reductions, respectively); in the other 2 patients, wound areas were reported to be reduced to less than 20% of their initial size but the exact percentages were not reported. None of the 5 patients with diabetic ulcers were reported to have experienced AEs.

The third included case series (Katzman et al. 2014) reported that LeucoPatch was applied once weekly for up to 20 weeks among 17 patients with 21 non-ischaemic (TcPO2 ≥30 mmHg) DFUs with a duration of at least 6 weeks and a positive probing to bone test (Wagner grade 3 or more), treated at Lund, Sweden. Outcomes included healing with complete epithelialization. Details were sparse as this was reported only as an abstract, but 13/21 ulcers (61.9%) were reported to have healed. AEs were not reported.

Studies excluded by the EAC at full text are shown in appendix A.

Table 4.3 and Table 4.4 below shows details of the patient and wound characteristics and the methodology for each of the studies included in the EAC analysis.

Table 4.3: Patient and wound characteristics

	Denominator N	Mean (SD) or median (IQR) or range age (years)	Men n (%)	Mean (SD) or median (IQR) BMI	Type 1 diabetes n (%)	Smoking n (%)	Outpatients n (%)	Mean (SD) or median (IQR) or range wound duration (weeks or months)	Duration >6 months n (%)	Patients with healthy peri-wound skin	Ankle Brachial Pressure Index n (%)
Game et al. (2018)	266 in ITT population	61.9 (11.6)	217 (82)	NR	44 (17)	NR	266 (100)	NR	NR	NR	0.5–0.79: 30 (11%); 0.8–0.99: 53 (20%); 1.0–1.4: 138 (52%); >1·4: 45 (17%)
Löndahl et al. (2015)	44 in ITT population	Modified ITT: median 63 (IQR 58-73)	Modified ITT: 35 (79.5)	Modified ITT: 29.7 (IQR 25.6-32.5)	Modified ITT: 8 (18.2)	NR	44 (100)	Modified ITT: 35 (IQR 16-60; range 7-490) weeks	At baseline: 29(65.9)	NR	NR
Jørgensen et al. (2011)	5 at baseline	47-65	5 (100)	NR	NR	NR	5 (100)	3-72 months	3 (60.0)	NR	NR
Katzman et al. (2014)	17 patients and 21 ulcers	NR	NR	NR	NR	NR	17 (100)	Median 27 weeks	NR	NR	NR
Abbreviations: IQR – interquartile range; ITT – intention-to-treat; NR – not reported; SD – standard deviation											

Table 4.4: Studies selected by the EAC as the evidence base

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC Comments
Game et al. (2018) UK, Denmark, and Sweden http://dx.doi.org/10.1016/S2213-8587(18)30240-7 This trial is registered with the ISRCTN registry, number 27665670, and ClinicalTrials.gov, number NCT02224742.	Multinational RCT comparing 20 weeks of prespecified good standard care alone or care plus weekly application of 3C Patch (previously known as LeucoPatch), with subsequent 6-week observation period. Funding: Reapplix ApS. Published in full. ●	Patients aged 18 years and older. 269 randomised (137 to standard care and 132 to 3C). 100% of patients had diabetes. 217 (82%) men, 49 (18%) women. Mean (SD) age 61.9 (11.6) years. 134 participants in the standard care group (1 lost to follow-up, 1 withdrawal of consent and 1 randomised in error) and 132 in the 3C Patch group were included in the ITT population. 32 centres with specialist diabetic foot clinics in the UK, Denmark and Sweden. All ulcers were hard-to-heal, meaning that the cross-sectional area decreased by less than 50%, and the cross-sectional area of the index ulcer (usually largest or more clinically significant at screening for patients with >1 eligible ulcer) was 50–1000 mm², at the end of the 4-week run-in period. Ulcer duration not stated. Extensive exclusion criteria reported, including but not limited to: clinical infection or suspected	Primary: the proportion of ulcers that healed within 20 weeks (ITT population, that is, all participants with post-randomisation data collected), defined as complete epithelialisation without drainage (confirmed by a trained observer masked to randomisation group), and remained healed for 4 weeks. Secondary ulcer-related outcomes: time to healing, proportion of healed ulcers at 12 and 26 weeks, change in ulcer area at 4, 12, 16, 20, and 26 weeks (vs. week 0), assessed from digital images of acetate tracings, incidence of secondary infection, and number of days of systemic antibiotic therapy administered for infection of the foot ulcer during the 20 weeks after randomisation.	Meets scope Inclusion criteria more restrictive than in the IFU document. High quality RCT. Multi-centre study. The study was funded by the company and 2 investigators had also received research funding from them. The chief investigators had final responsibility for the decision to submit for publication.

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC Comments
		infection of the index ulcer; revascularisation or planned revascularisation in the 4 weeks prior to baseline visit; prior treatment (<8 weeks before) with growth factors, stem cells, or equivalent preparations or continued need for negative pressure wound therapy; Hb <105 g/L at screening; presence of haemophilia, sickle cell anaemia, leukaemia or blood dyscrasias, ongoing dialysis, participation in another study, or expected poor adherence. ●	Secondary patient-related outcomes: incidence of major (above ankle) amputation affecting the target limb by 12, 20, and 26 weeks, incidence of major amputation affecting the contralateral limb by 26 weeks, incidence of minor (below ankle) amputation affecting the target limb by 12, 20, and 26 weeks, incidence of minor amputation affecting the contralateral limb by 26 weeks, incidence of new anaemia (Hb concentration below 105 g/L [6.5 mmol/L]), and a decrease of more than 10% compared with baseline, quality of life measured using Short Form-12 and EuroQol 5-dimensions at baseline, week 12, and week 20, and pain measured by a visual analogue scale. ●	
Löndahl et al. (2015)	Prospective, multicentre open, case series of 3C Patch (LeucoPatch) once a	44 patients (older than 18 years) with non-ischaemic Wagner grade 1 or 2 DFUs with a duration of > 6	Ulcer healing at 20 weeks (primary endpoint) and 12	Meets scope

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC Comments
Secondary or tertiary multidisciplinary diabetic foot clinics in Denmark or Sweden. DOI: 10.12968/jowc.2015.24.4.172 This trial is registered with ClinicalTrials.gov, number NCT01454401.	week for up to 19 treatments or until the target ulcer was completely epithelised. This study was financed by Reapplix A/S. Time to data analysis and manuscript preparations have been financed by Medical Faculty Lund University, Lund Sweden. Published in full. ●	weeks and a maximal area of 10cm^2, with ≤40% change in ulcer area during the 2-week run-in period. 100% of patients had diabetes. Median (IQR) age 63 (58–73) years; 9 (20.5%) women. Median (IQR) ulcer duration 35 (16-60) weeks. Exclusion criteria for study participation were inability to tolerate venesection, Hb concentration below 6.5 mmol/l (105 g/l), HbA1c>12.0% (108 mmol/mol), platelet concentration below 100 x 109/l, ongoing dialysis, presence of haemophilia, sickle cell anaemia, leukaemia or blood dyscrasias, child-bearing potential without appropriate contraception, lactation, participation in another study, or expected poor adherence. Patients were also excluded if they had vascular reconstruction in the lower limbs within four weeks before the study. Secondary or tertiary multidisciplinary diabetic foot clinics in Denmark or Sweden. ●	weeks (secondary endpoint). Other secondary endpoints: Time to healing. Change in ulcer area. Safety. Feasibility. ●	Small observational pilot study; <50 patients started treatment with <40 in PP population. Multi-centre study. The study was funded by the company and 2 authors have received consultation fees from the company. One author is a co-inventor of the technology.

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC Comments
Jørgensen et al. (2011) Copenhagen Wound Healing Center, Bispebjerg Hospital DOI: 10.1177/1534734611426755	Prospective, uncontrolled pilot study Treated weekly with Leucopatch for 6 weeks, or until healing was complete. The study was supported by Reapplix Aps. Published in full. ●	Patients (older than 18 years) attending the Copenhagen Wound Healing Center, Bispebjerg Hospital with chronic cutaneous ulcers on the lower extremities, chronic DFUs (grade I-II according to the Wagner scale) or amputation wounds, that had been present for at least 2 months and had failed to heal by conventional means (n=5 patients with DFUs). Exclusion criteria included clinical signs of infection or osteomyelitis; significant medical conditions likely to impede wound healings; wound necrosis; ischaemia demanding vascular reconstruction or amputation, haemophilia, sickle cell anaemia, thrombocytopenia, and leukemia or blood dyscrasia; uncontrolled diabetes (HbA1c ≥10% [13.7 mmol/L]). Patients with diabetes reported separately. Age 47-65 years; all male. Ulcer duration 3 to 72 months. Outpatient clinic visits in Copenhagen, Denmark. ●	The primary efficacy outcome was the proportional change in wound area during the 6-week treatment period. Secondary outcome measures were the change in the proportion of granulation tissue within the wound, the proportion of wounds that completely healed and the proportion of wounds showing a significant improvement in wound area during treatment. ●	Meets scope Very small pilot study including only 5 patients with diabetes. Single-centre study. The study was funded by the company. One author is a co-inventor of the technology.

Study name and location	Design and intervention(s)	Participants and setting	Outcomes	EAC Comments
Katzman et al. (2014) Lund, Sweden Diabetes,2014, 63, A581	Consecutive case series Leucopatch was applied once weekly for up to 20 weeks. Supported By: Lund University Abstract only. ●	Patients with non-ischaemic (TcPO2≥ 30 mmHg) DFUs with a duration of at least 6 weeks and a positive probing to bone test. 100% of patients had diabetes; median ulcer duration 27 weeks; no further demographic details (abstract only). Lund, Sweden and Birkerød, Denmark. ●	Bone covered; healed with complete epithelialization; AEs. ●	Meets scope Abstract only; few details. Small case series study of 17 patients, conducted in 2 centres. All patients were initially receiving oral antibiotics.
Abbreviations: AE – adverse event; DFU – diabetic foot ulcer; EAC – External Assessment Centre; Hb – haemoglobin; HbA1c – glycated haemoglobin; IFU – Instructions For Use; IQR – interquartile range; ITT – intention-to-treat; PP – per protocol; RCT – randomised controlled trial; SD – standard deviation; TcPO2 - transcutaneous oxygen pressure				

Table 4.5: Studies included by company and excluded by the EAC

Study name and location	Design and intervention(s)	Participants	Outcomes	EAC comments
Hogh et al. (2019) Multi-disciplinary outpatient clinic specialized in advanced wound treatment, Denmark. Leuko_landskab_ESVS19	Case series Leucopatch weekly as a supplement to standard wound treatment; overall median (range) 3 (1-19) treatments per patient. Published as an abstract only. ●	Patients with hard-to-heal wounds (wound duration>6 weeks); both with and without diabetes. Overall mean (SD) age 65 years; 58% male; median (IQR) pre-treatment time 21.5 (28) weeks. ●	Wound size; time to healing; AEs; patients with diabetes not shown separately. ●	26 patients included but only 4 with diabetic ulcer and baseline data and results for these individuals not shown separately.
Abbreviations: AE – adverse event; EAC – External Assessment Centre; IQR – interquartile range; SD – standard deviation				

5 Clinical evidence review

5.1 Overview of methodologies of all included studies

One RCT was found (Game et al. 2018a; n=269 patients). There were two non-comparative studies published in full (Löndahl et al. 2015; n=44 patients and Jørgensen et al. (2011); including n=5 patients with diabetes). One further case series was only published as an abstract (Katzman et al. 2014; n=17 patients with 21 ulcers).

Two of the abstracts linked as supplementary papers to the Löndahl et al. (2015) study (Löndahl et al. 2012a and 2012b) mention a “matched control group” but with no further information. The company was asked if any information on the “matched control group” was available. The company reported that speaker notes for a presentation included: "When we matched our patients in the study with a control group from our diabetic foot unit, with the same ulcer location, duration, size and Wagner grade, the Leucopatch treated patients seemed to have better healing rates compared with the reference group. However, we cannot draw any conclusions from this result since this was not a randomised controlled study." As no further information is available on the number of people in this “control group” or their demographic or clinical features, this group is not considered further, and only the patients receiving the LeucoPatch treatment are reported as a case series.

All studies evaluated the intervention specified in the Scope (NICE 2021) but its use was inconsistent with expected NHS clinical practice. In all of the studies new patches were applied on a weekly basis until healing or the end of the study. In clinical practice their use will be discontinued if there is no sign of better healing with the patch than standard care. Jørgensen et al. (2011) had an intervention period of about 6 weeks which is similar to expected clinical practice. Each of the other studies used the patches for about 20 weeks. The RCT compared 3C Patch (LeucoPatch) plus standard care versus standard care only; the other studies were uncontrolled. All the studies included patients with diabetic hard-to-heal ulcers.

The RCT (Game et al. 2018a) included 22 sites in the UK with 10 sites in Denmark and Sweden, whereas the other studies were set in centres in Denmark and Sweden.

In the Game et al. (2018a) study, the mean (SD) age was 61.9 (11.6) years; 82% of participants were men; and the ulcer duration was not stated. In the Löndahl et al. (2015) study, the median (IQR) age was 63 (58–73) years; 79.5% were men; the median (IQR) ulcer duration was 35 (16-60) weeks. In the Jørgensen et al. (2011) study, the age range was 47-65 years; all were

male; the ulcer duration ranged from 3 to 72 months. Baseline characteristics were not reported in the Katzman et al. (2014) abstract.

Patients were followed up for 6 weeks in the Jørgensen et al. (2011) study, 20 weeks in the 2 non-comparative studies (Löndahl et al. 2015 and Katzman et al. 2014), and a total of 26 weeks (20-week intervention and 6-week observation period) in the Game et al. (2018a) RCT.

The wound healing outcome was assessed in a standardised way in the Game et al. (2018a) study (clinical investigators who assessed outcomes were unaware of group assignment; backed up with digital imaging), the Löndahl et al. (2015) study (wounds were debrided and cleaned before being photographed according to a standard procedure with ulcer areas measured centrally by an independent investigator using ImageJ software), and the Jørgensen et al. (2011) study (wounds were cleaned using a standard protocol and photographed before each treatment; wound edges were drawn on Visitrak for estimation of wound size; estimates were also made of the proportion of granulation tissue in the wound). Measurement was not reported in the Katzman et al. (2014) abstract.

The three fully published papers reported AEs, but not the Katzman et al. (2014) abstract.

5.2 Critical appraisal of studies and review of company's critical appraisal

Company assessment

The RCT (Game et al. 2018a) was reported to be of high quality but the risk of bias assessment for this was not presented in the company evidence submission. No critical appraisal of the other included studies was provided.

EAC assessment

The RCT (Game et al. 2018a) was assessed as high quality with a low risk of bias. However, there are several concerns with its external validity. The full risk of bias assessment for each study is shown in appendix B and summarised in Table 5.1.

Table 5.1: Summary of internal and external validity of the included studies

Study	Internal validity[1]	External validity[2]
RCT		
Game et al. (2018)	High. Computer-generated, web-based, randomisation. Clinical investigators who assessed outcomes were unaware of group assignment, as was the study statistician before the clinical database had been cleaned and locked. Participants, caregivers, and site investigators were not masked to treatment allocation. The use of sham venepuncture was rejected as being unethical, but assessment of the primary outcome was undertaken by an independent and masked observer and backed up with digital imaging. In the event of a disagreement between site investigators and the masked clinical primary outcome assessor, or if a blinded assessment was not done or was delayed beyond the permitted window described in the protocol, a masked adjudication committee reviewed the digital images. The groups were well matched. The target number of participants were recruited and retention was high, with few dropouts. Reasons for patient withdrawal was documented as similar between groups. All pre-specified efficacy outcomes were reported.	Partially acceptable. Experts advised patients included in RCT are similar to current clinical practice despite these patients will now be pre-treated with UrgoStart. However, the inclusion criteria and decision on whether to continue using the 3C Patch in the RCT are different from clinical practice. The latter will rely on clinical judgement and patient's history rather than formal rules to identify patients and will use clinical judgement after 4 to 6 weeks to judge if healing is accelerating with use of the Patch. Intervention is in line with Scope but in expected clinical practice a review of relative healing progress will take place at 4 to 6 weeks and people showing no relative benefit from the Patch should revert to standard care. There is also no 20 weeks ceiling on use of 3C Patch, nor a maximum of 2 Patches specified in IFU. About 1% of patients in the control arm used Urgostart for at least 1 week but expected clinical practice is that UrgoStart will normally be used before 3C Patch. Clinic visits will be every 2 weeks, not weekly. Outcomes in line with Scope. 32 centres with specialist diabetic foot clinics, of which 22 were in the UK

Study	Internal validity[1]	External validity[2]
		and the balance in Denmark and Sweden.
Case series		
Löndahl et al. (2015)	Acceptable. Recruitment unclear. Patients (older than 18 years) were treated at secondary or tertiary multidisciplinary diabetic foot clinics in Denmark or Sweden. Exposure measured via medical records. Measurement of outcome: Wounds were debrided and cleaned before being photographed according to a standard procedure. Ulcer edges were drawn on an acetate, and ulcer areas were measured centrally by an independent investigator using ImageJ (free software; http://imagej.en.softonic.com). Confounding factors: Authors tabulated baseline factors such as ulcer area, depth and location, HbA1c, Hb, platelets, leukocytes and renal function, but data only shown for duration of ulcer as a confounding factor. No loss to follow up. Only p values reported for the time to healing according to ulcer duration at baseline.	Partially acceptable. Similar limitations with the patients, intervention, comparator and outcomes as the RCT,. Patients with non-ischaemic Wagner grade 1 or 2 DFUs with a duration of > 6 weeks and a maximal area of 10cm^2, with ≤40% change in ulcer area during the 2-week run-in period. 100% of patients had diabetes. Secondary or tertiary multidisciplinary diabetic foot clinics in Denmark or Sweden.
Jørgensen et al. (2011)	Acceptable. Recruitment unclear. Patients (older than 18 years) attending the Copenhagen Wound Healing Center, Bispebjerg Hospital. Mixed population with chronic ulcers on the lower extremities and amputation wounds; only 5 patients with diabetes. Exposure measured via medical records with clinical tests also conducted to establish diagnosis. Measurement of outcome: Wounds were cleaned using a standard protocol and photographed before each treatment. Wound edges were drawn on Visitrak (Smith & Nephew A/S, Hørsholm, Denmark) for estimation of wound size. Estimates were also made of the proportion of granulation tissue in the wound. No confounding factors reported. All patients followed to 6 weeks. Outcome reporting unclear. Percentage reduction in wound area reported for 3 of the 5 patients; the other 2 reported to be reduced to less than 20% of their initial size.	Not acceptable. Included chronic DFUs (grade I-II according to the Wagner scale) that had been present for at least 2 months and had failed to heal by conventional means, but only 5 relevant patients so generalisability unclear.

Study	Internal validity[1]	External validity[2]
Katzman et al. (2014)	Low. Patients with non-ischaemic DFUs with a duration of at least 6 weeks and a positive probing to bone test recruited consecutively. Exposure measured via medical records. Measurement of outcome, confounding factors, follow up and outcome reporting unclear.	Not acceptable. Abstract only

[1]Overall internal validity for each study has been assessed as 'High', 'Acceptable' or 'Low'.

For RCTs:
A rating of 'High' was assigned if ≥3 key criteria (sequence generation, allocation concealment, blinding) were met and ≤1 of all other criteria were unclear/not met.
A 'Acceptable' rating was assigned to those reporting met/unclear judgements for the majority of criteria.
A 'Low' rating was assigned if ≥2 key criteria (sequence generation, allocation concealment, blinding) or the majority of all criteria were not met.

For observational studies:
A 'High' rating was assigned if all 3 key criteria (patient group, measurement of exposure, measurement of outcome) were met and established guidelines were used in both groups.
An 'Acceptable' rating was assigned to those with established guideline use and ≥1 criteria met.
A 'Low' rating was assigned if ≥2 key criteria and the requirement for use of established guidelines were unclear/not met.

[2]Overall external validity for each study has been assessed as 'Acceptable' or 'Not acceptable'.

'Not acceptable' has been assigned if there is any uncertainty in the relevance of the patients, intervention, comparator, or outcomes in relation to the scope, or the study report is an abstract/poster with limited information.
All others have been rated as 'Acceptable'.

Abbreviations: DFU - diabetic foot ulcer; Hb - haemoglobin; HbA1c - glycated haemoglobin; RCT - randomised controlled trial

5.3 Results from the evidence base

Table 5.2, Table 5.3 and Table 5.4 show the wound healing, outcomes, complications of non-healing wounds and other effectiveness outcomes.

Table 5.2: Outcomes - wound healing

Study	Proportion of people with complete epithelialization or healing n (%) or OR (95% CI)	Time to complete epithelialization or healing: median (IQR) days	Change in ulcer area
Game et al. (2018a) (3C plus standard care: ITT)	45 (34%).	ITT population: Shown graphically (see Figure 5.1 reproduced from Game et al. 2018a publication). Among the 45 who healed within 20 weeks: 72 (56-103).	Shown graphically (see Figure 5.2 reproduced from Game et al. 2018a publication).
Game et al. (2018a) (Standard care: ITT)	29 (22%).	ITT population: Shown graphically (see Figure 5.1 reproduced from Game et al. 2018a publication). Among the 29 who healed within 20 weeks: 84 (64-98).	Shown graphically (see Figure 5.2 reproduced from Game et al. 2018a publication).
Game et al. (2018a) (comparison between treatments: ITT)	Unadjusted: OR 1.58 (95% CI 1.04–2.40), p=0.0235; adjusted for baseline wound size (≤100 mm^2 vs >100 mm^2): 1.89 (1.07–3.40), p=0.0237 in favour of 3C.	ITT population: Hazard ratio 1.709 (95% CI 1.071–2.728); p=0.0246 in favour of 3C.	p=0.0168 in favour of 3C.

Study	Proportion of people with complete epithelialization or healing n (%) or OR (95% CI)	Time to complete epithelialization or healing: median (IQR) days	Change in ulcer area
		Among the subgroup who healed: p=0.0343 in favour of 3C.	
Game et al. (2018a) (3C plus standard care: PP)	44 (39%).	NA	NA
Game et al. (2018a) (Standard care: PP)	28 (26%).	NA	NA
Game et al. (2018a) (comparison between treatments: PP)	Unadjusted: 1.47 (0.98–2.23), p=0.0488 in favour of 3C; adjusted for baseline wound size (≤100 mm^2 vs >100 mm^2): 1.795 (0.98–3.32), p=0.0480 in favour of 3C.	NA	NA
Löndahl et al. (2015)	15 patients (ITT 34%; PP 38%) at 12 weeks and 23 patients (ITT 52%; PP 59%) at 20 weeks. In the 15 patients with ulcer duration < 6 months, 11 (73.3%) of ulcers healed within 20 weeks. In the 14 patients with duration 26-46 weeks, 8 (57.1%) healed within 20 weeks. In the 15 patients with duration >46 weeks, 4 (26.7%) healed within 20 weeks.	Shown graphically. Median around 12 weeks; IQR 5-15 weeks.	Shown graphically for healers and non-healers.
Jørgensen et al. (2011)	0 (0%).	NR	Percentage reduction in wound area reported for 3 of the 5 patients (4.5%, 38.9% and 82.9%, respectively); the other 2 reported to be reduced to less than 20% of their initial size.
Katzman et al. (2014)	13/21 ulcers (61.9%).	NR	NR

Figure 5.1: Time to healing (Reproduced from Game et al (2018a) publication)

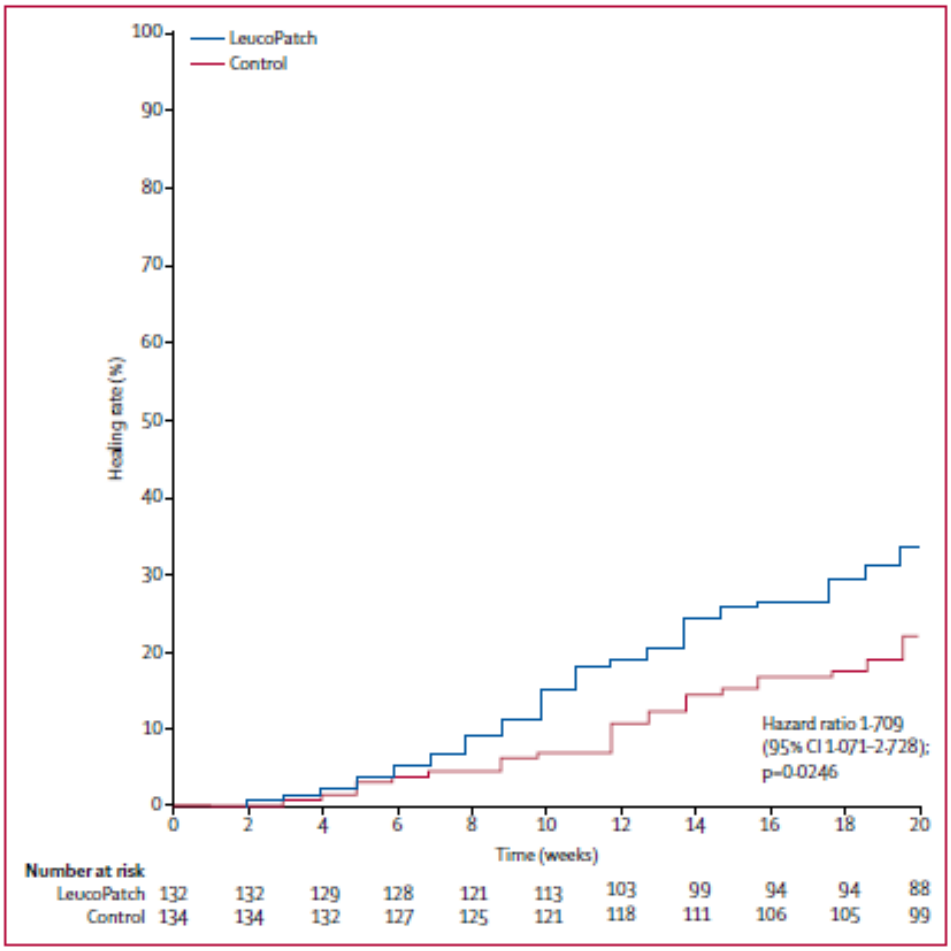


Figure 2: **Time to healing**

Survival curve showing proportion of ulcers healed, with healing defined as complete epithelialisation without any drainage sustained for at least 4 weeks, in the intention-to-treat population randomly assigned to standard care alone (n=134) or standard care and LeucoPatch (n=132).

Figure 5.2: Reduction in ulcer area (Reproduced from Game et al. (2018a) publication)

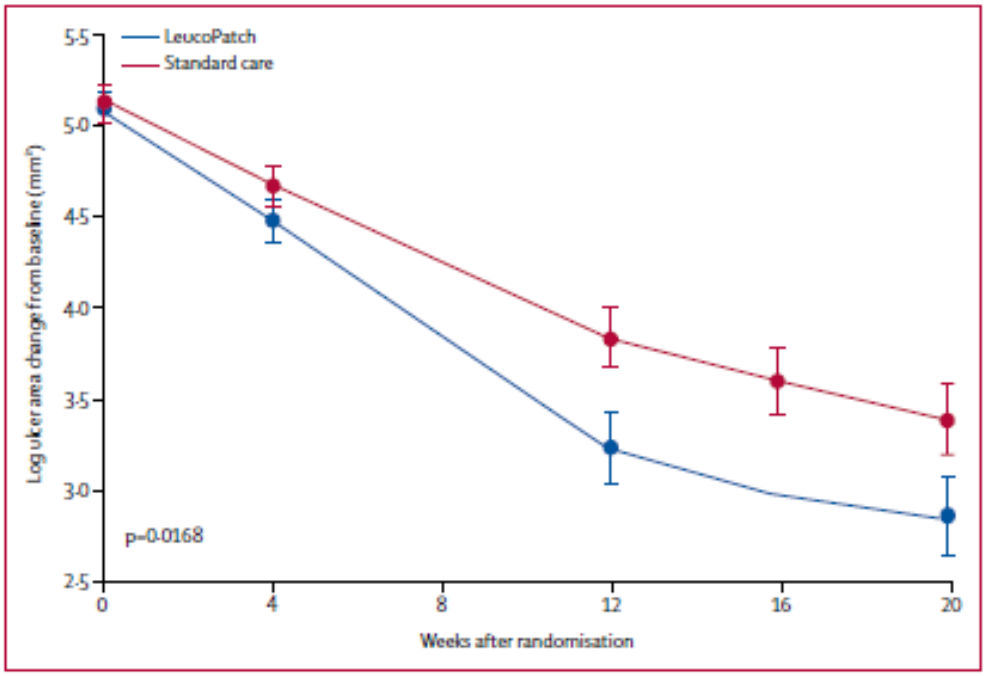


Figure 3: Reduction in ulcer area
Data are mean of log, with 95% CI error bars.

Table 5.3: Complications of non-healing wounds

Study	Patients with new infection within 20 weeks, n (%)	Visits reporting infection as a proportion of total visits (%)	Total days of antibiotic therapy	Amputations (n) or OR (95% CI)	Revascularisation of the index limb by 26 weeks (i.e. requirement for further intervention), n (%)
Game et al. (2018a) (3C plus standard care: ITT)	51 (39%)	8.6%	2,662 altogether (mean 20.2 per person)	New minor amputations of index limb: 12 weeks: 5. 20 weeks: 8. 26 weeks: 8. New major amputations of index limb: 12 weeks: 0. 20 weeks: 2. 26 weeks: 2. New minor amputations of contralateral limb: 12 weeks: 4. 20 weeks: 7. 26 weeks: 7. New major amputations of contralateral limb: 12 weeks: 0. 20 weeks: 1. 26 weeks: 1.	3 (2%)
Game et al. (2018a) (Standard care: ITT)	63 (47%)	10.1%	2822 (mean 21.0 per person)	New minor amputations of index limb: 12 weeks: 2. 20 weeks: 5. 26 weeks: 9. New major amputations of index limb: 12 weeks: 0	6 (5%)

Study	Patients with new infection within 20 weeks, n (%)	Visits reporting infection as a proportion of total visits (%)	Total days of antibiotic therapy	Amputations (n) or OR (95% CI)	Revascularisation of the index limb by 26 weeks (i.e. requirement for further intervention), n (%)
				20 weeks: 2. 26 weeks: 2. New minor amputations of contralateral limb: 12 weeks: 1. 20 weeks: 2. 26 weeks: 3. New major amputations of contralateral limb: 12 weeks: 0. 20 weeks: 1. 26 weeks: 1.	
Game et al. (2018a) (comparison between treatments: ITT)	OR 0.8350 (95% CI 0.63-1.11), p=0.2080	OR 0.8417 (95% CI 0.70–1.02), p=0.0728	OR 0.92 (95% CI –9.14 to 7.35), p=0.8314	New minor amputations of index limb: 12 weeks: OR 2.49 (95% CI 0.48–12.80), p=0.4526. 20 weeks: 1.63 (0.53-4.96), p=0.4196. 26 weeks: 0.90 (0.35–2.34), p=1·000. New major amputations of index limb: 12 weeks: NA 20 weeks: 1.02 (0.14–7.21), p=1.000. 26 weeks: 1.02 (0.14–7.21), p=1.000. New minor amputations of contralateral limb:	OR 0.44 (95% CI 0.08–3.31), p=0.49

Study	Patients with new infection within 20 weeks, n (%)	Visits reporting infection as a proportion of total visits (%)	Total days of antibiotic therapy	Amputations (n) or OR (95% CI)	Revascularisation of the index limb by 26 weeks (i.e. requirement for further intervention), n (%)
				12 weeks: 3.98 (0.44–35.57), p=0.3746. 20 weeks: 3.56 (0.74–17.11), p=0.1062. 26 weeks: 2.37 (0.61–9.15), p=0.2226. New major amputations of contralateral limb: 12 weeks: NA 20 weeks: 1.02 (0.06–6.24), p=1.000. 26 weeks: 1.02 (0.06–16.23), p=1.000. All non-significant differences and based on small numbers of events.	
Game et al. (2018a) (3C plus standard care: PP)	NA	NA	NA	NA	NA
Game et al. (2018a) (Standard care: PP)	NA	NA	NA	NA	NA
Game et al (2018a) (comparison between treatments: PP)	NA	NA	NA	NA	NA
Löndahl et al. (2015)	7 (15.9%) foot ulcer infections occurred, of which 3 in target ulcers.	NR	NR	NR	NR

Study	Patients with new infection within 20 weeks, n (%)	Visits reporting infection as a proportion of total visits (%)	Total days of antibiotic therapy	Amputations (n) or OR (95% CI)	Revascularisation of the index limb by 26 weeks (i.e. requirement for further intervention), n (%)
Jørgensen et al. (2011)	0 (0%)	NR	NR	NR	NR
Katzman et al. (2014)	3/21 ulcers (14.3%)	NR	NR	NR	NR

Table 5.4: Outcomes - other

	Reduction in pain among those who had pain at baseline (% change VAS)	HRQoL	Total number of 3C Patch treatments needed	Frequency and total number of secondary dressing changes	Demand for NHS DFU care – outpatient, community, primary care and inpatient care	Withdrawal/differences between ITT and PP populations
Game et al. (2018a) (3C plus standard care: ITT)	–54.5%; n=71	An abstract (Löndahl et al. 2019) reports a very small sub-analysis of HRQoL in 18 patients with ulcers extending into tendon (3C Patch group, n=10; standard care group, n=8). At 20 weeks, compared with baseline, 40% of the 3C Patch group improved at least one level in the EQ-5D dimension usual activities (p=0.046, Wilcoxon Rank-test) and 30% at least one level in mobility (n.s.).	NR in paper but company submission reported 14.3 patches per patient and mean treatment duration of 17.1 weeks.	NR	NR	132 people were included in ITT population in the intervention group, of whom 114 (86.4%) were included in the per-protocol analysis. Those not included in the PP population were: • 9 protocol violation (6.8% of ITT population) • 8 surgery that removed index ulcer (6.1%) • 1 withdrawal of consent (0.8%).
Game et al. (2018a) (Standard care: ITT)	–45.5%; n=85	For standard care, no improvements were noted in any of the five EQ-5D health-related quality of life dimensions.	NR	NR	NR	134 people were included in ITT population in the control group, of whom 107 (79.9%) were included in the per-protocol analysis. Those not included in the PP population were:

	Reduction in pain among those who had pain at baseline (% change VAS)	HRQoL	Total number of 3C Patch treatments needed	Frequency and total number of secondary dressing changes	Demand for NHS DFU care – outpatient, community, primary care and inpatient care	Withdrawal/differences between ITT and PP populations
						• 20 protocol violation (14.9% of ITT population) • 2 death (1.5%) • 2 major amputation (1.5%) • 2 surgery that removed index ulcer (1.5%) • 1 withdrawal of consent (0.7%).
Game et al. (2018a) (comparison between treatments: ITT)	OR 1.20 95% CI – 1.22 to 10.54, p=0.1194	NR	NR	NR	NR	The difference between the proportions completing the study PP is not significant.
Löndahl et al. (2015)	NR	NR	Altogether 519 treatments were given during the study (mean 11.8 per patient).	Secondary bandages were applied as decided on a case-by-case basis and changed depending on wound fluid leakage, patients, relatives and home care nurses. Neither the patch nor the wound contact layer was	In a small study, time spent on the patch production and administration was evaluated. In absence of severe problems with venepuncture, the procedure including cutting and application of the final leukocyte platelet fibrin patch could be accomplished within a few extra	44 in ITT population; 39 in PP population; withdrawals due to: • 1 death (2.3%) • 1 hospitalised (2.3%) • 2 osteomyelitis (4.5%) • 1 non-adherence (23%).

	Reduction in pain among those who had pain at baseline (% change VAS)	HRQoL	Total number of 3C Patch treatments needed	Frequency and total number of secondary dressing changes	Demand for NHS DFU care – outpatient, community, primary care and inpatient care	Withdrawal/differences between ITT and PP populations
				removed between weekly treatments.	minutes. Thus, it could easily be applied within routine clinical management.	
Jørgensen et al. (2011)	NR	NR	Each patient had a total of 6 treatments, once a week for 6 weeks.	NR	NR	5 patients with diabetes included and reported.
Katzman et al. (2014)	NR	NR	Median number of treatments was 9.	NR	NR	NR
Abbreviations: CI - confidence interval; DFU - diabetic foot ulcer; EQ-5D - EuroQol 5 dimensions; HRQoL – health related quality of life; ITT - intention-to-treat; NHS – National Health Service; NR - not reported; n.s. - not significant; OR - odds ratio; PP – per protocol; VAS - visual analogue scale						

Game et al. (2018a) RCT:

In the ITT population, healing within 20 weeks was achieved in 45 (34%) participants in the intervention group versus 29 (22%) in the standard care group: OR 1.58 (95% CI 1.04–2.40), p=0.0235; adjusted for baseline wound size (≤100 mm^2 vs >100 mm^2): 1.89 (1.07–3.40), p=0.0237 in favour of 3C Patch.

In the per-protocol population, healing within 20 weeks was achieved in 44 (39%) participants in the intervention group versus 28 (26%) in the standard care group (OR 1.47 [95% CI 0.98–2.23], p=0.0488).

The point estimate of OR 1.58 (ITT) reflects a relative increase of almost 60% in the percentage of people healing, which is a clinically and statistically significant benefit in this population of people with hard-to-heal ulcers. The fact that the p-value found in the study is very similar to the OR of 1.6 used in the sample size calculation, indicates the sample size used is just sufficient to demonstrate statistical significance. This is appropriate ethically as the sample size is not excessively large, which would increase the number of people in the control group who have not received the more effective intervention.

The EAC notes that time to complete healing is the most important outcome, since a smaller ulcer that persists for a longer time period can still be a source of infection and lead to the need for amputation, therefore the faster rate of healing for the first 12 weeks is an important benefit, even if the rates are similar thereafter.

Time to healing was shorter in the intervention group than in the standard care group: Hazard ratio 1.709 (95% CI 1.071–2.728); p=0.0246 (see Figure 5.1 reproduced from the Game et al. (2018a) publication above; median time to complete healing in the ITT population not stated). This is the data taking into account the whole population (those who healed or did not heal). In the subgroup of only those who healed within 20 weeks during the study, the median time to healing was 72 days (IQR 56–103) in the intervention group (n=45) and 84 days (IQR 64–98) in the standard care group (n=29; p=0.0343). This reflects an important reduction in time to healing among the subgroup of patients who healed. For every 100 people in each treatment group, 39 would be healed in a median of 72 days with 3C and 26 would be healed in a median of 84 days with standard care, so the difference between the groups would be 13 people and 12 days, or 156 person-days less time with an unhealed ulcer.

The fact that the ITT and PP analyses were similar implies that the analyses have not been biased by any drop out; the per-protocol analysis included 114

(86.4%) of treated patients in the intervention group and 107 (79.9%) of treated patients in the standard care group.

There was no significant difference in the rates of infections, antibiotic therapy, amputations, revascularisations, withdrawals, AEs or serious AEs between the groups. Reductions in pain were similar, and there were no device-related AEs in either group.

Health-related QoL was evaluated in a small subgroup of this RCT (reported in Löndahl et al. 2019), involving 18 patients with ulcers extending into tendons (10 intervention and 8 controls), at the 20 week follow-up visit, 4 (40%) of the participants in 3C Patch group improved at least one level in the EQ-5D dimension of “usual activities” (p=0.046, Wilcoxon Rank-test) and 3 (30%) at least one level in “mobility” (not significant) compared with baseline. In the control group, no improvements in any of the five EQ-5D health-related quality of life dimensions were seen.

Although RCT evidence was available, there was only one RCT, so while uncontrolled case series represent a lower strength of evidence in the hierarchy, for completeness, the efficacy data from the case series are included below.

The uncontrolled studies also reported wound healing:

- Löndahl et al. (2015): 15 patients (34% of the 44 in the ITT population) at 12 weeks and 23 patients (52%) at 20 weeks. In the 15 patients with ulcer duration < 6 months, 11 (73.3%) of ulcers healed within 20 weeks. In the 14 patients with duration 26-46 weeks, 8 (57.1%) healed within 20 weeks. In the 15 patients with duration >46 weeks, 4 (26.7%) healed within 20 weeks.

- Jørgensen et al. (2011): 0 (0%) healed at 6 weeks. Percentage reduction in wound area was reported for 3 of the 5 patients (4.5%, 38.9% and 82.9%, respectively); the other 2 ulcers were reported to be reduced to less than 20% of their initial size.

- Katzman et al. (2014): 13/21 ulcers (61.9%) healed at 20 weeks.

They also reported infection rates:

- Löndahl et al. (2015): 7 (15.9%) foot ulcer infections occurred, of which 3 were in target ulcers.

- Jørgensen et al. (2011): 0 (0%).

- Katzman et al. (2014): 3/21 ulcers (14.3%).

Withdrawals were:

- Löndahl et al. (2015): 11.4%.
- Jørgensen et al. (2011): none.
- Katzman et al. (2014): not reported.

AEs were:

- Löndahl et al. (2015): 12 (27.3%) with any severe adverse event (SAE); 1 death (2.2%).
- Jørgensen et al. (2011): none.
- Katzman et al. (2014): not reported.

There were no device-related AEs in any of these three studies.

Gaps in the evidence

There is no published evidence comparing 3C Patch with UrgoStart or its use with patients who have failed on UrgoStart. UrgoStart was not widely available for use in standard care when the 3C Patch RCT was conducted.

Experts suggest that the 3C Patch would not be used in the patient pathway as an alternative to UrgoStart but after it, because the latter is easier to use. Hence the 3C Patch is positioned in the pathway as a treatment option when other advanced dressings have failed. The dressings used in the 4-week run-in period in the Game et al. (2018a) study were mostly iodine or foam, although 40% of patients did receive protease-modulating-matrix dressings for at least 1 week in the run-in period, rising to 60% for control arm of the trial.

There is also no evidence on use of the 3C Patch in accordance with the expected NHS pathway, in particular the impact of adopting a review at 4 to 6 weeks to judge if using the 3C Patch is expediting progress to healing. This step will change discontinuation rates, healing rates and number of 3C Patches compared with the RCT results. The company advises that it expects treatment duration to be shorter in clinical practice than reported by Game et al. (2018a).

A further evidence gap is use of 3C Patch in wounds of greater than 10 cm^2, which require 3 or 4 3C Patches per wound change. Finally, in the RCT patients with a new infection continued to receive 3C Patch. Half of the clinical experts advised they would discontinue the Patch when a patient had an infection, one would continue if the infection was mild and the other two would

continue with 3C Patch. Given 39% of people in the 3C Patch arm developed a new infection within 20 weeks, then adopting differing stopping criteria across settings for those with new infections, in comparison to the study protocol, is likely to change the achieved healing times and healing completeness from those reported by Game et al. (2018a).

6 Adverse events

A hand search of the Medicines & Healthcare products Regulatory Agency (MHRA) and Food and Drug Administration (FDA) Manufacturer and User Facility Device Experience (MAUDE) databases were conducted on 22 April 2021 using the terms ‘Reapplix’, ‘Leucopatch’, ‘Leukopatch’ and ‘3C Patch’. No AEs have been reported to either database. The FDA (MAUDE) search dates were limited from 1 January 2010 to 31 March 2021. The EAC agrees with the company's assessment of no AE records on either database.

The company search looked for safety studies/ AEs separately from the main efficacy searches; the EAC searches combined AE with efficacy outcomes in one search. Table 6.1 reports the AEs identified by the EAC.

Table 6.1: Outcomes - AEs

	Any AE n (%)	Any SAE n (%)	Device-related AEs n (%)	Patient tolerance and acceptability	Incidence of new anaemia, n (%)	Death n (%) or OR (95% CI)
Game et al. (2018a) (3C plus standard care: ITT)	81 (61%) of 132 [274 reports]	51 (39%) of 132 [98 reports]. The most common SAE was diabetic foot infection; there were 24 events in the 3C Patch group (24% of all SAEs). Of these diabetic foot infections, 16 (67%) in the 3C Patch group were attributed to the index ulcer.	0 (0%)	NR	13 (10%)	3 (2%)
Game et al. (2018a) (Standard care: ITT)	90 (66%) of 137 [240 reports]	42 (31%) of 137 [74 reports]. The most common SAE was diabetic foot infection; there were 20 events in the standard care group (27% of all SAEs). Of these diabetic foot infections, 12 (60%) in the standard	0 (0%)	NR	11 (8%)	5 (4%)

	Any AE n (%)	Any SAE n (%)	Device-related AEs n (%)	Patient tolerance and acceptability	Incidence of new anaemia, n (%)	Death n (%) or OR (95% CI)
		care group were attributed to the index ulcer.				
Game et al (2018) (comparison between treatments: ITT)	OR 0.93 (95% CI 0.78–1.12), p=0.4607	OR 1.26 (95% CI 0.91–1.76), p=0.1689	NA	NR	OR 1.20 (95% CI 0.56–2.58), p=0.6408	OR 0.60 (95% CI 0.14–2.56), p=0.7221
Löndahl et al. (2015)	33 AEs were reported during the run-in-, treatment- and follow-up phases of the study for all 60 patients enrolled in the trial and not for the 44 subsequently treated. None of the AEs were judged related to the 3C Patch treatment.	12 (27.3%) patients during the run-in-, treatment- and follow-up phases of the study.	0 (0%)	Three scheduled 3C Patch applications were missed because of difficulties in blood sampling and 2 because of technical device failure, thus <1% of scheduled treatments were inhibited because of device/treatment-related technical failure.	NR	1 (2.2%)
Jørgensen et al. (2011)	0 (0%)	0 (0%)	0 (0%)	NR	NR	0 (0%)
Katzman et al. (2014)	Tissue infections occurred in 3 patients but resolved with a	NR	NR	NR	NR	NR

	Any AE n (%)	Any SAE n (%)	Device-related AEs n (%)	Patient tolerance and acceptability	Incidence of new anaemia, n (%)	Death n (%) or OR (95% CI)
	change in oral antibiotic treatment.					
Abbreviations: AE - adverse event; CI - confidence interval; ITT - intention-to-treat; NA - not applicable; NR - not reported; OR - odds ratio; SAE - severe adverse event						

7 Evidence synthesis and meta-analysis

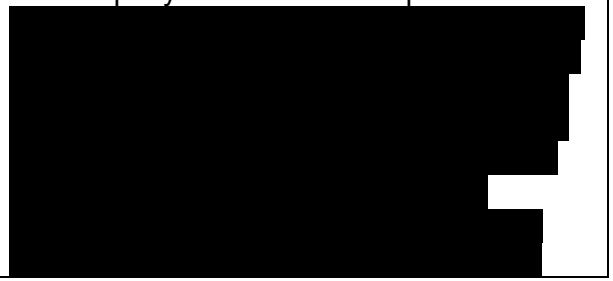
Only one RCT was found, supplemented by three small non-comparative studies. Therefore, meta-analysis was not possible.

7.1 Critique of the company's assessment of the evidence

Table 7.1 shows the benefits claimed in the company submission and the EAC comment (highlighted green for agreement and orange for partial disagreement).

Table 7.1: Benefits claimed in the Company submission and the EAC comment

From company submission			From EAC
Claimed benefit	**Supporting evidence**	**Rationale**	**EAC comment**
Patient benefits			
Heals more wounds and reduces wound healing time	Game et al. (2018a) Jørgensen et al. (2011) Löndahl et al. (2015)	In the RCT (Game et al. 2018a) the 3C Patch reduced the time to complete healing and increased the number of healed ulcers compared with standard care and thereby reduced the treatment times and need for continued care. The 2 pilot studies showed that the 3C Patch was an effective treatment for hard-to-heal ulcers some of which were of a long duration.	The EAC agrees that in the Game et al. (2018a) RCT the 3C Patch reduced the time to complete healing and increased the number of healed ulcers within 20 weeks compared with standard care and the 2 pilot studies showed that the 3C Patch was associated with ulcer healing in some patients .Concerns relate to generalisability of the results because the intervention is different to expected NHS practice ●
Helps to avoid wound-related complications, including amputation and infection, reducing the need for further treatment	Game et al. (2018a)	Many hard-to-heal ulcers are of very long duration and some never heal. Increased ulcer duration carries increased risk of complications such as amputation, infection and death. In the study by Game et al. (2018a), the 3C Patch reduced the time to heal and increased the number of healed ulcers thereby lowering the risk of wound associated complications. In addition, the number of infections and days on antibiotics were reduced.	In the RCT, the ORs for numbers of amputations, infections and days on antibiotic therapy all favoured 3C Patch versus standard care only but none were statistically significantly different between the groups. However, the RCT was not powered to detect differences in these outcomes. ●

From company submission			From EAC
Claimed benefit	**Supporting evidence**	**Rationale**	**EAC comment**
Improved quality of life through reduced ulcer duration and the avoidance of complications, enabling people to return to activities of daily living sooner and avoid long term reduction in quality of life	Game et al. (2018a)	Multiple studies have indicated that DFUs are associated with substantial decrements in quality of life (Ragnarson Tennvall and Apelqvist 2000). This was also observed in the RCT: EQ5D-3L scores show a mean increase of 0.14 (95% CI 0.05-0.24, p<0.05) between week 0 and week 20 for patients who became ulcer free during that period.	Quality of life is included as an outcome measure in the methods section of Game et al. (2018a) but was only reported in an abstract for a small subgroup (Löndahl et al. 2019). This included 18 patients with ulcers extending into tendons (10 using 3C Patch and 8 standard care). At the 20 week follow-up visit, 4 (40%) of the participants in 3C Patch group improved at least one level in the EQ-5D dimension of “usual activities” (p=0.046, Wilcoxon Rank-test) and 3 (30%) at least one level in “mobility” (n.s.) compared with baseline. In the control group, no improvements in any of the five EQ-5D health-related quality of life dimensions were seen. ● The company was asked to clarify the source of the quality of life data reported in the company submission It responded: 

From company submission			From EAC
Claimed benefit	**Supporting evidence**	**Rationale**	**EAC comment**
			[redacted] (See EAC correspondence log 2021)
System benefits			
Reduced demand for ulcer care, across all care settings	Game et al. (2018a)	The 3C Patch reduced the time to heal and increased the number of healed ulcers thereby leading to a shorter period of treatment and therefore reduced demand for NHS care across outpatient community, primary and inpatient settings.	The treatment period is likely to be shorter due to ulcer healing within 20 weeks but no data on demand for NHS care across outpatient, community, primary and inpatient settings were presented. ●
Reduced need for follow-on treatment including amputation and associated rehabilitation	Game et al. (2018a)	The 3C Patch reduced the time to healing and increased the number of completely healed ulcers which will in turn reduce the risk of ulcer-	The numbers of amputations was not statistically significantly different between the groups in the Game et al. (2018a) RCT. ●

From company submission			From EAC
Claimed benefit	**Supporting evidence**	**Rationale**	**EAC comment**
		associated complications including the need for amputation.	
Cost benefits			
Reduced overall costs associated with treating hard-to-heal DFUs	Game et al. (2018a) Kerr et al. (2019)	Increased ulcer healing and reduced ulcer duration will reduce ulcer treatment volumes and complication rates. The weekly outpatient, community and primary care costs for ulcer care in 2014/15 was estimated at £162 per ulcerated patient. In addition there are ulcer-related inpatient care and complications such as amputations. The total cost of healthcare for foot ulceration and amputation in diabetes in England was estimated at £837- 962m, 0.8%-0.9% of the total NHS budget.	No cost data were presented in Game et al. (2018a) paper but see section 9. ●

From company submission			From EAC
Claimed benefit	**Supporting evidence**	**Rationale**	**EAC comment**
Sustainability benefits			
Reduced visits	Game et al. (2018a)	The 3C Patch reduced ulcer duration and increased the number of healed ulcers thereby leading to a shorter period of treatment and therefore a reduced number of visits.	The number of visits is likely to be less due to ulcer healing but no data were presented. ●
Reduced numbers of dressings, medication, offloading devices, wheelchairs and single use plastic	Game et al. (2018a)	By reducing the need for continued care and thereby lowering the number of complications, the 3C Patch reduced the need for dressings, medications, offloading devices, wheelchairs and single use plastic.	The numbers of dressings, medication, offloading devices, wheelchairs and single use plastic are likely to be less due to ulcer healing but no data were presented. ●
Abbreviations: CI - confidence interval; DFU - diabetic foot ulcer; EAC - External Assessment Centre; EQ-5D - EuroQol 5 dimensions; OR - odds ratio; RCT - randomised controlled trial; TTO – Time trade off.			

Thus. the EAC agrees with the company's submission that using the RCT protocol, the 3C Patch can heal diabetic ulcers more rapidly than standard care but did not find evidence to support the other claimed benefits.

The EAC notes that the Game et al. (2017) protocol also specified cost end-points which were not reported. The company submission states that "The study did collect data on additional secondary outcomes including resource use but the data was not considered to be of an acceptable quality for use."

8 Interpretation of clinical evidence

The evidence base identified by the EAC included 3 published studies (Game et al. 2018a, Löndahl et al. 2015, Jørgensen et al. 2011) and 1 abstract (Katzman et al. 2014). Multiple publications were found for the 4 studies, and the company confirmed the groupings of these publications (see section 4.2; EAC correspondence log 2021). Only 1 of these studies was a high quality RCT (Game et al. 2018a; n=269 patients). Two were non-comparative pilot studies (Löndahl et al. 2015; 44 patients and Jørgensen et al. 2011; 5 patients with diabetes), and the final was a case series published as an abstract (Katzman et al. 2014; 17 patients with 21 ulcers). Two additional studies were included in the company submission (Zink et al. 2021, Hogh et al. 2019), but these were excluded by the EAC. Therefore, the EAC mostly agrees with the company on the available evidence base and notes that this mainly relies on 1 well-designed and executed RCT.

The EAC agrees that 3C Patch reduced the time to complete healing and increased the number of healed ulcers within 20 weeks compared with standard care in the Game et al. (2018a) trial. The EAC notes that 3C Patch was also associated with healing among some hard-to-heal ulcers, some of which were of a long duration, in the uncontrolled pilot studies (Löndahl et al. 2015, Jørgensen et al. 2011). Thus, the EAC agrees with the company's claimed benefit that 3C Patch heals more wounds within 20 weeks and reduces wound healing time compared with best standard of care. The EAC notes that time to complete healing is the most important outcome, since a smaller ulcer can still be a source of infection and a cause of amputation (EAC correspondence log 2021). The EAC concludes that there is insufficient direct trial evidence to support the other claimed benefits included in the company submission (for example, helps to avoid wound-related complications and reduces demand for ulcer care and follow-on treatments). The EAC notes that only an illustrative measure of the potential for 3C Patch to improve quality of life has been submitted. Complete EAC comments for each of the claimed benefits included in the company submission can be found in section 7.1.

The EAC agrees that the evidence for effectiveness of 3C Patch is limited to the population included in the Game et al. (2018a) RCT and that treatment pathway. The EAC notes that there are differences between the RCT, the IFU, the company's pathway, and the clinical experts' advice in respect of the expected eligible NHS population and use and discontinuation decisions about 3C Patch. For example, discontinuation rates are expected to be higher in clinical practice because clinicians will regularly review healing progress and will stop using the patch when this stalls. Clinicians will also stop in event of some infections. These differences are likely to impact on complete healing rate and the timing to achieve this.

The patients in the RCT were not an UrgoStart-experienced population. This is important because the clinical experts advised that UrgoStart would be used before 3C Patch in patients with hard-to-heal ulcers, being easier to use than 3C Patch, with 3C Patch only used if the ulcer was not healing using UrgoStart (EAC correspondence log 2021). Therefore, there is no published evidence using 3C Patch in patients who have previously been treated with UrgoStart.

The EAC notes that the exclusion criteria used in the RCT meant that those patients with the largest ulcers (>1000 mm^2) or with ulcers increasing in size (≥25%) during the 4-week run-in period were excluded. Patients with larger ulcers require up to 4 3C Patches per week. Hence treating patients with these larger wounds may increase the number of patches per patient, albeit the experts advised this is a small cohort (EAC correspondence log 2021).

Patients with severe ischaemia and severe renal disease were also excluded. Furthermore, the inclusion criteria in the RCT were more restrictive than those stated in the IFU for 3C Patch. For example, the RCT excluded patients with baseline HbA1c above 12%, but this subgroup is not listed in the IFU. A clinical expert noted that in practice it would be challenging to restrict use of 3C Patch by HbA1c level (Clinical feedback on draft 3C Patch pathway 2021).

However, the clinical experts agreed that the population in the Game et al. (2018a) RCT is broadly representative of the population which would receive 3C Patch if it were to be used in the UK NHS (EAC correspondence log 2021). The participants in this trial were predominantly male (82%). The experts agreed that this high proportion of male patients reflects what is typically seen in UK clinical practice (EAC correspondence log 2021).

The EAC notes that further high-quality research is needed to assess whether these preliminary findings are generalisable to a greater proportion of patients with hard-to-heal DFUs (for example, an UrgoStart-experienced population who would be eligible according to the IFU).

The EAC concludes that given these discrepancies, the clinical evidence is only partial, and there are considerable uncertainties about generalising the findings to UK clinical practice.

8.1 Integration into NHS

The EAC notes the following in relation to the integration of 3C Patch into the NHS.

The clinical experts agreed that it could be quite a burden for patients to attend weekly for the patch to be changed as recommended in the IFU (EAC correspondence log 2021). They also stated that there were no significant differences between the ITT and per-protocol analyses, and that the vast majority of dropouts in the study were due to missed visits. They added that this suggests it might not be necessary to change the patch each week, as missed visits in the trial did not appear to make a significant difference to outcomes (EAC correspondence log 2021).

The NICE guidance (NG19, 2015a) recommends all people with hard-to-heal foot ulcers are managed by a multidisciplinary foot care service but does not define whether this service should be in primary or secondary care.

The experts advised that currently many patients change their own dressings, or these are changed by the district nurse or GP practice nurse in the community or primary care (EAC correspondence log 2021). One expert suggested that it depends on local policy but approximately 50% of patients manage their own dressings (EAC correspondence log 2021). Another expert noted that in their experience, 60% of patients are managed in the diabetes foot clinic based in secondary care and 40% with active wounds are managed in community intermediate care clinics (EAC correspondence log 2021). This expert also stated that for 10% of the caseload, there will be a shared care element where the district nursing team are involved in at least 1 dressing change per week (EAC correspondence log 2021). Another expert stated that in their trust, all patients with DFUs are treated in a specialist outpatient clinic at the hospital and that there are no hard-to-heal DFU community clinics (EAC correspondence log 2021). A final expert advised that all patients with active disease are seen in multidisciplinary team (MDT) clinics with dressing changes between clinic visits undertaken by practice/district nurses or the patient (EAC correspondence log 2021). This expert also noted that some MDT clinics see patients for every dressing change (EAC correspondence log 2021).The experts also commented on the frequency that standard dressings are replaced currently (EAC correspondence log 2021). The answers given varied and included: every 1 to 3 days, 1 to 3 changes per week, 2 changes per week, 2 to 3 times per week, and daily to twice per week. Most experts

agreed that this depends on the characteristics of the wound (EAC correspondence log 2021).

As noted, using 3C Patch would seem to require all patients to attend a secondary care setting to access the device and practitioners able to do venepuncture. The experts agreed that this could also present an inequitable service for housebound patients (EAC correspondence log 2021).

Initially, adopting 3C Patch will increase demand for outpatient appointments by requiring services to adopt weekly visits, with fortnightly visits being the norm under standard care (Clinical feedback on draft 3C Patch pathway 2021). In addition, each visit will take slightly longer (about 10 minutes) because of the need to draw blood and create the patch. On the other hand, with 3C Patch, some patients may require fewer mean appointments. Two experts noted that the impact on services would be minimal given the low number of patients likely to be treated with 3C Patch at any one time (EAC correspondence log 2021).

However, the experts noted that clinical practice varies between different centres and individual wounds, with some centres adopting weekly visits and others fortnightly visits or longer for patients with DFUs (EAC correspondence log 2021). As described in section 3, the experts mostly agreed that adopting weekly visits for 3C Patch should be possible for services (EAC correspondence log 2021). Two experts suggested that weekly visits may be difficult for clinics initially, but if more DFUs healed quickly then this would release capacity in the long term (EAC correspondence log 2021).

Currently, many services do not have the skill set required to take bloods and will need to expand their multidisciplinary working. The EAC also notes that some training will be required to operate the 3CP centrifuge and administer 3C Patch. The company confirmed that they provide practical training focused around making and applying the patch (EAC correspondence log 2021). The company stated that this is provided free of charge whenever needed and that initial training ideally takes place alongside the first patient's treatment in each clinic (EAC correspondence log 2021). The company explained that the training involves:

- attaching the device to the needle holder for blood collection
- powering the centrifuge
- operating the centrifuge's function buttons
- understanding and processing the messages on the centrifuge display
- loading the device into the centrifuge and knowing when a counterbalance is needed
- recognising the 3-step process (the 3 cs) for making a patch: centrifugation, coagulation, and compaction

- handling and practical application of the patch treatment
- routine cleaning of the centrifuge

The EAC observes that using the 3CP centrifuge may also give rise to logistical issues within a clinic should multiple patients require patches simultaneously. However, the clinical experts noted that if services are well managed, this is unlikely to be an issue due to the small numbers of patients receiving 3C Patch (EAC correspondence log 2021). Zink et al. (2021) [redacted]

The experts also raised other issues on the practicalities of using 3C Patch in clinical practice (EAC correspondence log 2021). These included:

- That it is difficult to take blood from some patients on such a regular basis (especially given the multi-morbidity in this population).
- That it is sometimes difficult and time-consuming to get a complete blood sample (18 ml of blood) to fill the device and this may be a barrier to treatment for some patients. Moreover, as the device is single-use and cannot be refilled, when this happens it must be discarded causing wastage. The company noted this occurs in about 5% of cases and when it happens the company provides a free Patch kit (EAC correspondence log 2021).

As explained in section 3, the EAC concludes that objectively measuring wound progress in hard-to-heal wounds is challenging and gives no weight to patient preferences. Hence adopting a single rule such as a 50% reduction in size is unlikely to be workable in practice.

The EAC notes inconsistencies about the mean expected treatment duration with the 3C Patch:

- The IFU states that 3C Patch can be used weekly but does not specify the maximum number of treatment weeks for which 3C Patch can be continued.
- The mean treatment duration in the RCT was 17.1 weeks, with a maximum treatment period of 20 weeks.
- The company submission states the initial treatment with 3C Patch is recommended for between 4 and 6 weeks (with treatment continuing for patients who demonstrate adequate improvement).

The EAC notes that the company submission also states that 3C Patch can be used once per week for up to 20 weeks at the discretion of the treating healthcare practitioner. According to the company submission, expert opinion indicates that treatment with the 3C Patch would be unlikely to continue for up

to 20 weeks in routine practice. These inconsistencies give rise to concerns about generalising from the RCT protocol to clinical practice.

The experts advised they would manage patients failing on 3C Patch with other aspects of standard care (offloading, infection control or vascular interventions), together with appropriate dressings. Hence improved healing should reduce the need to use these more challenging aspects of standard care.

8.2 Ongoing studies

The company submission identified the studies shown in the tables in appendix D (Table 14.13: ongoing studies; Table 14.14: grey literature; Table 14.15: Wounds UK website), which also shows the EAC identification of the studies (from a replication of these searches in these sources) and their eligibility according to EAC criteria.

Both the Company Submission and the EAC search identified the same ongoing study.

One ongoing study was found by EAC: Reapplix. (2019). The population, intervention, comparator and outcomes meet the Scope. It is currently recruiting, with an expected completion date of 31 December 2022. A more detailed description is provided in appendix D.

9 Economic evidence

9.1 Published economic evidence

9.1.1 Search strategy and selection

Critique of the company's search strategy

Appendix A of the company submission contained a description of the search methodology used to retrieve relevant economic evidence. The extent to which the EAC could assess the appropriateness of the search methodology was restricted due to lack of detail in the search reporting, though there appeared to be some limitations that could potentially impact on search sensitivity and the identification of relevant evidence. Details of the EAC critique of the company search strategy are provided in appendix E.

Due to the limitations in search reporting, the company search methods were not reproducible. As the EAC was unable to replicate and re-run the searches conducted by the company, the EAC conducted a de novo literature search to identify evidence. A single set of searches was conducted to identify clinical and economic evidence.

The EAC search was conducted in a range of resources containing details of published, unpublished and ongoing research. The EAC search retrieved 2,102 records. After deduplication 1,577 records remained for assessment. Full details of the EAC's de novo search methods are provided in appendix A.

Critique of the company's study selection

Company's study selection

The selection criteria applied by the company were not well defined using a PICO framework. Rather, inclusion relating to 3C Patch, DFUs and hard-to-heal wounds as well as costs and resource use were mentioned in appendix A of the company's submission. Studies reporting on the use of platelet-rich plasma products or non-3C Patch products were reported to be excluded. Given the lack of definition of the criteria applied by the company it is difficult to critique these for accuracy and alignment with the scope (NICE 2021).

EAC's study selection

The selection criteria adopted by the EAC to select relevant economic studies are summarised in Table 9.1. These are consistent with the scope (NICE 2021).

Table 9.1: Selection criteria adopted by the EAC for economic study selection

	Inclusion criteria	Exclusion criteria
Population	People with DFUs that are not healing despite standard wound care	Patients with other wound types or not having received standard wound care
Intervention	3C Patch	
Comparators	Standard conventional and advanced wound dressings for DFUs, including UrgoStart. Standard care is likely to vary depending on the characteristics of the wound (size, depth, and position) and stage of healing	
Outcomes	Not specified to maximise sensitivity	
Study design	Health economic studies (3C Patch v. comparator) • cost-effectiveness • cost-utility • cost-benefit • cost-minimisation • cost-consequence	Non-comparative cost analyses including cost of illness studies. Clinical studies reporting on cost of treatment in the discussion only without more formal analyses
Limits	No language restrictions	Studies published before 2010

	A date limit of 2010 was applied to the search	
Abbreviations: DFU – diabetic foot ulcer		

The EAC applied the selection criteria listed in Table 4.1 to the literature search reported in section 4.1.

Included and excluded studies

Company's selected studies

The company included 1 study within its economic review – the RCT published by Game et al. (2018a). The EAC does not agree with the inclusion of this study given that it does not report any cost or economic outcomes. It is understood that it was included by the company due to the reporting of resource use outcomes. However, while these are relevant for populating an economic model, the EAC judges that that these outcomes do not mean the paper constitutes an economic study.

EAC's selected studies

Those records identified during the clinical searches (reported in section 4.1) were sifted. In total, 1,578 unique records were screened based on the initial searches. No studies met the EAC's inclusion criteria, as listed in Table 9.1.

The trial protocol for the RCT published by Game et al. (2017) reports a plan to undertake a cost-effectiveness and cost-utility analysis of 3C Patch using data from the RCT. The EAC contacted Professor Game (EAC correspondence log 2021) who provided the unpublished health economic report (Farr et al. unpublished). The report meets the EAC's selected criteria and is, therefore, summarised in sections 9.1.2 and 9.1.3.

In total, the EAC screened a total of 1,579 records, of which 1 met the inclusion criteria. A PRISMA is provided in appendix A (Figure 14.3).

9.1.2 Published economic evidence review

One unpublished economic study [redacted] (Farr et al. unpublished). [redacted]

[redacted]

[redacted] Reapplix advises it did not receive replies to their concerns and was not aware of the existence of the final report.

9.1.3 Results from the economic evidence

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted] The report does, however, provide very useful data inputs which will be included within the EAC's critique of the company's model.

9.2 Company de novo cost analysis

9.2.1 Economic model structure

A de novo model was developed by the company which was appropriate given the lack of published economic evidence available. The clinical data within the model were largely based on Game et al. (2018a).

PICO analysis

Patients

The company states that the population entering the model are people with DFUs that are not healing despite standard wound care, including the use of advanced dressings where appropriate. The NICE Scope does not explicitly include the use of advanced dressings.

Experts suggested that there is limited evidence around the effectiveness of most advanced dressings and that the only advanced dressings with proven efficacy in people with DFUs is UrgoStart. They did confirm, however, that UrgoStart would likely be used prior to 3C Patch in clinical practice (EAC correspondence log 2021). Therefore, the company's addition of use of 'advanced' dressings to people entering the model seems appropriate.

The company submission stated that patients in Game et al. (2018a) received UrgoStart during the run-in period. However, one of the Chief Investigators to the RCT (Professor Game who is also one of the clinical experts) advised this was not the case because UrgoStart was not yet recommended for use at the time of the trial, with the trial for UrgoStart running at a similar time (EAC correspondence log 2021). Supplementary evidence provided by the company showed UrgoStart was used for at least 1 week during the run in period in the Game et al. (2018a) RCT in 0.2% of patients and all protease modulators in 40% of patients. Therefore, the clinical evidence used in the model is in a population that had not used UrgoStart but would have used other protease modulator dressings (EAC correspondence log 2021).

This is judged to be a limitation of the economic modelling because, according to experts, in clinical practice 3C Patch would not be used be used unless UrgoStart had not worked due to it being easier to use. Given UrgoStart is now recommended for use, the use of this dressing could increase in future.

Experts did comment on the differences in selection criteria between the UrgoStart trial and the 3C Patch trial and noted that inclusion criteria were more permissive for 3C Patch and therefore it is possible that some patients in the 3C Patch trial would have had ulcers that could be considered 'harder to heal' ulcers than those in the UrgoStart trial (EAC correspondence log 2021). Hence the patient groups in the two trials were different and so this may not have impacted greatly on the outcomes of the Game RCT, with those in Game et al. (2018a) being more representative of a group who have failed on UrgoStart. Hence the results might be generalisable to UrgoStart experienced patients in the NHS.

The company defined hard-to-heal ulcers as those with less than 50% progress towards healing during a 4-week run-in period which is aligned with the population entering the Game et al. (2018) RCT. However, experts advised that in clinical practice there would likely be no formal run-in period and they would not apply a 50% rule on change in ulcer size from baseline to determine which patients might benefit from 3C Patch. Rather the clinician would assess patient history to see if their wound was progressing with previous treatment. Therefore, criteria for the use of 3C Patch in clinical practice may be different from that in the trial. The bias this could introduce is difficult to assess. If more patients in practice were eligible for use of the 3C Patch this could impact on both the effectiveness of 3C Patch and standard care (i.e. if patients with ulcers that are not as hard-to-heal as those seen in the trial are eligible the effectiveness of both treatments is likely to be higher). Increasing the eligibility could also have a knock on effect in terms of capacity and training.

Technology

The intervention in the model is the 3C Patch as an adjunctive treatment in addition to standard care which is aligned with the NICE Scope.

Comparator(s)

The comparator in the model is standard wound care which includes conventional and advanced wound dressings. This is aligned with the NICE Scope. The company state in their submission that patients in the standard care arm of the trial received a full range of dressings, including UrgoStart. However, supplementary evidence provided by the company shows use of UrgoStart for at least 1 week of treatment in the comparator arm in only 1% of patients and other protease modulating dressings in 60% of patients (EAC correspondence log 2021). The NICE Scope specifies that the comparator in the model should be standard conventional and advanced dressings including UrgoStart. Therefore, the trial is not fully aligned with the Scope for the comparator due to the lack of use of UrgoStart, however, it is acknowledged

that this was not recommended for use in England at the time of conducting the Game et al. (2018a) RCT. Further, experts commented that the 3C Patch would likely be used as a treatment option for those in whom other advanced dressings (including UrgoStart) have failed and, therefore, this is unlikely to impact on the effectiveness of standard care if UrgoStart is deemed to be unsuccessful in this patient group. However, there are no data available to confirm this. Increasing use of UrgoStart could also impact on the costs of the comparator arm in the model. However, the cost difference between dressings is relatively small so this is not likely to have a material impact on the results. This is explored within sensitivity analysis. Experts also confirmed that the mix of dressings used in the standard care arm of the trial (60% protease modulators) was reflective of current clinical practice. These data were used to cost the standard care comparator in the model.

Model structure

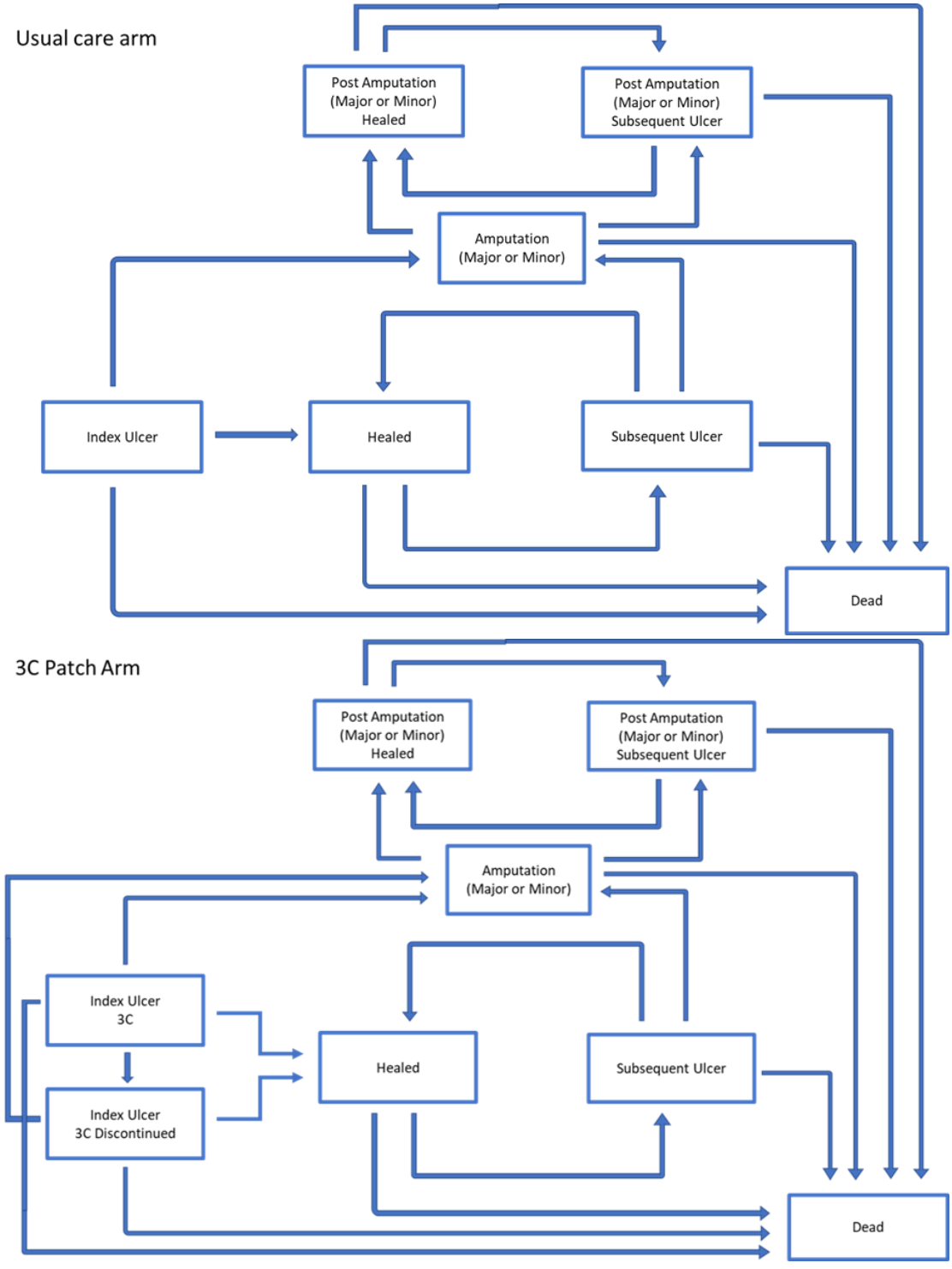
The company's model comprises a Markov structure with several health states based around wound healing and was developed in Treeage. The base case analysis is presented over a 2-year time horizon with weekly cycles. A 3-year time horizon was also explored by the company. The 2-year time horizon used by the company was deemed appropriate by the EAC. The majority of index ulcers have healed by this point and the model does not consider the use of 3C Patch in any subsequent ulcers that occur. Discounting was applied in line with the NICE reference case. A diagram of the company's model structure is shown below which is also presented in the company's submission (appendix B). The EAC judged the diagrams presented by the company to accurately reflect the model submitted, however, notes that the arrows denoting patients being able to remain in health states have been missed from the diagram. Patients can remain in all health states with the exception of minor and major amputation which are tunnel states.

Patients in the 3C Patch arm of the model receive the 3C Patch for up to 20 weeks, consistent with Game et al. (2018a), following this they switch to standard care dressings. Patients in the standard care arm receive standard care dressings for the full time horizon of the model provided they remain in the 'Index ulcer' health state. Patients in the model can also discontinue use of the 3C Patch at 5 weeks if there has not been adequate progress towards healing (defined as a reduction in ulcer area of 50% or more) in line with the suggested clinical pathway presented by the company. Ulcer recurrence was also modelled whereby patients in the healed ulcer health state can have a subsequent ulcer. A simplifying assumption was made by the company whereby 3C Patch was not used in subsequent ulcer health states. This was judged by the EAC to be appropriate because these ulcers may not initially be hard-to-heal. There was no modelling of these ulcers becoming hard-to-heal

and therefore qualifying for the use of 3C Patch because this would have led to a lot of additional model complexity. This was judged appropriate by the EAC because it is unlikely to have had a significant impact on the model results given the time horizon of the analysis.

Minor and major amputation as well as post amputation health states were also included.

Figure 9.1: Company model structure



The company's model was replicated in Microsoft Excel to check for errors and confirm the model matched what was presented in the company submission. No errors or discrepancies were identified.

Overall the company's model structure was judged to be appropriate, however, the following potential issues were identified by the EAC:

- *Use of a discontinuation rate in the model at 5 weeks for 3C Patch arm*

Clinical experts questioned the cut off metric (reduction in ulcer area of less than 50%) used to calculate:

- eligibility for 3C Patch; and
- discontinuation with 3C Patch at 5 weeks based on the company's suggested clinical pathway

They noted that they would not use such a measure to determine who should receive a 3C Patch but rather patient history and clinical judgement and that no formal run-in period as per the trial would be required. As discussed within the PICO section above the direction of bias is difficult to assess and therefore no changes were made in the EAC model to address this but, it is noted as a limitation of the evidence.

The clinical experts advised a 50% threshold could be too high to determine discontinuation and that any improvement in healing over and above what was seen with standard care could warrant continued use of the 3C Patch. They also noted that many clinics would not be able to undertake accurate measurements of size with their current tools. From a patient perspective it would be difficult to withdraw the 3C Patch from a patient who was responding better to treatment with the 3C Patch than they had with standard care even if this response was not as high as 50% reduction. They also noted that measures employed to determine ulcer area in many clinics are not very accurate and hence using an exact cut-off could be difficult in practice. One expert commented that they would be guided by the manufacturer and that on the manufacturer website, the guidance under FAQs is to stop or pause treatment at 6 weeks if there is no effect, rather than a 50% reduction in wound area (EAC correspondence log 2021).

Additionally, whilst Game et al. (2018a) adopted the 50% criterion as an exclusion criterion, it did not use a cut off or discontinue use of 3C Patch and therefore the published evidence presents the probability of healing over 20 weeks from use of 3C Patch in all 'eligible' patients until healing in the treatment arm. The company used unplanned post hoc analysis of the trial data to calculate the proportion of patients with less than 50% reduction in ulcer area at 5 weeks and assumed these patients (about 58% of those entering the model) would discontinue use of the 3C Patch in clinical practice, and therefore receive standard dressings. The associated probability of healing was calculated using the 'equivalent' cohort from the standard care

arm (i.e. also those who had seen less than 50% reduction in ulcer area). The figures used from the trial to calculate the discontinuation rate at 5 weeks for 3C Patch were provided to the EAC. The EAC confirmed that the discontinuation rate was calculated correctly. However, the company had been advised by NICE that it would not expect to receive raw data from the trial and hence none were provided. Therefore the EAC could not assess that the correct figures were used from the trial or assess the appropriateness of the post hoc analysis. The data used and the EAC assessment of this data are discussed further in section 9.2.2.

- *No explicit inclusion of infection*

A health state was not included for infection in the model. It is noted that the company model included antibiotic costs to reflect the occurrence of infection which were based on those reported to be used in Game et al. (2018a). However, patients with infection would continue to use the 3C Patch in the company's model because this was not captured as part of the discontinuation or in any other way. From further discussions with the company, it was confirmed that this was aligned with what happened in Game et al. (2018a) i.e. patients with infection continued to receive 3C Patch (although patients with an infected ulcer at the start of the trial were excluded) (EAC correspondence log 2021). However, experts gave conflicting statements on the use of the 3C Patch in patients with an infected ulcer which included:

- continue use (2 experts)
- discontinue use until infection subsides (4 experts)
- depends on extent of infection, discontinue in moderate/severe infection (1 expert)

The IFU provided by the company at the start of this project were from the USA. These stated that actively infected wounds were a contraindication to the use of the 3C Patch system and that treatment should be for up to 20 weeks. Later the company provided the UK IFU. This does not list any contraindications nor a maximum treatment period. However, this information came to light after the EAC model had already been developed.

The company also submitted a [redacted] (Zink et al. 2021). [redacted]

[redacted]

Additionally, it was judged by the EAC that further costs could be incurred by the health care system as a result of an infected ulcer, such as additional staff time, inpatient admissions or appointments which may not be fully captured within the company's model.

Table 9.3: Company model assumptions

Assumption	Justification	Source	EAC comments
All patients start with a hard-to-heal ulcer that is not healing despite standard care including advanced dressings where appropriate	These were the ulcers studied in the 3C Patch RCT and proposed in the draft clinical pathway.	Game et al. 2018, 3C Patch draft clinical pathway	This was judged appropriate being the only evidence available, although it is noted that the Game et al. (2018a) RCT only included use of UrgoStart in 0.2% of patients in the run-in period in the trial and this would likely be used prior to 3C Patch in clinical practice. Also patients were excluded from the RCT who may be treated in clinical practice i.e. those who saw a more than 50% reduction in ulcer area in the run-in period.
Patients receiving 3C Patch are reviewed after 5 weeks, and 3C Patch is continued only for patients whose ulcers have reduced in area by ≥50%.	This is in line with the draft clinical pathway, though the pathway also stresses the importance of clinical judgement.	3C Patch draft clinical pathway	Judged to be partially appropriate. It is acknowledged that clinical judgement would likely be used to decide which patients would continue use of 3C Patch at around 5 weeks and this was confirmed with clinical experts, however, the majority of experts (6 out of 7) did not agree with the use of ≥50% reduction in ulcer area as criteria for a discontinuation rule.
Patients who continue 3C Patch treatment after 5 weeks continue with 3C Patch until healing or up to 20 weeks if healing does not occur	This is in line with the 3C Patch RCT (though in the RCT it applied to all 3C Patch patients as the protocol did not include provision for stopping at 5 weeks if sufficient progress had not been made). It is also in line with the draft clinical pathway, though the pathway also allows for 3C Patch to be stopped at any point after 5 weeks if clinical	Game et al. (2018a) and 3C Patch draft clinical pathway	This is not in line with UK IFU but does accord with the RCT.

	judgement indicates either that progress toward healing has stalled, or that healing is likely to be completed without further use of 3C Patch. This is a conservative assumption.		
Patients in the 3C Patch arm have weekly clinic visits. At each visit clinicians decide whether to apply a new patch. Each patch lasts one week and is not replaced during that time.	This is in line with the 3C Patch RCT and the draft clinical pathway.	Game et al. (2018a), 3C Patch draft clinical pathway	This was judged to be appropriate.
Patients in the standard care arm of the model receive good standard care, including advanced dressings where appropriate. Clinic visits (MDFT or foot protection service) are fortnightly.	The use of good standard care is in line with the 3C Patch RCT. In the RCT, patients in the standard care arm had weekly clinic visits. However, expert opinion indicates that this is not usual practice in the NHS unless ulcers are infected. Conservatively, we adjust the frequency of clinic visits to fortnightly for standard care patients, relative to that observed in the RCT, but we do not adjust healing rates.	Game et al. (2018a), Expert opinion	This was judged to be appropriate by the EAC – the model will reflect the costs likely to be seen in practice rather than in the RCT.
The distribution of severe and less severe index ulcers is as seen in the NDFA. (Although these ulcers are hard-to-heal, they are not considered to be more severe in terms of SINBAD score than average ulcers, and weekly costs of treatment are assumed to be the same as for average ulcers, apart from cost adjustments specific to 3C Patch.)	Conservative assumption.	Expert opinion	This was judged to be appropriate by the EAC – no further data on costs for hard-to-heal ulcers could be specifically identified.
When patients stop 3C Patch treatment, they receive good standard care, as for	Expert opinion indicates that this is likely. It is also an important	Expert opinion	This was judged to be appropriate by the EAC.

patients in the standard care arm of the model.	modelling assumption, to avoid bias in the results.		
After ulcer healing, all patients receive care in line with NICE guidance for those at high risk of developing a diabetic foot problem.	Expert opinion indicates that this is likely.	NICE Guideline NG19 Diabetic Foot Problems: Prevention and Management	This was judged to be appropriate by the EAC.
Patients who have healed are at risk of re-ulceration. If re-ulceration occurs, the distribution of severe and less severe ulcers, and associated healing rates, are as seen in NDFA. It is not assumed that these subsequent ulcers are hard-to-heal.	No clinical evidence was found to indicate that subsequent ulcers are more likely than average to be hard-to-heal in patients who have had a previous hard-to-heal ulcer. Some studies indicate that subsequent ulcers tend to be less severe than index ulcers in patients who have been treated in a multidisciplinary setting, owing to good quality follow-up and patient education.	Expert opinion, Hicks et al. 2020	EAC confirmed this with clinical experts (EAC correspondence log 2021)
Amputations occur only when patients have active ulcers		Expert opinion	Judged to be appropriate.
A maximum of one amputation occurs in the model	This is considered a reasonable assumption over the 2-year model horizon, to avoid unnecessary complexity in the model. It is a conservative assumption, as additional amputations would be more likely in the standard care arm owing to increased risk of a first amputation in the index ulcer state, owing to increased ulcer duration.		EAC agrees with simplifying assumption given it is likely to make very little difference to the results of the model.
Abbreviations: EAC - External Assessment Centre; IFU - instructions for use; MDFT – multidisciplinary specialist diabetes foot clinic; NDFA - National Diabetes Footcare Audit; RCT – randomised controlled trial.			

EAC changes to model structure

The functionality to include ‘moderate/severe infection’ as a health state was included in the EAC model to account for patients discontinuing use of the 3C Patch for moderate/severe infections whilst their ulcer is infected. It was judged that the 3C Patch may continue to be used for mild infected ulcers, but based on expert responses it is less likely to be used for moderate/severe infections. This also allows for additional costs of infection that may be incurred by the health care system to be captured. Where infection was included as a health state, transitions were also altered so patients only transition to amputation following infection. Additionally, simplifying assumptions were made whereby patients do not transition to amputation or infection from the subsequent ulcer health state. The probability of subsequent ulcers in the model is low so the impact of altering these transitions was deemed to be unlikely to have a substantial impact on the results of the model. Additionally, subsequent ulcers will not start out as hard-to-heal so it was not necessarily deemed appropriate to apply the same transition probabilities to infection and amputation to those with subsequent ulcers as those with hard-to-heal ulcers from the trial.

Where infection is included as a health state, patients who have had an infection can transition back to the index ulcer state (therefore receiving 3C Patch) up until 20 weeks in the model. After 20 weeks has elapsed, they transition to the 3C Patch discontinued health state and therefore receive standard care. This is a simplifying assumption because in practice if a patient with an infected ulcer discontinued use of the 3C Patch for a period of time until the infection had cleared, this time may not count towards their 20 week treatment time with the patch. However, this was deemed necessary to avoid overcomplicating the model structure.

It should be noted that transitions for the model where infection is included as a health state are more uncertain due to the way the trial was conducted (with 3C Patch use continued despite infection) and a paucity of data around the transitions in and out of the infection health state. However, in collaboration with the NICE team, it was judged to be important to be able to present the model capturing this uncertainty around the use of 3C Patch when ulcers become infected. Therefore, the EAC analysis with and without the infection health state included is presented throughout this report and referred to henceforth as Model A (no infection health state), and Model B (infection health state). Diagrams of both EAC model structures can be found in appendix F.

The 3C Patch discontinued health state was still included in the EAC model but sensitivity analysis was conducted around the discontinuation at week 5

with no discontinuation occurring in the base case as per the Game et al. (2018a) RCT.

Half cycle correction was applied in the EAC model although this change would have had negligible impact on the results.

9.2.2 Economic model parameters

The key model parameters are discussed in this section with further clarification and inputs presented in sections 9.2.3 to 9.2.5.

As noted in section 9.2.1, a probability of discontinuation was applied in the company model at 5 weeks. This was based on a post hoc analysis of the Game et al. (2018a) RCT based on the number of patients that did not see a > 50% reduction in ulcer area at 5 weeks. Although clinical experts agreed a patients' response to treatment would likely be assessed between 4 and 6 weeks, the majority did not agree with the use of 50% ulcer area as a criteria and that any reduction over and above what was seen with standard care could warrant continued use of the 3C Patch (EAC correspondence log 2021). Further, the [redacted] (Zink et al. 2021).

The EAC also had additional concerns that the use of the discontinuation rate was based on unplanned post hoc analysis of the trial. The rates could not be properly assessed by the EAC because the company had been advised that it was not expected to submit raw data from the RCT. Additionally, patients in the Game et al. (2018a) RCT did not discontinue use until 20 weeks or ulcer healing. Therefore, there is no evidence available on what would have happened to these patients that did not see a more than 50% reduction in ulcer area if they had discontinued use of the 3C Patch. In the company model these patients switch to the standard care arm and have a probability of healing applied which is also calculated from post hoc trial analysis for the standard care arm. This probability is calculated using the equivalent cohort in the control arm i.e. those that had not seen a reduction of 50% or more in ulcer area therefore assuming that 3C Patch had no impact at all on healing rates for the initial 5-week period.

Further, use of this post hoc analysis for the company model also means the number of patients assessed for the probability of healing with 3C Patch in weeks 6 to 20 from the trial reduces by more than 50% to [redacted] patients for the treatment arm and to [redacted] patients for the probability of healing when 3C is discontinued. This therefore disregards a substantial amount of the data particularly from the 3C Patch arm of the trial for this time period resulting in further uncertainty in the derived probability. The probability of healing with 3C

Patch in weeks 6 to 20 is a key driver in the company model and a fairly small reduction (approximately 0.6%) could result in the direction of the results changing in their model.

For these reasons the EAC decided to amend the discontinuation rate at 5 weeks with 3C Patch to 0% in line with clinical evidence extracted from the Game et al. (2018a) RCT and test the impact of varying this in sensitivity analysis alongside changes in the probability of healing with the 3C Patch after discontinuation (to reflect that healing may be higher than that shown in the trial if patients who are not responding as well discontinue use of the 3C Patch). Where this is applied in sensitivity analysis in the EAC model, it is noted that patients who discontinue use of the 3C Patch and switch to standard care receive the same probability of healing as those in the standard care arm of the trial. This could overstate healing in these patients because the probability is based on all patients who received standard care dressings whereas those who have not responded adequately to 3C Patch could be patients with harder-to-heal ulcers and therefore may be less likely to respond to standard care dressings. This is also explored in sensitivity analysis.

The probability of healing with 3C Patch in the company model was calculated from post hoc trial analysis as described above. The EAC revised this and instead used the published RCT data. Transition probabilities were still applied for weeks 0 to 5, weeks 6 to 20 and week 21 onwards in line with the company's model structure. Transition probabilities were estimated using model calibration to align the proportion of patients healing with the 3C Patch to the proportion of patients healing in the trial at weeks 5 and 20. The proportion of patients healing in the trial was estimated based on the Kaplan Meier data reported by Game et al. (2018). The data from the curves presented in the published paper were extracted using Webplot digitizer. These time periods were chosen based on the company's analysis and to enable different probabilities of healing to be tested if discontinuation occurs in the model at 5 weeks. Beyond the 20-week time period, all patients are assumed to discontinue use of the 3C Patch which is in line with the company model and the Game et al. (2018a) RCT.

Similarly for the standard care arm, the company used post hoc analysis of the Game et al. (2018a) RCT to calculate different probabilities of healing for weeks 1 to 5, weeks 6 to 20 and week 21 onwards. Again, the EAC chose to use the published data from the Game et al. (2018a) RCT and also applied probabilities for weeks 0 to 5, 6 to 20 and 21+ in line with the 3C Patch arm in the model. The same method of model calibration to match proportion healing at week 5 and 20 in the model with the trial was used to estimate the transition probabilities for the standard care arm. Again, the probabilities from the trial were estimated using data extracted from the Kaplan Meier data

presented in Game et al. (2018a) using Webplot digitizer. Beyond 20 weeks a constant probability of healing was applied using the probability estimated by the company (applied in both arms of the model because all patients on 3C Patch have discontinued use after 20 weeks). This probability was estimated based on data from the Game et al. (2018a) RCT in weeks 21 to 52 which the EAC did not have access to. The company calculated this based on 169 patients who had not healed within the 20-week treatment time and for whom 52 week data were available from both treatment arms in the trial. Therefore the EAC was unable to assess the accuracy of the calculations used. However, given the lack of any other available data with which to estimate this probability it was judged to be the best available source. Without view of the data it is not possible to assess whether grouping the two arms is appropriate or whether different healing rates may have been observed following the 20-week treatment period (i.e. if 3C had any impact on healing past 20 weeks).

The probabilities of healing in both arms are shown in Table 9.4.

Table 9.4: Probabilities of healing in EAC model

Week	Proportion healed extracted from KM data – 3C Patch	Proportion healed extracted from KM data – Standard care	Probability of healing applied in the model			
			3C Patch – Model A	Standard care – Model A	3C Patch - Model B	Standard care – Model B
0-5	3.7% (at 5 weeks)	3.0% (at 5 weeks)	0.8%	0.6%	0.8%	0.6%
6-20	34.1% (at 20 weeks)	21.6% (at 20 weeks)	2.7%	1.5%	3.0%	1.7%
Model A = no infection health state, Model B = infection health state included						

Probabilities of healing are slightly higher when infection is included as a health state in the model because patients with infection in the model are removed from the 'ulcer' health state and therefore the denominator for the healing probability will be smaller. It is noted that 3C Patch was still used in patients with an infection in Game et al. (2018a), however, it was judged that it was unlikely that those patients would have had an ulcer heal without first having an uninfected ulcer. This does lead to some uncertainty because there are no data on whether use of the 3C Patch on infected ulcers increased their probability of healing after the ulcer became uninfected. However, one of the clinical experts stated their reasoning for not using 3C Patch on infected ulcers was that it is unlikely to be beneficial in an infected ulcer.

The probability of reulceration in the company model is taken from a paper by Armstrong et al. (2017). Within the paper point estimates at 1 year (40%) and 3 years (65%) are reported. The company calculated their probability of recurrence by adjusting the 3-year estimate to a weekly probability. The EAC

notes that according to the graph of incidence of recurrence presented in the paper, the use of the 3-year probability to estimate the transition probability is likely to understate recurrence during the first year in the model (0.6% per week). However, using the 1-year probability would likely overstate recurrence post 1 year in the model (1.0%). Clinical experts confirmed recurrence depends on a range of factors, and the fact someone has had a hard-to-heal DFU does not necessarily impact on their risk of recurrence. They also confirmed that they would not expect 3C Patch to impact on recurrence risk (EAC correspondence log 2021). Therefore, the EAC made no changes to the parameter but the impact of this is explored in sensitivity analysis. Varying this parameter within sensitivity analysis did not appear to have any substantial impact on the results of the model.

Weekly probability of healing for subsequent ulcers was taken from the NDFA. This was judged to be appropriate by the EAC because it will be reflective of all ulcers and is generalisable to the NHS setting. Clinical experts noted that hard-to-heal ulcers are hard-to-heal due to a range of factors that vary from each individual, and therefore having a hard-to-heal ulcer does not necessarily mean a subsequent ulcer will become hard-to-heal. The EAC updated this value to use data from the latest NDFA report, however, notes this latest report only reports 12 week rather than 24 week data. This results in a very similar transition probability.

Where infection was included as a health state by the EAC the following transition probabilities were calculated:

- Weekly probability of moderate/severe infection with 3C Patch and with standard care. This was estimated using data from Game et al. (2018a). Serious adverse events were presented within the supplementary appendix for each treatment arm at 20 weeks. The numbers reported for DFU infections, infections, gangrene and sepsis were taken for both treatment arms and divided by the median (mean was not reported) time to healing in each arm. These were calculated as rates rather than probabilities because it appeared infections occurred more than once in some patients. Separate probabilities were applied to each treatment arm because patients would be receiving different treatments (i.e. 3C Patch and standard care) so in theory this could have implications for infection rates although no statistically significant difference was observed in the trial. If patients discontinue from 3C Patch in the model they have the same probability of infection as those patients in the standard care arm. It should be noted that this overestimates infections in the model at 20 weeks likely due to the use of median time to healing rather than mean. The incremental difference between arms is also overestimated (in favour of standard care) and

therefore this could have increased costs in the 3C Patch arm of the model. This is explored in sensitivity analysis.

- Weekly probability of infected ulcer becoming uninfected.

Again this was estimated by the EAC using data from Game et al. (2018a). The total number of days of antibiotics was reported for each treatment arm. This was used as a proxy for number of days infected. The total number of days infected for both arms was divided by the total number of infections at 20 weeks reported in both arms and therefore the same probability of an infected ulcer becoming uninfected was applied to both arms. This approach was used because if the 3C Patch was not being used for these patients, they would be receiving the same treatment and therefore in theory should have the same probability of the infection clearing.

The weekly probability of amputation was estimated by the company using data from both arms in the trial. This was judged to be appropriate by the EAC because there was very little difference in those observed at 26 weeks and this also increases the sample size for the calculation (9 vs 8). Only the amputations occurring on the index limb were included within the estimation, and again this was judged to be appropriate. Therefore the EAC used the same probabilities as the company in their model. Where infection was included as a health state in the EAC model (Model B) these probabilities were recalculated so as to apply them to the infected ulcer health state rather than ulcer health states. Model calibration was used to match the amputations reported at 26 weeks in the trial to those reported at 26 weeks in the model.

The probabilities of death estimated by the company were judged to be from appropriate sources that were generalisable to the decision problem and therefore no changes were made by the EAC.

9.2.3 Clinical parameters and variables

Table 9.5 shows the clinical parameters used in the company's model and any changes made by the EAC.

Table 9.5: Clinical parameters used in the company's model and changes made by the EAC

Variable	Company value	Source	EAC value	EAC comment
Discontinuation of 3C Patch at 5 weeks	57.9%	Calculated based on post hoc analysis of Game et al. (2018a) RCT	0%	The EAC recognises that in practice clinical judgement will likely be used to determine whether patients should continue with 3C Patch. However, the published trial data did not include discontinuation of the patch. Therefore in the base case the EAC model aligns with the trial data and explores various discontinuation rates in sensitivity analysis alongside variation in the healing probability with 3C Patch.
Weekly probability of healing with 3C Patch	Weeks 0 to 5: 0.6% Weeks 6 to 20: 5.7% Week 21 onwards: 1.3%	Calculated based on post hoc analysis of Game et al. (2018a) RCT	**Model A** Weeks 0 to 5: 0.8% Weeks 6 to 20: 2.7% Week 21 onwards: 1.3% **Model B** Weeks 0 to 5: 0.8% Weeks 6 to 20: 3.0% Week 21 onwards: 1.3%	Transition to healing with 3C Patch was calculated using model calibration to match the proportion of patients healed at 5 weeks and 20 weeks in the trial.
Weekly probability of healing with standard care	Weeks 0 to 5: 0.8% Weeks 6 to 20: 1.4% Week 21 onwards: 1.3%	Calculated based on post hoc analysis of Game et al. (2018a) RCT	**Model A** Weeks 0 to 5: 0.6% Weeks 6 to 20: 1.5% Week 21 onwards: 1.3% **Model B**	Transition to healing with 3C Patch was calculated using model calibration to match the proportion of patients healed at 20 weeks in the trial.

Variable	Company value	Source	EAC value	EAC comment
			Weeks 0 to 5: 0.6% Weeks 6 to 20: 1.7% Week 21 onwards: 1.3%	
Weekly probability of healing with 3C Patch discontinued	Weeks 6 to 20: 0.7% Week 21 onwards: 1.3%	Calculated based on post hoc analysis of Game et al. (2018a) RCT. Data from the control arm for patients with ulcers that had reduced less than 50% after 5 weeks used to calculated probability of healing between weeks 6 and 20	Not used in base case. Assumed equal to standard care for sensitivity analysis.	EAC assumed equal to probability of healing with standard care. Note this only impacts the model in sensitivity analysis where discontinuation at 5 weeks is varied.
Weekly probability of minor amputation	0.3%	Game et al. (2018a) RCT data based on whole cohort. Amputations at 26 weeks were used to calculate weekly probabilities, adjusted by the number of ulcerated weeks. Game et al. (2018a) RCT data based on whole cohort	**Model A** 0.3% **Model B** 1.2%	Including infection as a health state necessitated altering the transition to infection because there were fewer patients in the infection state and it was assumed patients would only transition from the infection health state to amputation. These were calibrated using the model to match the number of amputations reported in the Game et al. (2018a) RCT at 26 weeks. Where infection was not included as a health state the EAC used the same values as calculated by the company. However, it should be noted that the EAC could not replicate these values exactly because they were adjusted to ulcerated weeks based on data from the Game et al. (2018a) RCT which the EAC did not have access to.
Weekly probability of major amputation	0.1%		**Model A** 0.1% **Model B** 0.2%	
Weekly probability of healing for subsequent ulcers	4.7%	NDFA 2014-17	5.4%	NDFA 2014-18. It was deemed more appropriate to use the most recent data from NDFA although it is acknowledged that the most recent report only presents 12 week rather than 24 week data.
Weekly probability of moderate/severe	NA	Not included as a health state by the company	**Model B only** 1.99%	Calculated using data from the Game et al. (2018a) RCT supplementary appendix. Serious AEs (n=27 infection,

Variable	Company value	Source	EAC value	EAC comment
infection with 3C Patch				gangrene and sepsis) at 20 weeks in the 3C arm was divided by the median (mean not reported) time to healing in the 3C Patch arm of 10.3 weeks (72 days) to calculate a weekly rate.
Weekly probability of infection with standard care	NA	Not included as a health state by the company	**Model B only** 1.49%	Calculated using data from the Game et al. (2018a) RCT supplementary appendix. Serious AEs (n=24 infection, gangrene and sepsis) at 20 weeks in the standard care arm was divided by the median (mean not reported) time to healing in the standard care arm of 12 weeks (84 days) to calculate a weekly rate.
Weekly probability of infected ulcer becoming uninfected	NA	Not included as a health state by the company	**Model B only** 9.5%	Estimated using total number of days of antibiotics reported in Game et al. (2018a) for each treatment arm (2822+2662) divided by total number of infections reported (63+51) to estimate average length of infection overall.
Weekly probability of reulceration	0.6%	Based on Armstrong et al. (2017)	0.6%	No change was made by the EAC
Probability of death - ulcer or infected ulcer (no amputation)	0.3%	NDFA 2015 to 2018	0.3%	No change was made by the EAC
Probability of death - no ulcer (no amputation)	0.2%	Based on Jupiter et al 2016	0.2%	No change was made by the EAC
Probability of death – following major amputation	0.5%	Based on average of probabilities reported by Icks et al 2011 and Ikonen et al 2010	0.5%	No change was made by the EAC
Model A = no infection health state, Model B = infection health state included				
Abbreviations: EAC – External Assessment Centre; NA – not applicable; NDFA - National Diabetes Footcare Audit; RCT – randomized controlled trial.				

9.2.4 Resource identification, measurement and valuation

Resource use and costs in the model were described in the company's economic submission. However, there was insufficient detail to enable the EAC to validate the values used and hence further information was requested. This was provided in a separate report (EAC correspondence log 2021).

Resources and costs were included to manage:

- hard-to-heal DFUs in inpatient, outpatient and community settings
- healed DFUs
- amputations (major and minor)

As stated in section 9.2.1, there was no infection health state within the company's model. Given the advice from experts that use of the 3C Patch might be discontinued when a patient had an infection, the EAC developed two models, without infection (model A) and with infection as a health state (model B). Separate costs are presented for each model when these differ depending on whether infection is a separate state. Unless stated otherwise, all costs within the tables and text are weekly cost per patient.

3C Patch resources and costs

Table 9.6 shows the costs used in the company's model and any changes made by the EAC for the 3C Patch arm.

Table 9.6: 3C Patch costs per patient per week from company model and changes made by the EAC at 2021 prices

Parameter	Company value	EAC value	Source
3C Patch: Additional NHS provided care for dressing changes between outpatient consultations.	-£25.71	£42.77	The company assumed 0.56 fewer district nurse visits per week with 3C than standard care, each took 30 mins, nurse was a band 6. Costs were from PSSRU (Curtis and Burns 2020). The EAC costed [redacted] visits per patient (Farr et al. unpublished) for 30 mins and staff costs of £89 per hour of patient contact time for a band 6 nurse (source PSSRU at 2019/20 prices and updated to 2021 prices).
3C Patch: Outpatient consultation	£135.97	£111.66	Company used a weekly cost for outpatients and the community derived from Kerr et al. (2019).It added 10 mins for band 4 nurse for phlebotomy and 20 minutes additional time for podiatry. PSSRU hourly rates were applied.
3C Patch: Additional nurse inputs for phlebotomy and centrifuge	£5.26	£5.22	The EAC used same source but deducted the cost of a district nurse (£28.21) to avoid double counting this. The EAC included an additional [redacted] minutes per outpatient appointment (Farr et al. unpublished and aligned with experts' opinion; EAC correspondence log [2021]). The [redacted] minutes additional time was applied to a podiatrist (band 6) and nurse (band 4) as both are assumed to be present during the appointment. This is an hourly rate from PSSRU (Curtis and Burns 2020; £48 for band 6 podiatrists and £30 for band 4 nurses, updated to 2021 prices).
3C Patch: Additional podiatry inputs	£16.22	£8.36	
3C Patch: Total outpatient attendance	£157.45	£125.24	
3C Patch: Inpatient cost for severe infections and revascularisation. (Model A)	£92.51	£52.51	The company used a cost per infected ulcer from Kerr et al. (2019). The same value was applied across both treatment arms. EAC assumed a cost per severe ulcer of £7052.26 in 2021 prices (NG19, 2015a from Kerr et al. (2014) .This was applied to [redacted] patients admitted with severe DFU infection. The company did not include revascularisation costs . The EAC calculated these costs from a weighted average HRG codes from NHS reference costs (NHS England 2019; YQ10A to YQ12D, £8,975.45) and applied it to [redacted] patients who underwent this procedure (Farr et al. unpublished). These were added to the cost of managing [redacted] severe infections. This total of £137,839 was divided by 132 patients and then by 20 to give a weekly cost per patient.
3C Patch: Inpatient cost for revascularisation. (Model B)	Not included	£6.80	In model B where infection is a health state, inpatient costs other than infection only relate to revascularisation. This was calculated as for model A.

Parameter	Company value	EAC value	Source
3C Patch: Infection cost (one off cost). Model B.	Not included	£2,373.62 (one off cost)	In model B, the cost of severe ulcer deterioration (£7052.56) from Kerr et al. (2014) was weighted by the proportion of infections that were severe ([redacted]) as reported in Farr et al. (unpublished) . Added to this was the antibiotic cost per patient (£22.87), updated from Farr et al. (unpublished) to current prices using BNF.
3C Patch: Standard care dressing cost when infected. (Model B)	Not included	[redacted]	The EAC applied unit costs from NHS Supply Chain (2021) to all dressings used in Game et al. (2018a) to calculate a mean cost per standard care dressing.
3C Patch: Device cost	£125.40	£125.40	0.836 patches used on average per week and unit cost £150. From company submission.
3C Patch: Secondary dressings cost	£0.39	[redacted]	A Soft Pore 10cm x 10cm, 3 per week. Company applied BNF costs but EAC used NHS Supply Chain (2021) costs.
3C Patch: Antibiotics to manage infections.	£7.13	£1.14	The EAC estimated the cost of medications from Farr et al. (unpublished), using BNF unit costs. These differ from the company submission, which conducted its own analysis on patient level data to estimate an antibiotic cost also using BNF and added staff costs for intravenous and intramuscular administration. The EAC did not include staff cost because we included the cost of all district nurse visits as a separate cost element.
3C Patch: training cost	£1.05 (weekly)	£18.63 (annually)	Company advised 2 band 3 healthcare assistants or band 4 nurses and 2 band 6 podiatrists are trained to use 3C Patch, and that training takes 2 hours per year on average. PSSRU unit costs were applied. EAC estimated annual training required per clinic: 2 hours for training (preparing centrifuge and practice applying Patch). This was applied to 4 band 4 nurses and 4 band 6 podiatrists and PSSRU rates applied. Hourly rate of patient contact time from PSSRU (Curtis and Burns 2020; £48 for band 6 podiatrist and £30 for band 4 nurse for patient contact time, updated to 2021 prices).
Abbreviations: BNF – British National Formulary; DFU – diabetic foot ulcer; EAC; External Assessment Centre; PSSRU; Personal Social Services Research Unit; HRG; Healthcare Resource Group			

Standard care resources and costs

Table 9.7 shows the costs used in the company's model and any changes made by the EAC for the standard care arm. The EAC's costs are reported separately for those adopted in model A, which has no infection state and model B, which has infection as a separate state, when there is a difference.

Table 9.7: Standard care costs per patient per week from company model and changes made by the EAC at 2021 prices

Parameter	Company value	EAC value	Source
Standard care: Additional NHS provided care for dressing changes between outpatient consultations	See Table 9.6	£45.09	The company assumed: 0.56 fewer district nurse visits with 3C than Standard care, each took 30 mins, nurse was a band 6. Costs were from PSSRU (Curtis and Burns 2020). Only including the incremental difference on the 3C arm (see Table 9.6). The EAC costed [redacted] visits per patient (Farr et al. unpublished) for 30 mins and staff costs of £89 per hour of patient contact time for a band 6 nurse (source PSSRU at 2019/20 prices and updated to 2021 prices.
Standard care: Ulcer outpatient attendance cost	£135.97	£78.29	Company used a weekly cost for outpatients and the community derived from Kerr et al. (2019). EAC assumed weekly standard care comprised of alternating outpatient appointments and podiatry in the community.(EAC correspondence log [2021]). Outpatient cost was £111.66 (see Table 9.6). The podiatry appointment was £44.92 (from NHS reference costs [A09A]). These are summed and divided by 2 for a weekly cost.
Standard care: Ulcer inpatient cost for severe infections and revascularisation (Model A)	£92.51	£43.06	The company used the same cost per infected ulcer for each treatment arm; the value was derived from the reported cost for all ulcers by Kerr (2019). EAC assumed a cost per severe ulcer of £7052.26 in 2021 prices (NG19 [NICE 2015b] from Kerr et al. (2014) .This was applied to [redacted] patients admitted with severe DFU infection (Farr et al. unpublished). The company did not include revascularisation costs. The EAC calculated these costs from a weighted average HRG codes from NHS reference costs (NHS England 2019; YQ10A to YQ12D, £8,975.45) and applied it to [redacted] patients who underwent this procedure (Farr et al. unpublished). These were added to the cost of managing [redacted] severe

Parameter	Company value	EAC value	Source
			infections. The total cost of £115,399.85 was divided by 134 patients and then by 20 to give a weekly cost per patient.
Standard care: Inpatient cost for revascularisation. (Model B)	Not included	£16.75	The company did not include an infection health state. For model B where infection is a health state, inpatient costs excluding infection only relate to revascularisation. These costs were calculated using the same methodology as for Model A.
Standard care: Infection cost (one off cost). (Model B)	Not included	£1,171.22 (one off cost).	In model B, the cost of severe ulcer deterioration (£7052.56) from (NG19 [NICE 2015b] from Kerr et al. (2014) was weighted by the proportion of infections that were severe ([redacted]) as reported in Farr et al. (unpublished) . Added to this was the antibiotic cost per patient (£51.81), updated from Farr (unpublished) to current prices using BNF (2021).
Standard care: Dressing cost when infected. (Model B)	Not included	[redacted]	The EAC applied unit costs from NHS Supply Chain (2021) to all dressings used in Game et al. (2018a).
Standard care: Medications cost for antibiotics to manage infections.	£9.70	£2.59	The EAC estimated the cost of medications from Farr et al. (unpublished), using BNF unit costs. This differs from the company submission, which conducted its own analysis on patient level data to estimate an antibiotic cost from BNF and NHS Electronic Drug Tariff (NHS Business Services Authority 2021). It added staff costs for intravenous and intramuscular administration. The EAC did not include staff costs because we included the cost of all district nurse visits as a separate cost element.
Standard care: Dressings cost	£12.47	[redacted]	The company applied a unit cost from the BNF to all dressings used in Game (2018). The EAC applied unit costs from NHS Supply Chain.
Abbreviations: EAC; External Assessment Centre. PSSRU; Personal Social Services Research Unit. DFU; Diabetic Foot Ulcer. BNF; British National Formulary . HRG; Healthcare Resource Group			

Amputation and healed costs

Table 9.8 shows the costs used in the company's model and changes made by the EAC for amputation and healed ulcer costs.

Table 9.8: Amputation and healed costs per patient per week from company model and changes made by the EAC at 2021 prices

Parameter	Company value	EAC value	Source
Healed DFU	£4.05	£9.32	The company assumed there would be a podiatrist appointment every 6 weeks for a check-up. This is costed as a band 6 podiatrist, equivalent to 15 minutes working time from PSSRU (Curtis and Burns 2020). The EAC used the cost of podiatry outpatient attendance of £54, updated to 2021 prices (NHS England 2019; NHS reference costs service code 653) divided by 6 to adjust to weekly visits, consistent with company and experts opinion (EAC correspondence log [2021]).
Major amputation cost - one off	£12,139.24 (One-off)	£12,556.53 (One-off)	As per company submission. Source is NHS reference cost (NHS England 2019) using HRG codes from Kerr et al. (2019) plus the cost of a wheelchair for 50% of patients (NICE 2015b; £379.57 per patient).
Post major amputation	£63.22 (year 1) £18.88 (year 2)	£97.01	The company submission uses costs derived from Kerr et al. (2019) to calculate a first and second year cost. The EAC uses the monthly cost of £452.13 from NICE NG19 prices minus the cost of a wheelchair for 50% of patients and divide by 4.34 to get a weekly cost.
Minor amputation cost - one off	£5,933.22 (One-off)	£5,951.66 (One-off)	As per company submission, using NHS reference cost (NHS England 2019) HRG codes indicated from Kerr et al. (2019) but in 2021 prices.
Post minor amputation	£20.23 (year 1) £0.59 (year 2)	£16.64	The company submission uses costs derived from Kerr et al. (2019) to calculate a first and second year cost. The EAC uses the monthly cost from NICE (2015b) NG19 of £72.32 in 2021 prices and divided by 4.34 to get a weekly cost.
Abbreviations: DFU – diabetic foot ulcer; EAC; External Assessment Centre; HRG; Healthcare Resource Group; PSSRU; Personal Social Services Research Unit.			

Table 9.9 shows the health state cost used in the EAC model, and the costs that are included within them, from the values provided above. The health state costs are used to run the sensitivity analyses.

Table 9.9: Health state costs used in the model by the EAC

Health state	EAC value	Costs included within the health state
Index ulcer: 3C Patch	Model A: £346.94 Model B: £301.53	Model A: 3C Patch additional NHS provided care for dressing changes between outpatient consultations, 3C Patch outpatient attendance, 3C Patch antibiotics to manage infections, 3C Patch device cost, 3C Patch secondary dressing, 3C Patch ulcer inpatient cost for severe infections and revascularisation. Model B: 3C Patch additional NHS provided care for dressing changes between outpatient consultations, 3C Patch outpatient attendance, 3C patch device cost, 3C patch secondary dressing, 3C Patch inpatient cost for revascularisation, 3C Patch antibiotics to manage mild infections.
Index ulcer: 3C Patch discontinued	Model A: £176.65 Model B: £150.34	Model A: Standard care additional NHS provided care for dressing changes between outpatient consultations, standard care ulcer outpatient attendance cost, standard care medications cost for antibiotics to manage infections, standard care dressing cost, standard care ulcer inpatient cost for severe infections and revascularisation. Model B: Standard care additional NHS provided care for dressing changes between outpatient consultations, standard care ulcer outpatient attendance cost, standard care dressing cost, standard care ulcer inpatient cost for revascularisation, standard care medications cost for antibiotics to manage mild infections.
Index ulcer: Standard care	Model A: £176.65 Model B: £150.34	Model A: Standard care additional NHS provided care for dressing changes between outpatient consultations, standard care ulcer outpatient attendance cost, standard care medications cost for antibiotics to manage infections, standard care dressing cost, standard care ulcer inpatient cost for severe infections and revascularisation. Model B: Standard care additional NHS provided care for dressing changes between outpatient consultations, standard care ulcer outpatient attendance cost, standard care dressing cost, standard care ulcer inpatient cost for revascularisation, standard care medications cost for antibiotics to manage mild infections.
Healed	£9.32	Model A: Healed DFU Model B: Healed DFU
Subsequent ulcer	Model A: £176.65	Model A: Standard care additional NHS provided care for dressing changes between outpatient consultations, standard care ulcer outpatient attendance cost, standard care medications cost for

Health state	EAC value	Costs included within the health state
	Model B: £150.34	antibiotics to manage infections, standard care dressing cost, standard care ulcer inpatient cost for severe infections and revascularisation. Model B: Standard care additional NHS provided care for dressing changes between outpatient consultations, standard care ulcer outpatient attendance cost, standard care dressing cost, standard care ulcer inpatient cost for revascularisation, standard care medications cost for antibiotics to manage mild infections.
Infection cost: 3C Patch (one-off cost)	Model B: £2,374	Model B: 3C Patch infection cost (one off cost), standard care dressing cost when infected.
Infection cost: Standard care (one-off cost)	Model B: £1,171	Model B: standard care infection cost (one off cost), standard care dressing cost when infected.
Amputation minor	£5,952	Minor amputation cost - one off.
Amputation major	£12,557	Major amputation cost - one off.
Post amputation healed minor	£16.64	Post minor amputation
Post amputation healed major	£97.01	Post major amputation
Post amputation unhealed minor	Model A: £193.29 Model B: £166.98	Model A: Post minor amputation, subsequent ulcer Model B: Post minor amputation, subsequent ulcer
Post amputation unhealed major	Model A: £273.66 Model B: £247.35	Model A: Post major amputation (weekly cost), subsequent ulcer Model B: Post major amputation (weekly cost), subsequent ulcer
Abbreviations: DFU – diabetic foot ulcer.		

The EAC has changed all of the company's cost inputs other than the cost of the 3C Patch. Most changes are relatively minor in nature. The three biggest differences relate to inpatient costs, infection costs and outpatient costs.

Inpatient costs

In model A with no infection health state, the EAC calculated inpatient costs using a mean cost for:

- Severe ulcer deterioration of £7052.56 (mean cost of £6,249 in 2014 prices, inflated to 2021 prices. (source: Kerr et al. (2014) as reported in NICE NG19).

- Revascularisation costs of £8,975.45 (Healthcare Resource Group [HRG] codes YQ10A to YQ12D in NHS Reference costs 2018/19, updated to 2021 prices).

The ulcer costs were applied to [redacted] inpatients admitted for severe infections in the 3C Patch and standard care arms respectively (Farr et al. unpublished)

The revascularisations costs were applied to[redacted] inpatients admitted for surgery in the 3C Patch and standard care arms respectively (Farr et al. unpublished) .

The total inpatient costs were summed for each arm and divided by the number of people in each arm cost (134 in standard care and 132 in the 3C Patch) and then divided by 20 to give weekly costs.

The company used the same costs in each arm which used weights from Kerr et al. (2019).

Where infection is included as a health state, only revascularisation costs were included for this parameter and calculated using the same methodology.

Infection costs

The infection cost relating to the health state is only included in model B. This is estimated using the cost of severe ulcer deterioration (£7052.56) from NG19 using Kerr et al. (2014). This was weighted by the proportion of severe infections [redacted]; Farr et al. [unpublished]) . Added to this was the total antibiotic cost per patient (£51.81), updated from Farr et al. (unpublished) to current prices using BNF. Everyone in the infected health state received the cost of standard care dressings of [redacted] (NHS Supply Chain). This assumed 3C Patch was discontinued in patients with moderate or severe infection (EAC correspondence log 2021).

Outpatient costs

The company used a weekly cost of an outpatients appointment of £135.97 from Kerr et al. (2019). It added the cost of an additional 10 minutes nurse (band 4) costs for phlebotomy and centrifuge activities and 20 minutes podiatrist (band 6) time per week. The total cost of an outpatients appointment was £157.45.

The EAC used the Kerr et al. (2019) reported composite cost for outpatient, community and primary care and removed the elements related to district nurse, antibiotics and dressings, to give an outpatients appointment cost of £111.66. This outpatient appointment cost is applied every week for the 3C Patch, but only once every 2 weeks for standard care. For standard care, the patient is assumed to have a podiatrist appointment on the alternate week. This podiatrist cost was taken from NHS reference costs (NHS England 2019; currency code A09A), £44.92 in 2021 prices. Hence the average weekly cost is an average of these (£111.66 and £44.92 =£78.29).

The EAC also added [redacted] minutes additional time for each of a nurse and a podiatrist (Farr et al. unpublished) and validated by experts (EAC correspondence log [2021]) to the 3C Patch arm. This time was costed using PSSRU (£50.14 for band 6 podiatrist and £31.34 for band 4 nurse time in 2021 prices).

Other changes to costs

Minor differences were made to the following:

- The company assumed 0.56 fewer weekly district nurse visits, of 30 minutes each, by a band 6 nurse were required to change dressings with 3C Patch. This gave a saving of £25.71 per week per patient. The 0.56 was derived from the [redacted] such visits recorded by Game et al. (2018a) and then adjusted for fortnightly clinic visits. The EAC costed the [redacted] visits per week with 3C Patch and [redacted] for standard care (Farr et al. unpublished), giving savings of [redacted] per patient per week with 3C Patch.

- The EAC calculated 3C Patch annual training costs per clinic of £651.92 to train 4 band 4 nurses and 4 band 6 podiatrists, each receiving 2 hours of primary training. Each clinic was assumed to see 35 patients a year, using the same methodology as applied by the company) , giving an annual cost per patient of £18.63.

- The EAC re-calculated all antibiotic costs using data on those prescribed (see Farr et al. unpublished), and applying unit costs from BNF.

- The company calculated standard dressing costs of £12.47, by applying BNF (2021) unit costs to the dressings used in Game et al. (2018a).The EAC re-calculated costs using NHS supply chain prices to give a cost of [redacted] per patient per week. ,The cost of secondary dressings in the 3C patch arm reduced to [redacted] per patient per week from £0.39 as calculated by the Company.

- The healed DFU cost was calculated by the company assuming a patient would see a podiatrist every 6 weeks for a 15 minute appointment. This was costed using the cost of a band 6 podiatrist from PSSRU and converted to a weekly cost of £4.05. The experts confirmed patients should receive a check up around every 6 weeks (EAC correspondence log 2021). The cost was revised using a podiatrist outpatient attendance (NHS England 2019; NHS reference costs service code 653, £55.90 in 2021 prices) and converted to a weekly cost of £9.32.

- The EAC agreed with the amputation costs used by the company except it added the cost of a wheelchair for 50% of patients (£379.57 per patient), as indicated in Kerr et al. (2019) to the major amputation cost. Other minor differences between these costs stem from inflating prices to 2021 in the EAC submission.

- Weekly post amputation costs used by the company were derived from Kerr et al. (2019) and split into year 1 and year 2 costs for both major and minor amputation. The EAC used the monthly cost from NICE (2015b) NG19 , updated to 2021 prices and converted to weekly costs. The wheelchair costs include in the major amputation costs were also removed.

9.2.5 Quality of Life

The company used the utility values reported by Ragnarson Tennvall and Apelqvist (2000). This study was judged by the EAC to have several limitations including the relatively few patients who had had an amputation and it did not report the mean age of respondents when they completed the EQ-5D questionnaire but only the age at diagnosis of a DFU, being 67 years. Hence respondents were materially older that those included in Game et al. (2018a) who had a mean age of 62 years. The authors noted the mean utility values were low for the entire study group compared with that for the general population. Hence, age may be a confounding factor. Furthermore, this is an

old study, with the study population being from Sweden, which likely has limitations surrounding the validity and generalisability to the UK population.

The EAC conducted a structured literature search which found no recent studies reporting utilities relating to DFUs. It did however, identify a paper by Redekop et al. (2004). This study identified 13 health states based on the presence or absence of DFU and amputation. Members of the public used the time trade-off method to value each state and these were transformed into utilities. The reported values were adopted in the modelling informing the NICE guideline (NG19) for DFUs. This paper has the further benefit of reporting utility scores for infected and not infected health states, as required for the EAC model.

The EAC also noted the results of the sub-group analysis reported in an abstract for a small subgroup (n=18) (Löndahl et al. 2019). Baseline utility was 0.601, rising to 0745 when DFU was healed. The values from Redekop et al. (2004) are more closely aligned with these data than Ragnarson Tennvall and Apelqvist (2000).

Table 9.10 shows the utilities used in the company's model and the changes made by the EAC in order to capture differences in the quality of life.

Table 9.10: Weekly and annual utilities values used in the company's model and changes made by the EAC

Health state	Company weekly and annual values from Ragnarson Tennvall and Apelqvist (2000)	EAC weekly and annual values from Redekop et al. (2004)
Index ulcer: 3C Patch, 3C Patch discontinued, standard care, subsequent ulcer	0.00846 0.44	0.0144 0.75
Healed	0.01154 0.60	0.0162 0.84
Infection	Not included	0.0135 0.70
Amputation minor and post amputation healed	0.01173 0.61	0.0131 0.68
Amputation major and post amputation healed	0.00596 0.31	0.0119 0.62
Post amputation unhealed minor	0.00846 0.44	0.0110 0.63
Post amputation unhealed major	0.00596 0.31	0.0121 0.57
Dead	0.00	0.00
Abbreviations: EAC - External Assessment Centre.		

9.2.6 Sensitivity analysis

Company scenario analysis

Four scenarios were conducted by the company which mainly centred around costs, all of which still resulted in cost savings with the introduction of 3C Patch. The following scenarios were presented by the company:

1. varying the weekly quantity of 3C Patches by +/-10%
2. increasing staff costs from band 4 to band 6 for those undertaking phlebotomy and centrifuge operation
3. decreasing district nurse visits to 0 for those on 3C Patch
4. increasing the weekly probability of healing for those who have discontinued 3C Patch to account for some benefit with the 3C Patch prior to discontinuation

The EAC judged the scenarios to be appropriate but not exhaustive. It is noted that the scenarios centre around costs rather than the probabilities of healing and none were conducted around the probability of discontinuation or probability of healing with the 3C Patch which is subject to increased uncertainty due to the reduction in trial data used to calculate this probability and are key drivers of the results. No further deterministic sensitivity analysis was presented by the company. Therefore the EAC deemed that the sensitivity analysis conducted does not fully explore the uncertainty in the model input parameters, particularly in terms of effectiveness of the patch.

Company probabilistic sensitivity analysis

The company also presented PSA results for 10,000 iterations of the model and reports mean probabilistic cost savings of £192 per patient over a 2-year time horizon. The EAC judged the distributions used to be appropriate. It was not possible to assess the sources used for the measures of variation used because they were not adequately described for each parameter. The company states that ‘for costs, where the standard deviation and sample size were known, these were used to generate parameters for the analysis. Where they were not known, it was assumed that 95% of values would fall within a range of 20% (10% above and below the mean), and standard deviations were estimated accordingly. For probabilities and utilities, it was assumed that 95% of values would fall within a range of 20% (10% above and below the mean), and standard deviations were estimated accordingly.’

EAC analysis

The EAC conducted deterministic and PSA, the ranges used are presented in Table 9.11.

Table 9.11: EAC ranges for deterministic and probabilistic sensitivity analysis

Parameter	Base case value	DSA values used	PSA distribution	Justification
Index ulcer: 3C Patch weekly cost (Model A)	£346.94	Low value: [redacted] High value: £396.94	Gamma SE: £34.69	Low value: Assume cost of 3C Patch same as Farr (unpublished) of [redacted] High value: assumed £50 greater than base case.
Index ulcer: 3C Patch weekly cost (Model B)	£301.53	Low value: [redacted] High value: £351.53	Gamma SE: £30.15	Low value: Assumed cost of 3C Patch same as Farr (unpublished) of [redacted]. High value: Assumed £50 greater than base case.
Index ulcer: 3C Patch discontinued weekly cost (Model A)	£176.65	Low value: £124.44 High value: £228.86	Gamma SE: £17.67	Low value: Assumed no inpatient ulcer cost (non-responding ulcer improves after 3C discontinuation) High value: Assumed double inpatient ulcer cost (non-responding ulcer deteriorates after discontinuing with 3C Patch)
Index ulcer: 3C Patch discontinued (Model B)	£150.34	Low value: £120.27 High value: £180.41	Gamma SE: £15.03	Low value: Assumed 20% below base case High value: Assumed 20% above base case
Index ulcer: Standard care (Model A)	£176.65	Low value: £141.32 High value: £211.98	Gamma SE: £17.67	Low value: Assumed 20% below base case High value: Assumed 20% above base case
Index ulcer: Standard care (Model B)	£150.34	Low value: £120.27 High value: £180.41	Gamma SE: £15.03	Low value: Assumed 20% below base case High value: Assumed 20% above base case
3C training cost (one-off)	£18.63	Low value: £9.31 High value: £27.93	Gamma SE: £1.86	Low value: Assumed 2 nurses and podiatrists need training High value: Assumed 6 nurses and podiatrists need training
Healed weekly cost	£9.32	Low value: £6.99 High value: £13.98	Gamma SE: £0.93	Low value: Appointment every 4 weeks instead of 6 weeks High value: appointment every 8 weeks instead of 6 weeks.
Subsequent ulcer weekly cost (Model A)	£176.65	Low value: £141.32 High value: £211.98	Gamma SE: £17.67	Low value: Assumed 20% below base case High value: Assumed 20% above base case

Parameter	Base case value	DSA values used	PSA distribution	Justification
Subsequent ulcer weekly cost (Model B)	£150.34	Low value: £120.27 High value: £180.41	Gamma SE: £15.03	Low value: Assume 20% below base case High value: Assumed 20% above base case
Infection cost 3C Patch (one-off cost) (Model B)	£2,374.62	Low value: £1,171.22 High value: £2,848.34	Gamma SE: £237.36	Low value: Assumed no difference in infection cost with standard care High value: Assumed 20% above base case
Infection cost standard care (one-off cost) (Model B)	£1,171.22	Low value: £936.98 High value: £2,374.62	Gamma SE: £117.12	Low value: Assumed adjusted to 20% below base case High value: Assumed no difference with infection cost in 3C
Amputation minor cost (one-off)	£5,952	Low value: £4761.33 High value: £7,149.99	Gamma SE: £595.17	Low value: Assumed 20% below base case High value: Assumed 20% above base case
Amputation major (one-off)	£12,557	Low value: £10,045.22 High value: £15,067.84	Gamma SE: £1,255.65	Low value: Assumed 20% below base case High value: Assumed 20% above base case
Post amputation healed minor weekly cost	£16.64	Low value: £10.41 High value: £19.97	Gamma SE: £1.66	Low value: Taken as an average from the company value to get a yearly cost High value: Assumed 20% above base case
Post amputation healed major weekly cost	£97.01	Low value: £41.05 High value: £116.41	Gamma SE: £9.70	Low value: Taken as an average from the company value to get a yearly cost High value: Assumed 20% above base case
Post amputation unhealed minor weekly cost(Model A)	£193.29	Low value: £148.20 High value: £238.38	Gamma SE: £19.33	Low value: Assumed no inpatient ulcer cost (now amputated wound improves) High value: Assume double inpatient ulcer cost (ulcer worse if unhealed despite amputation)
Post amputation unhealed major weekly cost (Model A)	£273.66	Low value: £228.57 High value: £318.75	Gamma SE: £27.37	Low value: Assumed no inpatient ulcer cost (now amputated wound improves)

Parameter	Base case value	DSA values used	PSA distribution	Justification
				High value: Assume double inpatient ulcer cost (ulcer worse if unhealed despite amputation)
Post amputation unhealed minor weekly cost (Model B)	£166.98	Low value: £133.58 High value: £200.38	Gamma SE: £16.70	Low value: Assumed 20% below base case High value: Assumed 20% above base case
Post amputation unhealed major weekly cost (Model B)	£247.35	Low value: £197.88 High value: £296.82	Gamma SE: £24.74	Low value: Assumed 20% below base case High value: Assumed 20% above base case
3C patch week 0-5 index ulcer 3C to ulcer 3C discontinued weekly transition probability	0.0%	Low value: 0.0% High value: 2.5%	Dirichlet	Low value: Remains the same as the base case, currently set at 0% High value: Assumption if people discontinue within the first 5 weeks
3C patch week 5 index ulcer 3C to ulcer 3C discontinued weekly transition probability	0.0%	Low value: 0.0% High value: 57.9%	Dirichlet	Low value: Remains the same as the base case, currently set at 0% High value: Assumed same the company base case.
3C patch week 6-19 index ulcer 3C to ulcer 3C discontinued weekly transition probability	0.0%	Low value: 0% High value: 2.5%	Dirichlet	Low value: Remains the same as the base case, currently set at 0% High value: Assumption if people discontinue after 5 weeks
3C patch week 0-5 index ulcer 3C to healed weekly transition probability	0.8%	Low value: 0% High value: 1.6%	Dirichlet	Low value: Assumes nobody heals within the first 5 weeks High value: Assumes double the amount of people healed within the first 5 weeks
3C patch week 6-20 index ulcer 3C to healed weekly transition probability (Model A)	2.7%	Low value: 1.35% High value: 5.7%	Dirichlet	Low value: Assumes half the rate of people healing in weeks 6-20 High value: Assumes same as company healing rate for weeks 6-20
3C patch week 6-20 index ulcer 3C to healed	3%	Low value: 1.5% High value: 5.7%	Dirichlet	Low value: Assumed half the rate of people healing in weeks 6-20 High value: Assumed same as company healing rate for weeks 6-20

Parameter	Base case value	DSA values used	PSA distribution	Justification
weekly transition probability (Model B)				
SoC index ulcer to healed week 0-5 weekly transition probability (Model A)	0.61%	Low value: 0.0% High value: 1.22%	Dirichlet	Low value: Assumes nobody heals within the first 5 weeks High value: Assumed double the amount of people healed within the first 5 weeks
SoC index ulcer to healed week 0-5 weekly transition probability (Model B)	0.63%	Low value: 0.0% High value: 1.26%	Dirichlet	Low value: Assumed nobody heals within the first 5 weeks High value: Assumed double the amount of people healed within the first 5 weeks
SoC index ulcer to healed week 6-20 weekly transition probability (Model A)	1.5%	Low value: 1.2% High value: 1.8%	Dirichlet	Low value: Assumed 20% below the base case High value: Assumed 20% above the base case
SoC index ulcer to healed week 6-20 weekly transition probability (Model B)	1.7%	Low value: 1.3% High value: 2.0%	Dirichlet	Low value: Assumed 20% below the base case High value: Assumed 20% above the base case
SoC index ulcer to healed week 21+ weekly transition probability (1.0%;1.5%)	1.3%	Low value: 1.0% High value: 1.5%	Dirichlet	Low value: Assumed 20% below the base case High value: Assumed 20% above the base case
Multiplier for healing rate discontinued	1	Low value: 0.8 High value: 1.2	N/A	Low value: Assumed 20% below the base case High value: Assumed 20% above the base case
Probability of ulcer recurrence weekly transition probability	0.6%	Low value: 0.1% High value: 1.1%	Dirichlet	Low value: Assumed the probability is 0.5% below the base case High value: Assumed the probability is 0.5% above the base case
Probability of healing for subsequent ulcers	5.4%	Low value: 4.3% High value: 6.5%	Dirichlet	Low value: Assumed 20% below the base case High value: Assumed 20% above the base case

Parameter	Base case value	DSA values used	PSA distribution	Justification
weekly transition probability				
Minor amputation rate weekly transition probability (Model A)	0.3%	Low value: 0.0% High value: 1%	Dirichlet	Low value: Assumed no minor amputations High value: Assumed a 1% rate of minor amputations
Major amputation rate weekly transition probability (Model A)	0.1%	Low value: 0.0% High value: 0.5%	Dirichlet	Low value: Assumed no major amputations High value: Assumed a 0.5% rate of major amputations
Minor amputation rate weekly transition probability (Model B)	3.6%	Low value: 0.0% High value: 7.2%	Dirichlet	Low value: Assumed no minor amputations High value: Assumed double the rate of minor amputations
Major amputation rate weekly transition probability (Model B)	0.9%	Low value: 0.0% High value: 1.8%	Dirichlet	Low value: Assumed no major amputations High value: Assumed double the rate of major amputations
Infected ulcer to uninfected ulcer 3C Patch weekly transition probability (Model B)	9.5%	Low value: 7.6% High value: 11.4%	Dirichlet	Low value: Assumed 20% below the base case High value: Assumed 20% above the base case
Infected ulcer to uninfected ulcer standard care weekly transition probability (Model B)	9.5%	Low value: 7.6% High value: 11.4%	Dirichlet	Low value: Assumed 20% below the base case High value: Assumed 20% above the base case
Infection rate 3C Patch weekly transition probability (Model B)	2.0%	Low value: 1.0% High value: 2.4%	Dirichlet	Low value: Assumed 0.5% lower than standard care High value: Assumed 20% above the base case
Infection rate standard care weekly transition probability (Model B)	1.5%	Low value: 1.2% High value: 2.0%	Dirichlet	Low value: Assumed 20% below the base case High value: Assumed equal to 3C patch
Abbreviations: DSA - deterministic sensitivity analysis; PSA - probabilistic sensitivity analysis; SE – standard error.				

Other parameters were not included within any analysis for DSA. The EAC judged utilities were less important than costs in terms of informing decisions and, therefore, no DSA was conducted on these values, while other transitions in the model are dependent on transitions already included within the DSA. However, these parameters were all included for PSA analysis, the appropriate distribution was selected for each of the parameters. This was a Dirichlet distribution for any transition probabilities, and beta distribution was selected for utilities used within the model. For utilities, it was assumed that a standard error of 10% would be applied for the beta distribution in order to capture any uncertainty with respect to quality of life.

Threshold analysis was conducted around any key drivers identified in deterministic sensitivity analysis.

In addition to this, two-way sensitivity analysis was conducted around the following input parameters:

1. *Probability of discontinuation of 3C Patch at 5 weeks and weekly probability of healing with 3C Patch in weeks 6 to 20.*

   This was conducted to address key uncertainties with the generalisability of the Game et al. (2018a) RCT to clinical practice. Discontinuation at 5 weeks was not conducted in the trial but the suggested clinical pathway from the company recommends assessing ulcer area reduction at 5 weeks and discontinuing use of the patch if a reduction of equal to or more than 50% has not been observed. As discussed in this report experts were not fully in agreement with the 50% measure used to decide discontinuation. However, they generally agreed with idea that patients would likely discontinue use around this time if 3C Patch did not appear to be working. Therefore, it is likely that probability of discontinuation at 5 weeks will lie somewhere between 0% as presented in the EAC model and the 58% estimate provided by the company. A further uncertainty with discontinuing patients at 5 weeks is the probability of healing with 3C Patch following this since discontinuation did not occur in the trial. It is likely that healing could be better than that observed in the trial if patients do discontinue because the trial represents use of 3C Patch in all patients rather than just in those in which 3C Patch appears to be more effective.

2. *Probability of discontinuation of 3C Patch at 5 weeks and weekly probability of healing for those who discontinued 3C Patch in weeks 6 to 20.*

   The probability of healing for those who discontinue 3C Patch before 20 weeks is also uncertain because this was not done in the trial.

Therefore, two-way sensitivity analysis was also conducted for the probability of discontinuation of 3C Patch at 5 weeks and the probability of healing for those who discontinued the patch following this period. The company estimated this probability using data for the 'equivalent cohort' in the control arm i.e. those who did not see a reduction of 50% or more with standard care.

Two scenarios were in Model B (with infection health state) to address some further uncertainties. First to assess the impact of some patients remaining on the 3C Patch up to 20 weeks despite moderate/severe infection in Model B. Secondly, to assess the impact of applying the same infection rate to both arms in the model based on overall data from both arms in the model which corresponds to an infection rate of 1.7%.

9.3 Results from the economic modelling

9.3.1 Base case results

The company and EAC base case results are presented in Table 9.12. The results for both EAC models: Model A without infection health state, and Model B with infection health state are presented in Table 9.12.

Table 9.12: Summary of base case results (per patient)

	Company's results			EAC results model A *Without* infection health state			EAC results model B *With* infection health state		
	3C Patch	**Standard care**	**Incremental cost**	**3C Patch**	**Standard care**	**Incremental cost**	**3C Patch**	**Standard care**	**Incremental cost**
Index ulcer (including 3C Patch cost and training cost)	£11,144	£11,331	-£187	£9,339	£7,711	£1,628	£7,258	£6,046	£1,212
Regular assessment for patients whose ulcers have healed	£148	£128	£20	£362	£300	£62	£344	£289	£55
Subsequent ulcers	£971	£867	£103	£556	£451	£105	£450	£371	£80
Infection	NA			NA			£1,417	£741	£676
Major amputation	£376	£411	-£34	£341	£392	-£52	£440	£454	-£14
Minor amputation	£779	£851	-£71	£685	£788	-£104	£858	£886	-£28
Post amputation costs	£255	£278	-£22	£382	£432	-£49	£450	£437	£13
Total	**£13,674**	**£13,865**	**-£191**	**£11,664**	**£10,074**	**£1,590**	**£11,217**	**£9,225**	**£1,993**

Changes made by the EAC have resulted in an incremental cost increase of around £1,600 to £2,000. The key difference between the company results and the EAC results appear to the cost of index ulcers i.e. those remaining unhealed. This incorporates costs of the dressings, costs of district nursing, outpatient/primary care, medications, and inpatient costs. This will be influenced both by changes made by the EAC to the costs applied to the index ulcer health state, as well as changes made to the probabilities of healing and probability of discontinuation at 5 weeks. The incremental difference between the index ulcer health states in the EAC model has been increased and the results will also be heavily influenced by the changes made to the probability of healing in weeks 6 to 20 with 3C Patch and the probability of discontinuation of 3C Patch at 5 weeks.

9.3.2 Sensitivity analysis results

Company sensitivity analysis results

The company presented a range of cost saving results for each of the scenarios described in section 9.2.6. The estimated results ranged from an £82 cost saving (scenario 1b, 10% more patches per week of treatment) to £360 cost saving (0.5 mean district nurse dressing change visits per week for 3C Patch). It was not possible to identify key drivers from the sensitivity analysis conducted by the company however additional analysis conducted by the EAC on the company's model suggested the results were not robust to changes in input parameters. In particular a small change of around 0.6% to the weekly probability of healing with 3C Patch between weeks 6 to 20 in the model resulted in the direction of the results changing. This parameter was deemed to be subject to a high level of uncertainty by the EAC due to the nature of the post hoc analysis conducted by the company (reducing the number of patients this was based on to 52) with which this estimate was derived.

The company's probabilistic analysis resulted in an estimated mean cost saving of £192. They also presented measures of variation around this as shown in Table 9.13.

Table 9.13: Company's PSA results

Mean	-£191.56
Std Deviation	£214.57
Minimum	-£1,082.61
2.5%	-£637.89
10%	-£470.43
Median	-£184.10
90%	£72.67
97.5%	£216.87
Maximum	£677.45

EAC sensitivity analysis results

EAC deterministic sensitivity analysis

The EAC conducted deterministic sensitivity analysis on all key parameters in the EAC model to assess the impact of varying individual parameters on the results of the model and identify key drivers of the analysis. The results for each model (model A without infection health state, model B with infection health state) are presented in tornado diagrams below with the top 15 drivers displayed. Parameters varied and ranges used are described fully in section 9.2.6.

Figure 9.2: Tornado diagram model A

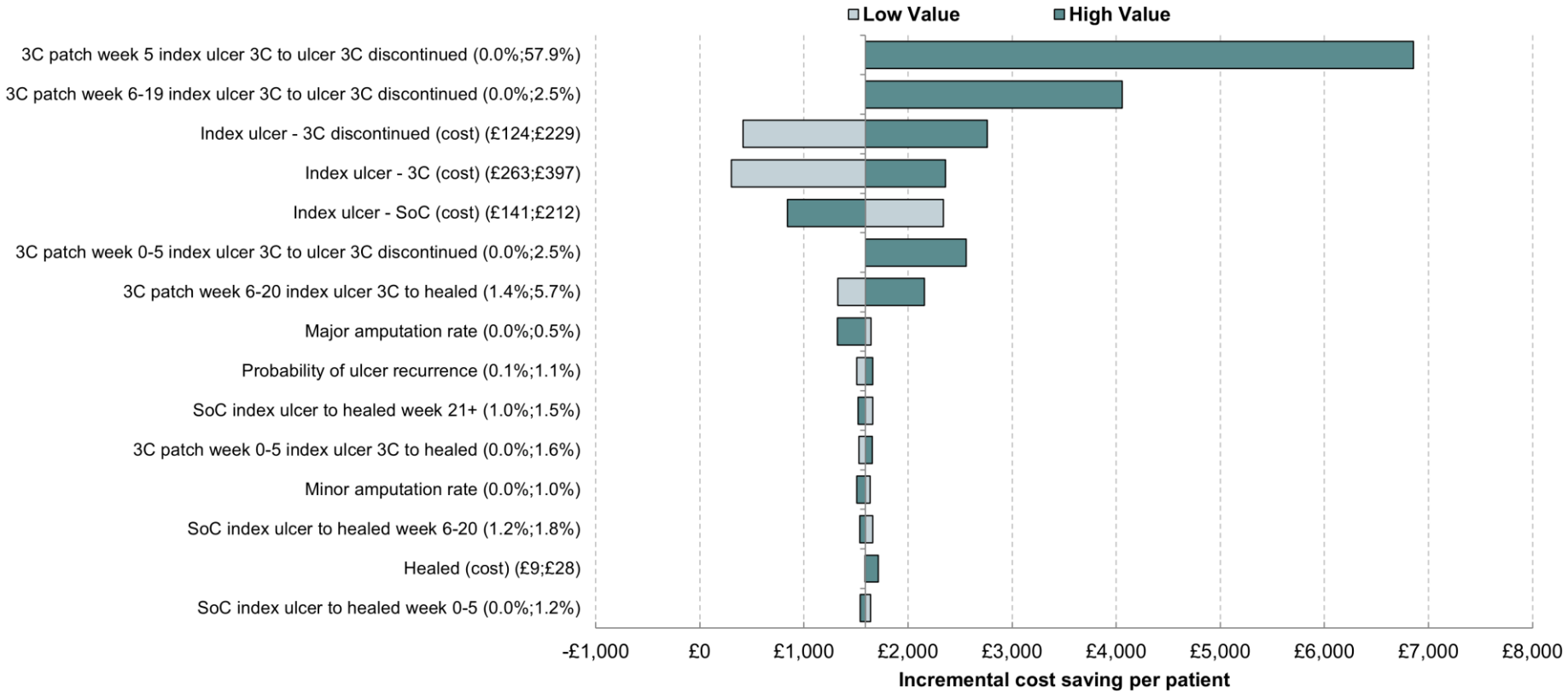
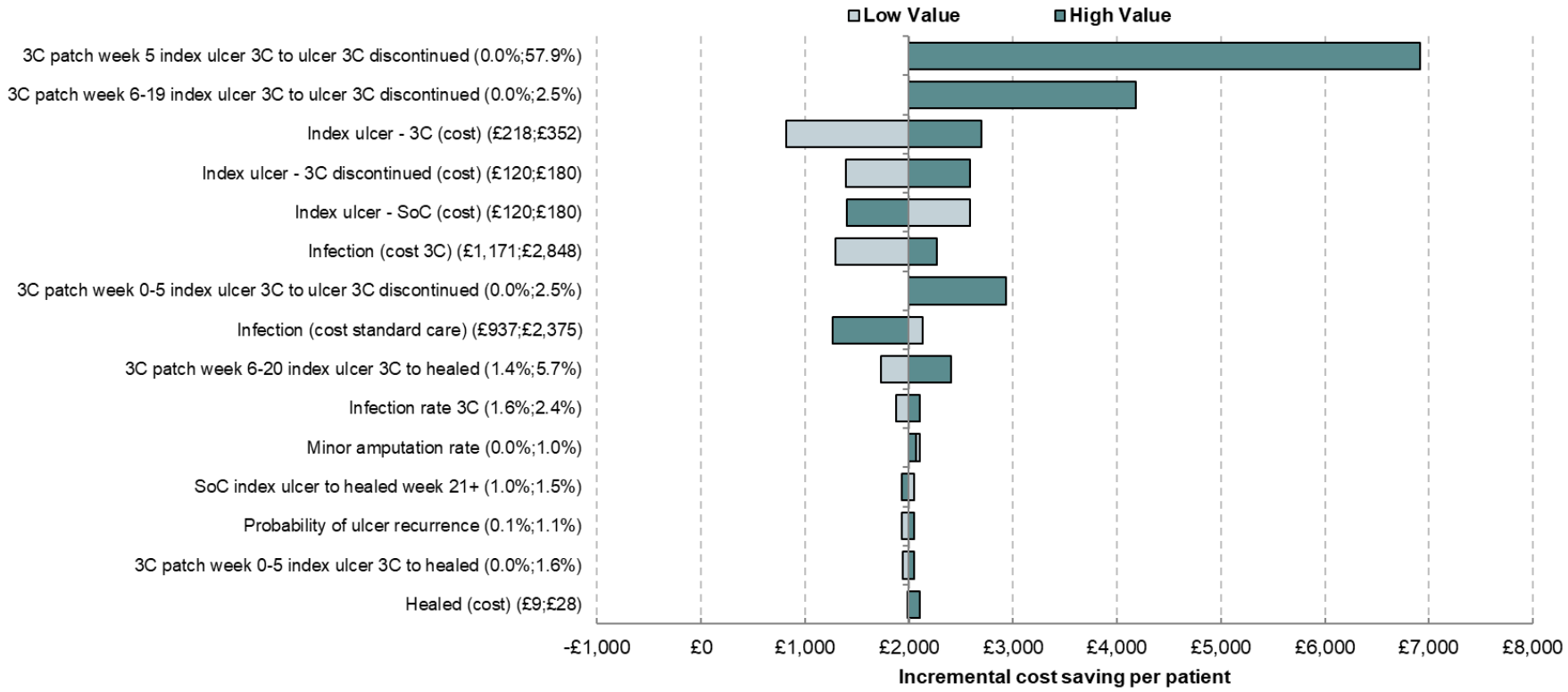


Figure 9.3: Tornado diagram model B



Deterministic sensitivity analysis indicated that the probability of discontinuing 3C Patch and the cost of index ulcers for both 3C Patch and standard care/3C Patch discontinued were key drivers of the analysis in both models.

Threshold analysis was conducted on the costs of 3C Patch and standard care. This was conducted in order to estimate the change in these inputs required to change the direction of the results in the model (i.e. 3C Patch would be cost saving). This is shown in Table 9.14. Two-way sensitivity analysis was conducted to further explore the impact of changing the probability of discontinuation with 3C patch. This was deemed more appropriate due to the interaction between this and the probability of healing for those who do and do not discontinue.

Table 9.14: Threshold analysis

Parameter	Base case input	Threshold value	EAC comments
Total weekly cost unhealed ulcer treated with 3C Patch	Model A: £347 Model B: £302	Model A: £243 Model B: £160	For model A this value is unlikely, given that even if the inpatient and outpatient cost (which are the biggest cost drivers in terms of the difference between standard care and 3C Patch index ulcer costs) were to equal standard care, this cost would still be around £47 greater than what is needed in order to be cost saving. This is amplified when comparing the costs for model B. In order to achieve this cost saving, it is likely that 3C patch would have to save a significant proportion of inpatient and outpatient care in relation to standard care.
Total weekly cost of standard care	Model A: £177 Model B: £150	Model A: £254 Model B: £250	Similar to the above, if the outpatient and inpatient costs were equal to 3C Patch in model A, this would still be £21 per patient short in order to be cost saving, despite the fact expert opinion has highlighted that 3C patch will need to use more outpatient resource (EAC correspondence log [2021]). This is a similar case for model B.
Weekly cost of 3C Patch (cost of patch x average number of weekly patches)	£125	Model A: £22 Model B: -£17	These do not represent plausible estimates based on number of patches needed per week alone and would require a significant reduction to the cost of the patch itself to around -£14 to £27 for model B and A respectively (assuming 0.836 patches per patient per week). In model B the cost is required to be negative. This occurs due to the increase in other resources, namely outpatient appointments, required with the use of 3C Patch.

Two-way sensitivity analysis was conducted around the probability of discontinuation at 5 weeks with 3C Patch and the probability of healing with 3C Patch in weeks 6 to 20 as described in section 9.2.6. It was deemed that two-way analysis was more appropriate for these variables because there is likely to be interaction between them and so varying each individually will not fully capture the uncertainty. Results of this two-way analysis are shown in Figure 9.4 and Figure 9.5. It should be noted that, where discontinuation is being varied in the EAC model, it is assumed those that discontinue the 3C Patch revert to the healing seen in the standard care arm in the trial i.e. 1.5%, rather than the company estimate of 0.7%. The values in the tables show the company estimates and the EAC estimates with a range of values in between to explore various scenarios; the numbers do not necessarily correspond with each other to represent a plausible scenario. For example, 0% discontinuation and 5.7% weekly probability of healing with 3C Patch would not be considered a plausible scenario.

Figure 9.4: Two-way analysis Model A

		Discontinuation at 5 weeks												
	£1,590.09	0.0%	5.0%	10.0%	15.0%	20.0%	25.0%	30.0%	35.0%	40.0%	45.0%	50.0%	57.9%	60.0%
Weekly probability of healing with 3C Patch (weeks 6 to 20)	2.7%	£1,590	£1,546	£1,502	£1,458	£1,414	£1,370	£1,326	£1,282	£1,238	£1,194	£1,150	£1,081	£1,062
	3.2%	£1,157	£1,135	£1,113	£1,091	£1,069	£1,047	£1,025	£1,003	£981	£959	£937	£902	£893
	3.7%	£750	£749	£747	£746	£745	£743	£742	£740	£739	£738	£736	£734	£733
	4.2%	£369	£387	£405	£423	£441	£459	£477	£494	£512	£530	£548	£577	£584
	4.7%	£11	£47	£83	£119	£156	£192	£228	£264	£300	£336	£372	£429	£444
	5.2%	-£324	-£271	-£218	-£165	-£112	-£59	-£6	£47	£101	£154	£207	£290	£313
	5.7%	-£611	-£543	-£476	-£408	-£340	-£273	-£205	-£137	-£70	-£2	£66	£172	£201

Figure 9.5: Two-way analysis Model B

		Discontinuation at 5 weeks												
	£1,992.60	0.0%	5.0%	10.0%	15.0%	20.0%	25.0%	30.0%	35.0%	40.0%	45.0%	50.0%	57.9%	60.0%
Weekly probability of healing with 3C Patch (weeks 6 to 20)	3.0%	£1,993	£1,964	£1,936	£1,908	£1,880	£1,852	£1,824	£1,795	£1,767	£1,739	£1,711	£1,667	£1,655
	3.5%	£1,632	£1,621	£1,610	£1,599	£1,588	£1,578	£1,567	£1,556	£1,545	£1,534	£1,524	£1,507	£1,502
	4.0%	£1,270	£1,276	£1,283	£1,289	£1,296	£1,303	£1,309	£1,316	£1,322	£1,329	£1,335	£1,346	£1,349
	4.5%	£930	£952	£975	£998	£1,021	£1,044	£1,067	£1,090	£1,113	£1,135	£1,158	£1,194	£1,204
	5.0%	£610	£648	£686	£724	£762	£801	£839	£877	£915	£953	£992	£1,052	£1,068
	5.5%	£309	£361	£414	£466	£519	£572	£624	£677	£729	£782	£834	£917	£940
	5.7%	£195	£253	£311	£369	£427	£485	£543	£601	£659	£717	£775	£866	£891

The EAC base case is highlighted in purple and the company base case values are highlighted in orange on the diagrams. The company assumed 58% of people receiving 3C Patch are discontinued at the 5 week review whilst the EAC modelled the values from the RCT which included no discontinuation as a result of clinical review. It is likely that the true value will lie somewhere in between the two. Consensus from experts is that clinical judgement may be used at around 5 weeks in order to assess whether 3C Patch is working effectively and, therefore, there may be some discontinuation. This therefore could impact on the healing rate because the trial is reflective of no discontinuation at this time point and so patients in whom 3C Patch did not appear to be effective would still have received the patch in the trial. The company estimated a probability based on those in the trial that had ulcer reduction of 50% or more at 5 weeks. However, this estimate was deemed too high by the EAC on the basis of expert responses and at an increased level of uncertainty because it was based on fewer patients from the trial ([redacted]).

Depending on the probability of healing used, the impact of discontinuation appears to vary. Where the probability is of healing is higher, increasing discontinuation appears to reduce the cost effectiveness of 3C Patch because the reduced costs associated with the probability of healing seems to outweigh the additional cost of the patch. However, where the estimated probability of healing is lower, increasing discontinuation has the opposite effect – removing patients from 3C Patch earlier reduces the cost increase seen with 3C Patch because the difference in healing seen between 3C Patch and standard care is not enough to outweigh the additional cost. Where discontinuation increases, the healing rate with 3C is also likely to increase. Therefore, estimates in the lower left-hand corner of the table may be less plausible i.e. higher healing rate but lower discontinuation. It appears weekly probability of healing with 3C Patch for those continuing to use it must be around 5.0%-5.5% in order to produce a cost saving result in the EAC model A and at no likelihood of healing in model B.

Two-way analysis was also conducted on probability of discontinuation of 3C Patch at 5 weeks and weekly probability of healing for those who discontinued 3C Patch in weeks 6 to 20. Again these parameters are likely to be linked. If people discontinue the patch at 5 weeks they will likely have a different probability of healing than those who discontinue use of the Patch at 20 weeks. The company estimated this based on the equivalent cohort in the control arm i.e. those on standard care who had not seen a reduction in ulcer area of 50% or more at 5 weeks. The EAC notes that these patients had received a different treatment up to this point and so this may still not be reflective of what would have happened to patients that had received 3C Patch up to this point. The direction of bias is difficult to assess because in

theory patients who do not respond to 3C Patch may be harder to heal than those who do not respond to standard care if despite a more effective treatment they still do not see adequate reduction in their ulcer size. However, they also may have had some benefit from the 3C Patch during those 5 weeks and so could potentially have a higher probability of healing. Varying the probability used for discontinuation would likely also have an impact on the estimated probability of healing because this was calculated assuming patients without a reduction in ulcer area of 50% was used as the discontinuation rule. The two-way analysis is presented in Figure 9.6 and Figure 9.7.

Figure 9.6: Two-way analysis Model A

		Discontinuation at 5 weeks												
	£1,590.09	**0.0%**	5.0%	10.0%	15.0%	20.0%	25.0%	30.0%	35.0%	40.0%	45.0%	50.0%	**57.9%**	60.0%
Weekly probability of healing with 3C Patch discontinued (weeks 6 to 20)	0.5%	£1,590	£1,594	£1,598	£1,602	£1,606	£1,610	£1,614	£1,618	£1,622	£1,626	£1,630	£1,636	£1,638
	0.6%	£1,590	£1,589	£1,588	£1,587	£1,586	£1,585	£1,585	£1,584	£1,583	£1,582	£1,581	£1,579	£1,579
	0.7%	£1,590	£1,585	£1,581	£1,576	£1,572	£1,567	£1,562	£1,558	£1,553	£1,549	£1,544	**£1,537**	£1,535
	0.9%	£1,590	£1,575	£1,560	£1,544	£1,529	£1,514	£1,498	£1,483	£1,468	£1,452	£1,437	£1,413	£1,407
	1.1%	£1,590	£1,566	£1,541	£1,516	£1,492	£1,467	£1,443	£1,418	£1,393	£1,369	£1,344	£1,306	£1,295
	1.3%	£1,590	£1,556	£1,523	£1,489	£1,456	£1,422	£1,388	£1,355	£1,321	£1,287	£1,254	£1,201	£1,186
	1.5%	**£1,590**	£1,546	£1,502	£1,458	£1,414	£1,370	£1,326	£1,282	£1,238	£1,194	£1,150	£1,081	£1,062

Figure 9.7: Two-way analysis Model B

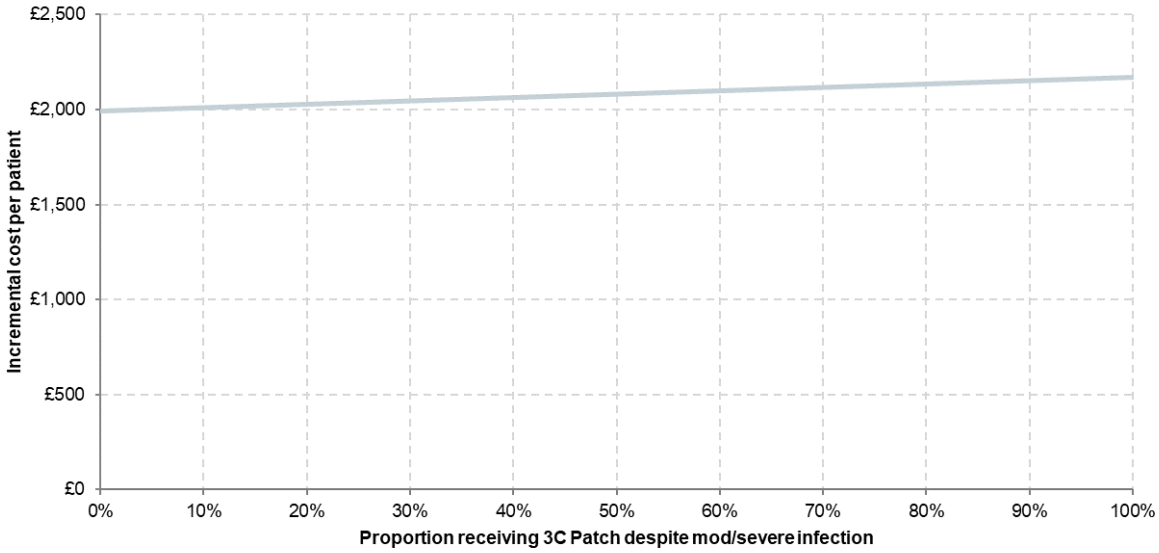
		Discontinuation at 5 weeks												
	£1,992.60	**0.0%**	5.0%	10.0%	15.0%	20.0%	25.0%	30.0%	35.0%	40.0%	45.0%	50.0%	**57.9%**	60.0%
Weekly probability of healing with 3C Patch discontinued (weeks 6 to 20)	0.5%	£1,993	£2,013	£2,034	£2,055	£2,076	£2,096	£2,117	£2,138	£2,159	£2,179	£2,200	£2,233	£2,242
	0.6%	£1,993	£2,009	£2,025	£2,042	£2,058	£2,074	£2,091	£2,107	£2,123	£2,140	£2,156	£2,182	£2,189
	0.7%	£1,993	£2,005	£2,018	£2,031	£2,044	£2,057	£2,070	£2,083	£2,095	£2,108	£2,121	**£2,141**	£2,147
	1.0%	£1,993	£1,992	£1,991	£1,990	£1,990	£1,989	£1,988	£1,987	£1,986	£1,986	£1,985	£1,984	£1,983
	1.2%	£1,993	£1,984	£1,975	£1,966	£1,957	£1,948	£1,939	£1,929	£1,920	£1,911	£1,902	£1,888	£1,884
	1.4%	£1,993	£1,976	£1,958	£1,941	£1,924	£1,907	£1,890	£1,873	£1,856	£1,839	£1,822	£1,795	£1,788
	1.7%	**£1,993**	£1,964	£1,936	£1,908	£1,880	£1,852	£1,824	£1,795	£1,767	£1,739	£1,711	£1,667	£1,655

Varying the probability of healing when 3C Patch has been discontinued is less of a driver of the model results and none of the values tested changed the direction of the results.

EAC scenario analysis

The EAC ran two scenario analyses in Model B (with infection health state) as described in section 9.2.6. First to assess the impact of some patients remaining on the 3C Patch (up to 20 weeks) despite having a moderate/severe infection. The results of this analysis are presented in Figure 9.8.

Figure 9.8: Use of 3C Patch in moderate/severe infections



Use of 3C Patch during infection increases the incremental cost estimate per patient by around £180. It is important to note that no other parameters are varied in this scenario i.e. this assumes no impact of 3C Patch on how quickly the infection may clear and healing rates and other resource use (for those with an infection) remain static. Where not all patients receive 3C Patch they can only go back onto the 3C Patch once their infection has cleared up to 20 weeks. Therefore, not all patients would receive 20 weeks of treatment with 3C Patch.

The second scenario conducted assesses the impact of applying the same infection rate to both arms in the model. No significant difference was observed in the trial in infection. However, the EAC chose to use the infection rates reported in the trial to calculate the transition probability from index ulcer to infection because there were higher numbers of serious AEs related to infection reported for the 3C Patch arm. This scenario explores the impact of assuming there is the same rate of a moderate/severe infection from index

ulcer in both treatment arms in the model. The rate was calculated using both treatment arms from Game et al. (2018) (1.7%). Results are presented in Table 9.15. All other input parameters (including the differential cost of infection) remain static.

Table 9.15: Results from equal infection rate scenario

	3C Patch	Standard care	Incremental
Cost per patient – base case	£11,217	£9,225	£1,993
Cost per patient - scenario	**£11,234**	**£9,342**	**£1,892**

This scenario results in a reduction in the incremental cost of around £100 and therefore does not appear to have a meaningful impact on the results.

EAC probabilistic analysis

The EAC conducted PSA as described in section 9.2.6. The model was run for 2,000 iterations and resulted in an average cost increase per patient of £1,459 in model A (without infection health state) and £1,858 in model B (with infection health state).

The estimated probability that the intervention is cost saving is 31% in model A and 25% in model B. A cost-effectiveness plane is presented in Figure 9.9 and Figure 9.10. Note the results fall in all 4 quadrants around the intersection of the axes. The plot suggests that there is such uncertainty with the results that it is not possible to advise if 3C Patch is likely to be cost saving or cost incurring relative to standard care. There is similar uncertainty about the direction of the relative QALY benefits and harms.

Figure 9.9: Cost effectiveness plane Model A

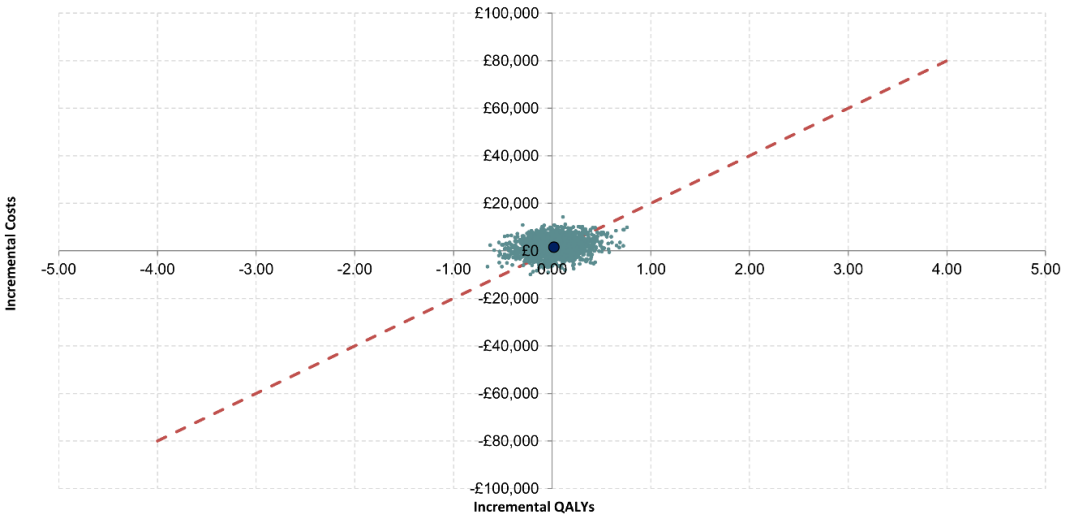
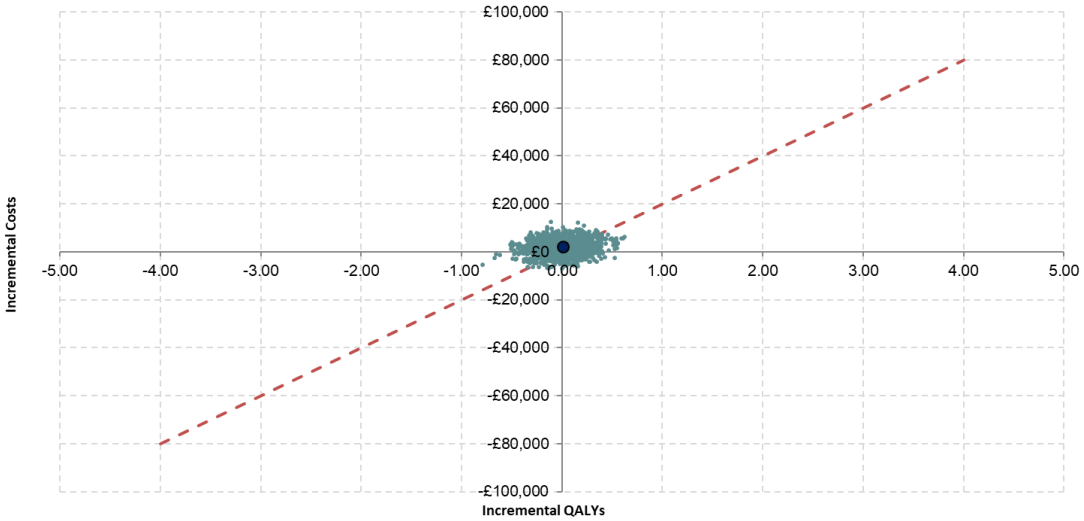


Figure 9.10: Cost effectiveness plane Model B



Summary of sensitivity analysis

Results from the sensitivity analysis identify the probability of discontinuation at 5 weeks and the resulting probability of healing with 3C Patch in weeks 6 to 20 as a key uncertainty in the model. There is very little evidence on which to base these estimates on and they potentially could change the direction of the results. In model A (without infection health state) where the weekly probability of healing with 3C Patch in weeks 6 to 20 is around 4% or higher and discontinuation at 5 weeks in around 50% or lower, 3C Patch may be cost saving. In model B (with infection health state) 3C Patch is not cost saving in any of the sensitivity analyses considered. Estimates from model A are more favourable for 3C Patch. The company's estimate of healing of around 5.7% was based on only [redacted] patients and quite a strict discontinuation rule of 50% or more ulcer area reduction required by 5 weeks to stay on treatment. Additionally expert input has indicated it is unlikely that a strict rule of 50% reduction or more in ulcer area will be adhered to in practice.

9.3.3 Additional results

The company also produced QALY estimates over the time horizon of their model. The EAC revised the QALYs estimates used for each health state as discussed in section 9.2.5. Results from company model and EAC models are presented in Table 9.16.

Table 9.16: QALY estimates over 2 years

	Company's results			EAC results model A Without infection health state			EAC results model B With infection health state		
	3C Patch	Standard care	Incremental	3C Patch	Standard care	Incremental	3C Patch	Standard care	Incremental
Costs per patient	£13,674	£13,865	-£191	£11,664	£10,074	£1,590	£11,217	£9,225	£1,993
QALYs per patient	0.896	0.880	0.016	1.326	1.308	0.018	1.313	1.300	0.013
Calculated ICER	-£11,938* (Dominant)			£87,930			£149,630		
ICER: incremental cost-effectiveness ratio *Note calculated by the EAC									

The company also estimated the base case results over a 3-year time horizon resulting in an estimated cost saving of £321. The EAC model when run for 3 years estimates a cost incurred of £1,474 (Model A, without infection health state) and £1,933 (Model B with infection health state). Cost savings are slightly better when the models are run for longer periods of time because there is more time for benefits of healing to accrue. However, it should be noted that subsequent ulcers are not modelled fully in either the company's model or the EAC model because this would result in a much more complicated model structure which was not deemed feasible within the timelines. Subsequent ulcers are assumed to heal in line with the average ulcers reported by the NDFA and therefore are not deemed to be hard-to-heal. The use of 3C Patch in any subsequent ulcers is also not captured.

9.4 EAC Interpretation of economic evidence

The key changes to the company's model were:

- Discontinuation of 3C Patch at 5 weeks and subsequent probabilities of healing with 3C Patch were aligned with the published trial data rather than unplanned post hoc trial analysis conducted by the company. This can change the results of the model in either direction depending on other parameters. In the company model decreasing the probability of discontinuation at 5 weeks increases the cost savings with 3C Patch because the difference between 3C Patch and standard care weekly healing is sufficient to outweigh the cost of keeping people on the 3C Patch. However, this is only when the company's probability of healing with 3C Patch in weeks 6 to 20 is used which is based on only those from the trial who saw a reduction of 50% or more in ulcer area at 5 weeks ([redacted]). Combining this change to discontinuation with the change to the weekly probability of healing in weeks 6 to 20 to around 2.7% as per what was demonstrated in the trial in the whole cohort receiving 3C Patch results in a change in the company model results of an increase in costs of around £370 resulting in a change in the direction of results.

- Other transition probabilities were revised slightly as described in section 9.2.2 and 9.2.3. The impact of these changes was mixed in terms of increasing or decreasing costs associated with 3C Patch. Overall the changes averaged out to increase the costs with 3C Patch by around £50.

- The functionality to include moderate/severe infection as a health state in the model was included so as to capture the impact of people with moderate/severe infections stopping 3C Patch whilst their ulcer was infected as well as additional costs associated with these infections. Costs in each arm are lower due to lack of use of 3C patch with an

infection and lower overall costs in the index unhealed ulcer state. However, inclusion of this health state increases the cost difference between 3C Patch and standard care by around £400 because more serious infections appeared to occur in the trial in the 3C Patch arm. The change to the company model is more difficult to assess because this is a structural change and so has implications for a lot of parameters.

- The majority of the costs estimated by the company were altered. Key changes include updates to outpatient attendance to incorporate that an outpatient attendance is required every week for the 3C Patch; differences across treatments arms for inpatient costs due to weighting costs by severe ulcer deterioration and revascularisation in Farr et al. (unpublished). Furthermore, for Model B infection costs are incorporated within the EAC model, which are not fully captured in the company submission. Changes to the costs in the model also had a mixed influence on the results with some increasing and some decreasing costs associated with the 3C Patch. Overall changes to costs increase costs associated with 3C in the EAC model by around £800.

- Other structural changes to the model such as the inclusion of half cycle correction increased costs associated with the 3C Patch by around £100.

These changes do not total to the full amount by which the results changed because of interaction between parameters i.e. making the changes on their own as described above has less of an impact than when they are made incrementally because for example, reducing the healing rate with 3C Patch influences the impact of changing the cost of the 3C Patch index ulcer health state.

The uncertainty demonstrated in the results of the EAC model does not support the case for adoption of the technology. Increases in the probability of healing demonstrated in the published trial data do not justify the costs of the device. There is substantial uncertainty around how 3C Patch would be used in practice in terms of which patients would continue with the patch after 5 weeks and what their subsequent probability of healing would be. The trial conducted by Game et al. (2018a) does not appear to align with how the company suggests the patch should be used in practice and therefore the results from the trial cannot easily be generalised to the economic model. If the company's proposed proportion of people discontinuing at 5 weeks and subsequent estimated weekly probability of healing with 3C Patch in weeks 6 to 20 were to be accepted then the results of the EAC analysis still estimates

a cost increase of around £170 due to changes in the cost parameters. Additionally the EAC notes that there is increased uncertainty around the probability of healing calculated by the company because of the reduced sample size. Even in the company model a small reduction in this probability of around 0.6% results in cost increases with the introduction of 3C Patch.

10 Conclusions

10.1 Conclusions on the clinical evidence

The evidence base comprises a well-designed and executed RCT, 2 non-comparative pilot studies and a small case series published as an abstract. The RCT provides unbiased evidence of a statistically significant faster time to, and higher likelihood of, complete healing at 20 weeks (the most important outcomes clinically) of hard-to-heal DFUs with 3C Patch as adjuvant to standard care, versus standard care. It also reported non-significant reductions in infections, pain, days on antibiotics and amputation of the index limb at 26 weeks. No AEs related to using the 3C Patch were identified. No evidence was reported on any subgroups.

The main limitations with this evidence in relation to the decision problem are:

- The population excluded those with little chance of healing within the 20 weeks of the study (for example, very large ulcers [1000 mm²], those with severe ischaemia, and those with severe renal disease). This was reasonable for this first RCT of the intervention.

- In the RCT new patches were applied weekly until healing or the study end at 20 weeks.

The experts advised that, in clinical practice, they will review healing progress with 3C Patch after 4 to 6 weeks and regularly thereafter, and will continue using the patch if the wound is healing better than with standard care. The population receiving the patch may also differ from the RCT, being those whom clinicians judge have hard-to-heal ulcers, having failed on UrgoStart. Finally, experts also advised many clinics will stop using 3C Patch whilst there is active infection.

The majority of experts agreed weekly appointments for 3C Patch could be accommodated because so few patients would require this treatment. Potential issues were noted with patient compliance with a weekly schedule and difficulties of giving blood with such regularity.

Overall the evidence base is specific to the RCT. The population in clinical practice is likely to be broader than the RCT and similar to that in the IFU. The major uncertainties arise because the expected clinical pathway, with regular

reviews from 4 to 6 weeks, and using criteria weighted to judgements based on the relative improvement in healing rates with 3C Patch compared with standard care, will alter healing rates, discontinuation rates and the number of patches compared with the values reported in the RCT. Hence the RCT evidence does not generalise to expected clinical practice.

10.2 Conclusions on the economic evidence

There are no published economic evaluations of 3C Patch. The company submitted a cost and a utility analysis, using a Markov model, comparing 3C Patch with standard care in people with hard-to-heal DFUs. The EAC reviewed the model. Following advice from experts that people with moderate to severe infections would stop receiving 3C Patch until the infection had resolved, it incorporated a separate infection health state into the model. The time horizon and cost parameters were consistent with the decision problem.

The company derived efficacy data from an unplanned, post hoc analysis of patient level data from Game et al. (2018a). It included weekly healing probabilities obtained from 42% of patients who had a 50% or greater improvement in ulcer area at 5 weeks. The remaining 58% of the 3C Patch cohort were assumed to move on to standard care, with a weekly healing rate of about half the rate reported for patients in standard care in the RCT (0.7% versus 1.5%).

The EAC disagreed with the company on the discontinuation rates and the related healing rates in the 3C Patch arm. It adopted the healing rates observed in the RCT for both arms. The EAC also changed various cost parameters, particularly for inpatient and outpatient costs, so they are no longer equal across treatment arms. The EAC also used a more recent quality of life study.

The company's model results showed that over 2 years, 3C Patch was cost saving compared with standard care (saving £191 per patient) and associated with higher QALYs (0.02 per patient). PSA gave a very similar result, with mean savings of £192 per patient. After applying the EAC's updated clinical and cost parameters, 3C Patch was cost incurring (higher cost of around £1,600 to £2,000 per patient), with similar changes in QALYs to the company submission. Key changes made by the EAC include changes to the unit costs which accounted for about £800 of the higher costs, and changes to the discontinuation and healing rates which accounted for an increase of around £370. The PSA estimated the probability that 3C Patch was cost saving at 31%. The cluster of results around the intersection of the axes indicated high internal uncertainty.

The key uncertainties with the economic model mirror the uncertainties with the clinical evidence. These relate to how 3C Patch will be used in practice in terms of which patients will continue with the 3C Patch after 5 weeks and what their subsequent probability of healing will be. Neither the results from the trial, nor the post hoc analysis provide values which can inform an economic model of the expected impact of 3C Patch on clinical practice. The impact of the uncertainty is shown in a two-way analysis of healing rates and discontinuation rates. These suggest that, if clinicians continue with 3C Patch when weekly healing rates are under 4.5%, then 3C Patch will be cost increasing. This is triple the rate observed with standard care (1.5%). Some clinicians have indicated they will continue with 3C Patch if any improvement on standard care rates is observed.

11 Summary of the combined clinical and economic sections

The efficacy of 3C Patch is supported by evidence provided by the Game et al. (2018a) RCT. However, the clinical experts advise that clinical practice will differ from that adopted in the RCT, where patches were applied weekly until complete healing or the end of 20 weeks. In clinical practice, clinicians advise they will review progress regularly and discontinue 3C Patch based on a range of factors including healing rate relative to standard care and patient preferences. Hence the efficacy data from the RCT will not generalise to the UK clinical setting.

The company has tried to address this by undertaking a post hoc analysis which applied a strict rule that if the ulcer area reduction is less than 50% at 5 weeks then 3C Patch should be stopped. The resulting discontinuation and healing rates were applied in its model. However, the clinical experts noted this rule was too inflexible and they would continue using the device on patients showing a lower healing rate than 50%. The EAC's model adjusted some cost parameters and adopted the efficacy data reported in the RCT. It found 3C Patch to be cost incurring even with the discontinuation rates adopted by the company. Neither model can claim to be representative of expected clinical practice. The PSA results using the EAC's values suggest that there is a lot of uncertainty around the economic case and these do not support the case for adopting 3C Patch.

12 Implications for research

The EAC notes that further high-quality research is needed to assess whether the intervention is effective in a wider population of patients with hard-to-heal DFUs who would attend a specialist diabetic foot clinic and who are UrgoStart-experienced. Discontinuation criteria should reflect current practice. In addition, research should be undertaken to determine the optimal

frequency of 3C Patch changes and the treatment duration needed with this intervention.

13 References

AHSN Network. (2019) National Wound Care Strategy Programme [Online]. Available: https://www.ahsnnetwork.com/about-academic-health-science-networks/national-programmes-priorities/national-wound-care-strategy-programme [Accessed 20th May 2021].

Armstrong, D. G., Boulton, M. D. & Bus, S. A. (2017) Diabetic foot ulcers and their recurrence. NEJM, 376, 2367-75.

BNF. (2021) BNF [Online]. NICE. Available: https://bnf.nice.org.uk/ [Accessed].

Clarivate Analytics. (2020) Endnote [X9.3.3 for Windows & Mac]. Philadelphia: Clarivate Analytics.

Clinical feedback on draft 3C Patch pathway (2021). Clinical feedback on draft 3C Patch pathway - version 1.0.

Curtis, L. & Burns, A. (2020) Unit costs of health & social care 2020. Kent: PSSRU, University of Kent.

Diabetes.co.uk (2019) Foot Ulcers [Online]. Available: https://www.diabetes.co.uk/diabetes-complications/diabetic-foot-ulcers.html [Accessed 20th May 2021].

EAC correspondence log (2021). Correspondence log for MT539 3C Patch System for treating DFUs.

Edmonds, M., Lázaro-Martínez, J.L., Manuel Alfayate-García, J., Martini, J., Petit, J-M., Rayman, G., Lobmann, R., 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. Lancet Diabetes Endocrinology, 6(3) 186-96.

Fagher, K., Katzman, P., Asmundsson, Å., Ley, M. R., Larsson, G., Ahlberg, M., Fröjd, M. & Löndahl, M. Treatment with a leukocytes and platelet rich fibrin patch on hard-to-heal diabetic foot ulcers probing to bone. ISDF, 2015 Den Haag.

[redacted]

Game, F., Jeffcoate, W., Tarnow, L., Day, F., Fitzsimmons, D. & Jacobsen, J. (2017) The LeucoPatch system in the management of hard-to-heal diabetic foot ulcers: study protocol for a randomised controlled trial. Trials, 18, 469.

Game, F., Jeffcoate, W., Tarnow, L., Jacobsen, J. L., Whitham, D. J., Harrison, E. F., Ellender, S. J., Fitzsimmons, D., Löndahl, M. & LeucoPatch I. I. trial team. (2018a) LeucoPatch system for the management of hard-to-heal diabetic foot ulcers in the UK, Denmark, and Sweden: an observer-masked, randomised controlled trial. The Lancet Diabetes & Endocrinology, 6, 870-878.

Game, F., Jeffcoate, W., Tarnow, L., Jacobsen, J. L., Whitham, D. J., Harrison, E. F., Ellender, S. J. & Löndahl, M. (2018b) The Leucopatch system in the management of hard-to-heal diabetic foot ulcers - a multicentre, multinational, observer-blinded, randomised controlled trial. Diabetes, 67.

Game, F., Jeffcoate, W., Tarnow, L., Jacobsen, J., Whitham, D., Harrison, E., Ellender, S. & Löndahl, M. (2018c) The LeucoPatch system in the management of hard-to-heal diabetic foot ulcers: a multicentre, multinational, observer-blinded, randomised controlled trial. Diabetologia, 61, S6.

Guest, J. F., Fuller, G.W., Vowden, P. (2018) Diabetic foot ulcer management in clinical practice in the UK: costs and outcomes. International Wound Journal, 15, 43-52.

Hogh, A., Andersen, J. W. & Dashnaw, B. (2019) The effect of autologous blood patch treatment among patients with hard-to-heal wounds; a clinical perspective. European Journal of Vascular and Endovascular Surgery, 58, e751-e752.

Jeffcoate, W. J., Villeikyte, L, Boyko, E.J, Armstrong, D.G, Boulton, A.J.M (2018) Current challenges and opportunities in the prevention and management of diabetic foot ulcers. Diabetes Care, 41, 645-652.

Jørgensen, B., Karlsmark, T., Vogensen, H., Haase, L. & Lundquist, R. (2011) A pilot study to evaluate the safety and clinical performance of Leucopatch, an autologous, additive-free, platelet-rich fibrin for the treatment of recalcitrant chronic wounds. International Journal of Lower Extremity Wounds, 10, 218-23.

Jørgensen, B., Löndahl, M., Tarnow, L., Nielsen, A. M., Michelsen, M., Nilsson, A., Mariusz Zakrzewski, M. & Karlsmark, T. Treatment of hard-to-heal diabetic foot ulcers with a leucocyte and platelet-rich fibrin patch – a prospective Scandinavian multicenter study. EWMA Meeting, 2013.

Katzman, P., Fagher, K., Lundquist, R. & Löndahl, M. (2014) Treatment of hard-to-heal diabetic foot ulcers probing to bone with leucopatch, a leukocytes and platelet rich fibrin patch. Diabetes, 63, A581.

Kerr, M., Barron, E., Chadwick, P., Evans, T., Kong, W. M., Rayman, G., Sutton-Smith, M., Todd, G., Young, B. & Jeffcoate, W. J. (2019) The cost of diabetic foot ulcers and amputations to the National Health Service in England. Diabetic Medicine, 36, 995-1002.

Kerr, M., Rayman, G. & Jeffcoate, W. J. (2014) Cost of diabetic foot disease to the National Health Service in England. Diabet Med, 31, 1498-1504.

Lefebvre, C., Glanville, J., Briscoe, S., Littlewood, A., Marshall, C., Metzendorf, M.-I., Noel-Storr, A., Rader, T., Shokraneh, F., Thomas, J. & Wieland, L. (2021) Chapter 4: Searching for and selecting studies. In: Higgins, J., Thomas, J., Chandler, J., Cumpsron, M., Li, T., Page, M. & Welch, V. (eds.) Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021).

Löndahl, M. (2017) Clinical experiences with LeucoPatch and status of the large RCT: Leucopatch system in the management of hard-to-heal diabetic foot ulcers. Innovation in Wound Healing. Bahamas.

Löndahl, M., Jeffcoate, W., Tarnow, L., Jacobsen, L. J. & Game, F. (2019) Use of an autologous platelet and leucocyte patch is associated with improved usual daily activities in people with diabetic foot ulcers. Wound Repair and Regeneration, 27, A36.

Löndahl, M., Jørgensen, B., Tarnow, L., Nielsen, A. M. & Michelsen, M. LeucoPatch seems to improve healing of diabetic foot ulcers – outcome from an open multicenter clinical study. Poster Diabetic Foot Study Groups 10th Annual Meeting, 2012a Potsdam.

Löndahl, M., Jørgensen, B., Tarnow, L., Nielsen, A. M., Michelsen, M., Nilsson, A., Mariusz Zakrzewski, M. & Karlsmark, T. LeucoPatch seems to improve healing of diabetic foot ulcers – outcome from an open multicenter clinical study. DFSG Meeting, 2012b Potsdam.

Löndahl, M., Larsson, G., Elgzyri, T., Asmundsson, Å., Dupros, I., Ley, M. & Katzman, P. Treatment of hard-to-heal diabetic foot ulcers probing to bone with an autologous leucocyte and platelet-rich fibrin patch. EWMA, 2013.

Löndahl, M. & Lundquirst, R. An autologous fibrin, leucocyte and platelet rich patch (3C Patch) in the healing of hard-to-heal diabetic foot ulcers – outcomes from a large Anglo-Scandinavian RCT. Innovation in Wound Healing, 2018 Key West.

Löndahl, M., Tarnow, L., Karlsmark, T., Lundquist, R., Nielsen, A. M., Michelsen, M., Nilsson, A., Zakrzewski, M. & Jørgensen, B. (2015) Use of an autologous leucocyte and platelet-rich fibrin patch on hard-to-heal DFUs: a pilot study. Journal of Wound Care, 24, 172-4, 176-8.

McGowan, J., Sampson, M., M. Salzwedel, D., Ccogo, E., Foerster, V. & Lefebvre, C. (2016). PRESS peer review of electronic search strategies: 2015 guideline statement. Journal of Clinical Epidemiology, 75, 40-46.

McIntosh, C., Ivory, J. D. & Gethin, G. (2019) Managing wound exudate in diabetic foot ulcers [Online]. Wounds International. Available: https://www.woundsinternational.com/resources/details/managing-wound-exudate-in-diabetic-foot-ulcers [Accessed 20th May 2021].

Monteiro-Soares, M., Boyko, E. J., Jeffcoate, W., Mills, J. L., Russell, D., Morbach, S. & Game, F. (2020) Diabetic foot ulcer classifications: a critical review. Diabetes Metab Res Rev, 36, e3272.

National Institute for Health and Care Excellence (2015a) Diabetic foot problems: prevention and management NICE guideline. London. www.nice.org.uk/guidance/ng19

National Institute for Health and Care Excellence (2015b) Diabetic foot problems: prevention and management - appendix J: health economics. London. https://www.nice.org.uk/guidance/ng19/evidence/appendix-j-health-economics-pdf-15672915541

National Institute for Health and Care Excellence (2015c) Wound care products. London. https://www.nice.org.uk/advice/ktt14

National Institute for Health and Care Excellence (2016a) Chronic wounds: advanced wound dressings and antimicrobial dressings. London. https://www.nice.org.uk/advice/esmpb2/chapter/Key-points-from-the-evidence

National Institute for Health and Care Excellence (2016b) Woundchek Protease Status for assessing elevated protease status in chronic wounds. London. https://www.nice.org.uk/advice/mib83/chapter/The-technology

National Institute for Health and Care Excellence (2019) UrgoStart for treating diabetic foot ulcers and leg ulcers. London. https://www.nice.org.uk/guidance/mtg42

National Institute for Health and Care Excellence (2020) NATROX oxygen wound therapy for managing diabetic foot ulcers and complex or chronic non-healing wounds. London.

National Institute for Health and Care Excellence (2021). Medical technology guidance scope: 3C Patch for treating diabetic foot ulcers. London. https://www.nice.org.uk/advice/mib208/chapter/The-technology

National Wound Care Strategy Programme (2020) Recommendations for lower limb ulcers.

National Wound Care Strategy Programme (2021) Recommendations for surgical wounds.

NHS Business Services Authority. (2021) Drug tariff [Online]. Available: https://www.nhsbsa.nhs.uk/pharmacies-gp-practices-and-appliance-contractors/drug-tariff [Accessed].NHS England. (2019) National cost collection for the NHS [Online]. Available: https://www.england.nhs.uk/national-cost-collection/ [Accessed 21st May 2021].

NHS Supply Chain. (2021) NHS Supply Chain [Online]. Available: https://www.supplychain.nhs.uk/ [Accessed].

Nottingham University Hospitals NHS Trust (2013) Leucopatch in the management of hard to heal diabetic foot ulcers. London: BioMed Central Limited.

Nottingham University Hospitals NHS Trust (2014) LeucoPatch in the management of hard-to-heal diabetic foot ulcers. Bethesda: US National Library of Medicine.

Ragnarson Tennvall, G. & Apelqvist, J. (2000) Health-related quality of life in patients with diabetes mellitus and foot ulcers. Journal of Diabetes & its Complications, 14, 235-41.

Rayman, G., Vas, P., Dhatariya, K., Driver, V., Hartemann, A., Löndahl, M., Piaggesi, A., Apelqvist, J., Attinger, C., Game, F. & International Working Group on the Diabetic Foot (IWGDF) (2020) Guidelines on use of interventions to enhance healing of chronic foot ulcers in diabetes (IWGDF 2019 update). Diabetes Metab Res Rev, 36, e3283.

Reapplix (2010) LeucoPatch study a multicenter study on the effect of LeucoPatch in diabetic foot ulcers. Bethesda: US National Library of Medicine.

Reapplix (2019) 3C Patch medicare claims study. Bethesda: US National Library of Medicine.

Redekop, W. K., Stolk, E. A., Kok, E., Lovas, K., Kalo, Z. & Busschback, J. J. V. (2004) Diabetic foot ulcers and amputations: estimates of health utility for use in cost-effectiveness analyses of new treatments. Diabetes Metab, 30, 549-56.

Rethlefsen, M. L., Kirtley, S., Waffenschmidt, S., Ayala, A. P., Moher, D., Page, M. J., Koffel, J. B. & PRISMA-S Group (2021) PRISMA-S: an extension to the PRISMA statement for reporting literature searches in systematic reviews. Systematic Reviews in Pharmacy, 10, 39.

14 Appendices

14.1 Appendix A: Searches, PRISMA

Critique of the company search strategies to identify clinical evidence

Appendix A of the company submission contained a description of the search methodology used to retrieve relevant clinical evidence.

The extent to which the EAC could assess the company search methods was restricted by limitations in the search reporting. Although the company submission reported some elements of the search methods reasonably clearly (name of resources searched, date span of searches, search dates) the overall reporting did not reflect standard requirements for transparent, reproducible reporting (as outlined, for example, in the PRISMA-S (Preferred Reporting Items for Systematic reviews and Meta-Analyses literature search extension) checklist) (Rethlefsen et al. 2021). Key reporting issues included lack of clarity regarding:

- which platform / interface was used to search each database
- whether individual search line(s) in each database search strategy were combined using boolean, and if so, how
- which search line(s) in each database search strategy were used to output results for assessment
- the total number of records identified from each database and other information sources

The above issues meant that only limited assessment of the company search methods was possible.

Currency of searches

The searches were conducted between 08/03/2021 and 15/03/2021. The searches therefore had good currency at the date of submission (26/03/2001).

Search sources

The search sources included a reasonably wide selection of bibliographic databases (MEDLINE, PubMed, Embase, CINAHL), registers of ongoing studies (ClinicalTrials.gov, ISRCTN registry), and potential sources of studies not included in bibliographic databases (The Grey Literature Report, OpenGrey, the UK Government Web Archive, Wounds UK website). The selection of search sources could have been enhanced by including the following resources:

- Cochrane Central Register of Controlled Trials (CENTRAL). CENTRAL is recommended by organisations such as Cochrane as a key search resource (Lefebvre et al. 2021).

- WHO International Clinical Trials Registry Platform (ICTRP) portal. ICTRP is one of the two register resources considered to be the most important when searching to identify studies for a systematic review (Lefebvre et al. 2021). The submission text appeared to suggest that a search of ICTRP was included by searching ClinicalTrials.gov ("www.clinicaltrials.gov (including ICTRP)") but ClinicalTrials.gov does not include ICTRP, so this would appear to be incorrect.

- The HTA Database. The HTA database contains bibliographic information about ongoing and published health technology assessments commissioned or undertaken by HTA organisations from around the world.

- Conference Proceedings Citation Index-Science (CPCI-S). The submission methods did not detail any search for conference abstracts. The resources searched included Embase, which does contain some conference abstracts, but search methods would have been enhanced by including an additional source of abstracts, such as CPCI-S.

Search strategies

From the reported search strategies for bibliographic databases, it was not possible to know which search lines were used to output results. Therefore, it was not possible to assess in any detail the search strategy structure, search terms or syntax (for example, using the Peer Review of Electronic Search Strategies (PRESS) Checklist (McGowan et al. 2016). There appeared to be some limitations that could potentially impact on search sensitivity and the identification of relevant evidence (for example: subject headings searched as major descriptors; restricted range of variant search terms for bibliographic database strategies; syntax reported for some databases, for example, PubMed potentially not being appropriate for use in the database; search terms for study register strategies limited to brand / company name terms only).

The methods stated that the date span of the search was 2000 to present (although no such restrictions are shown in the strategy syntax itself). This date span was appropriate, given the product was first developed as a manual process in 2009 and the initial device was developed in 2010.

Details of EAC de novo searches

The reporting limitations meant the EAC was unable to replicate the search conducted by the company. The EAC therefore conducted a de novo literature search to identify evidence. A single set of searches was conducted to identify clinical and economic evidence.

A MEDLINE (OvidSP) search strategy was designed to identify studies of the 3C Patch in people with diabetic foot ulcers. The final MEDLINE strategy is presented in Figure 14.1.

The main structure of the strategy comprised two concepts:

- diabetic foot ulcers. Search lines 1 to 11
- 3C Patch. Search lines 12 to 35.

The search concepts were combined as follows: diabetic foot ulcers AND 3C Patch.

The terms for the 3C Patch included terms related to key aspects of the technology - platelet rich fibrin (search lines 12 to 22), platelets and leukocytes (search lines 23 to 31), autologous patches / blood patches (search lines 32 to 34)

The strategy also included stand-alone lines which searched on terms related to the technology brand name and manufacturer name (search lines 37 to 42).

Search concepts were captured using subject headings and textword searches in Title, Abstract and Keyword Heading Word fields. The search terms were identified through discussion within the research team, scanning background literature, assessing records of known relevant studies, browsing database thesauri and use of the PubMed PubReminer tool (http://hgserver2.amc.nl/cgi-bin/miner/miner2.cgi). The approach taken to search strategy development aimed to balance sensitivity and precision, reflecting the project resources and timelines. This balanced approach included, for example:

- Restricting the diabetic foot ulcer terms to retrieve records that explicitly referred to the diabetic ulcer / diabetic wound context, rather than also searching for records that only referred to a non-specific chronic wound context.
- Targeting database records where a reasonably close relationship between the diabetes context and the ulcer / wound context was suggested, for example, by the co-occurrence of diabetes and ulcer related subject headings in the same record, or by free text terms occurring in very close proximity.

The strategy excluded animal studies using a standard algorithm (search line 45). The strategy also excluded some publication types which were unlikely to yield relevant study reports (editorials, news items and case reports) and records with the phrase 'case report' in the title (search lines 46). Reflecting the eligibility criteria, the search was restricted to studies published in English from 2009 to date.

The performance of the draft MEDLINE strategy was tested by checking retrieval of the known relevant studies. The draft strategy successfully retrieved records for all known relevant studies available to be found in MEDLINE.

The final Ovid MEDLINE strategy was peer-reviewed by a second Information Specialist for errors in spelling, syntax and line combinations.

Figure 14.1: EAC search strategy for MEDLINE(R) ALL

1	Diabetic Foot/ (9294)
2	foot ulcer/ (1926)
3	exp Diabetes Mellitus/ and (Ulcer/ or leg ulcer/ or Skin Ulcer/ or Foot Diseases/ or Wound Healing/) (6660)
4	((diabet$ or dm or dm1 or t1dm or t1d or t1-d or iddm or dm2 or t2dm or t2d or t2-d or niddm or iidm) adj6 (foot or feet or plantar or pedis)).ti,ab,kf. (11997)
5	((diabet$ or dm or dm1 or t1dm or t1d or t1-d or iddm or dm2 or t2dm or t2d or t2-d or niddm or iidm) and (ulcer$ or ulcus)).ti,ab,kf. (13162)
6	((diabet$ or dm or dm1 or t1dm or t1d or t1-d or iddm or dm2 or t2dm or t2d or t2-d or niddm or iidm) and wound$).ti,ab,kf. (12543)
7	((diabet$ or dm or dm1 or t1dm or t1d or t1-d or iddm or dm2 or t2dm or t2d or t2-d or niddm or iidm) and sore$).ti,ab,kf. (471)
8	((foot or feet or plantar or pedis) adj6 (ulcer$ or ulcus)).ti,ab,kf. (8462)
9	((foot or feet or plantar or pedis) adj6 wound$).ti,ab,kf. (2412)
10	((foot or feet or plantar or pedis) adj6 sore$).ti,ab,kf. (118)
11	or/1-10 (31361)
12	platelet-rich plasma/ (4323)
13	platelet-rich fibrin/ (491)
14	exp Fibrin/ (29432)
15	fibrin$.ti,ab,kf. (110060)
16	(antithrombin i or anti-thrombin i or antithrombin 1 or anti-thrombin 1 or antithrombini or anti-thrombini or antithrombin1 or anti-thrombin1).ti,ab,kf,rn,nm. (6971)
17	(factor ia or factor 1a or factoria or factor1a).ti,ab,kf,rn,nm. (845)
18	(9001-31-4 or 232-597-0 or aq4k8i4r6f).ti,ab,kf,rn,nm. (15161)
19	(platelet-rich or thrombocyte-rich).ti,ab,kf. (12961)

20	(prp or prf).ti,ab,kf. (20147)
21	(lprp or lprf).ti,ab,kf. (34)
22	or/12-21 (147490)
23	Blood Platelets/ (78015)
24	(platelet$ or thrombocyte$).ti,ab,kf. (230172)
25	exp Leukocytes/ (763614)
26	(leukocyte$ or leucocyte$).ti,ab,kf. (181373)
27	(white blood adj (cell or cells or corpuscle or corpuscles)).ti,ab,kf. (34777)
28	(white adj (cell or cells or corpuscle or corpuscles)).ti,ab,kf. (6623)
29	(wbc or wbcs).ti,ab,kf. (19384)
30	(23 or 24) and (25 or 26 or 27 or 28 or 29) (37390)
31	((leukocyte$ or leucocyte$) and blood$).ti,ab,kf. (59895)
32	(autologous adj6 (patch$ or matrix$ or matric$ or gel or gels or gelat$ or dressing$)).ti,ab,kf. (2161)
33	(blood$ adj6 (patch$ or matrix$ or matric$ or gel or gels or gelat$ or dressing$)).ti,ab,kf. (6856)
34	bloodpatch$.ti,ab,kf. (7)
35	or/30-34 (97781)
36	11 and (22 or 35) (602)
37	(3c adj4 patch$).ti,ab,kf. (0)
38	(3c adj (system$2 or device$)).ti,ab,kf. (6)
39	(3cpatch$ or 3csystem$2 or 3cdevice$).ti,ab,kf. (0)
40	(leucopatch$ or leuco-patch$).ti,ab,kf. (8)
41	(leukopatch$ or leuko-patch$).ti,ab,kf. (0)
42	reapplix$.ti,ab,kf,in. (3)
43	or/37-42 (15)
44	36 or 43 (613)
45	exp animals/ not humans/ (4809908)
46	(news or editorial or case reports).pt. or case report.ti. (2980288)
47	44 not (45 or 46) (481)
48	limit 47 to english language (425)
49	limit 48 to yr="2009 -Current" (324)

Key to Ovid symbols and commands

$	Unlimited right-hand truncation symbol
$N	Limited right-hand truncation - restricts the number of characters following the word to N
ti,ab,kf,nm,rn	Searches are restricted to the Title, Abstract, Keyword Heading Word, Name of Substance Word, CAS Registry/EC Number/Name of Substance (RN) fields

adj	Retrieves records that contain terms next to each other in the specified order
adjN	Retrieves records that contain terms (in any order) within a specified number (N) of words of each other
/	Searches are restricted to the Subject Heading field
exp	The subject heading is exploded
pt.	Search is restricted to the publication type field
or/1-10	Combines sets 1 to 10 using OR

EAC de novo searches: resources searched

The EAC conducted the literature search in the databases and information resources shown in Table 14.1. The resources included a range of databases and information resources containing research published in the journal literature, research published outside the journal literature, conference abstracts and ongoing research.

Table 14.1: EAC de novo searches: databases and information sources searched

Resource	Interface / URL
MEDLINE ALL	OvidSP
Embase	OvidSP
Cochrane Database of Systematic Reviews (CDSR)	Cochrane Library / Wiley
Cochrane Central Register of Controlled Trials (CENTRAL)	Cochrane Library / Wiley
HTA Database	https://database.inahta.org/
Conference Proceedings Citation Index- Science (CPCI-S)	Web of Science
CINAHL Complete	EBSCOhost
Clinicaltrials.gov	https://clinicaltrials.gov/
WHO International Clinical Trials Registry Platform	https://ictrptest.azurewebsites.net/Default.aspx
NHS Economic Evaluation Database	https://www.crd.york.ac.uk/CRDWeb
Econlit	OvidSP
OpenGrey	http://www.opengrey.eu/
Grey Literature Report	http://www.greylit.org/home
3C Patch webpages	https://3cpatch.com/proven/references/
UK Government Web Archive	https://webarchive.nationalarchives.gov.uk/search/

In addition to the searches of the sources listed in Table 14.1, the EAC also screened one record that was sent by the client (Zink et al. 2021) but this was excluded at full text screening.

EAC de novo searches: running the search strategies and downloading results

We conducted searches using each database or resource listed above, translating the agreed Ovid MEDLINE strategy appropriately. Translation included consideration of differences in database interfaces and functionality, in addition to variation in indexing languages and thesauri. The full strategies (including search dates) for all sources searched are shown below.

Where possible, we downloaded the results of searches in a tagged format and loaded them into bibliographic software (EndNote) (Clarivate Analytics 2020). The results were deduplicated using several algorithms and the duplicate references held in a separate EndNote database for checking if required. Results from resources that did not allow export in a format compatible with EndNote were saved in Word or Excel documents as appropriate and manually deduplicated.

EAC de novo searches: literature search results

The searches were conducted between 07/04/2021 and 14/04/2021 and identified 2,103 records (Table 14.2). Following deduplication, 1,578 records were assessed for relevance.

Table 14.2: Literature search results

Resource	Number of records identified
Databases	
MEDLINE ALL	324
Embase	875
Cochrane Database of Systematic Reviews (CDSR)	6
Cochrane Central Register of Controlled Trials (CENTRAL)	243
HTA Database	29
Conference Proceedings Citation Index- Science (CPCI-S)	31
CINAHL Complete	131
Clinicaltrials.gov	343
WHO International Clinical Trials Registry Platform	72
NHS Economic Evaluation Database	4
Econlit	9
OpenGrey	0
Grey Literature Report	0
Total records identified through database searching	2067
Other sources	
3C Patch webpages	34
UK Government Web Archive	1
Sent by company	1
Total additional records identified through other sources	36
Total number of records retrieved	2,103
Total number of records after deduplication	1,578

EAC de novo searches: full search strategies

A.1: Source: Ovid MEDLINE(R) ALL

Interface / URL: OvidSP
Database coverage dates: 1946 to April 06, 2021
Search date: 07/04/2021
Retrieved records: 324
Search strategy:

1	Diabetic Foot/ (9294)
2	foot ulcer/ (1926)
3	exp Diabetes Mellitus/ and (Ulcer/ or leg ulcer/ or Skin Ulcer/ or Foot Diseases/ or Wound Healing/) (6660)
4	((diabet$ or dm or dm1 or t1dm or t1d or t1-d or iddm or dm2 or t2dm or t2d or t2-d or niddm or iidm) adj6 (foot or feet or plantar or pedis)).ti,ab,kf. (11997)
5	((diabet$ or dm or dm1 or t1dm or t1d or t1-d or iddm or dm2 or t2dm or t2d or t2-d or niddm or iidm) and (ulcer$ or ulcus)).ti,ab,kf. (13162)
6	((diabet$ or dm or dm1 or t1dm or t1d or t1-d or iddm or dm2 or t2dm or t2d or t2-d or niddm or iidm) and wound$).ti,ab,kf. (12543)
7	((diabet$ or dm or dm1 or t1dm or t1d or t1-d or iddm or dm2 or t2dm or t2d or t2-d or niddm or iidm) and sore$).ti,ab,kf. (471)
8	((foot or feet or plantar or pedis) adj6 (ulcer$ or ulcus)).ti,ab,kf. (8462)
9	((foot or feet or plantar or pedis) adj6 wound$).ti,ab,kf. (2412)
10	((foot or feet or plantar or pedis) adj6 sore$).ti,ab,kf. (118)
11	or/1-10 (31361)
12	platelet-rich plasma/ (4323)
13	platelet-rich fibrin/ (491)
14	exp Fibrin/ (29432)
15	fibrin$.ti,ab,kf. (110060)
16	(antithrombin i or anti-thrombin i or antithrombin 1 or anti-thrombin 1 or antithrombini or anti-thrombini or antithrombin1 or anti-thrombin1).ti,ab,kf,rn,nm. (6971)
17	(factor ia or factor 1a or factoria or factor1a).ti,ab,kf,rn,nm. (845)
18	(9001-31-4 or 232-597-0 or aq4k8i4r6f).ti,ab,kf,rn,nm. (15161)
19	(platelet-rich or thrombocyte-rich).ti,ab,kf. (12961)
20	(prp or prf).ti,ab,kf. (20147)
21	(lprp or lprf).ti,ab,kf. (34)
22	or/12-21 (147490)
23	Blood Platelets/ (78015)
24	(platelet$ or thrombocyte$).ti,ab,kf. (230172)
25	exp Leukocytes/ (763614)
26	(leukocyte$ or leucocyte$).ti,ab,kf. (181373)
27	(white blood adj (cell or cells or corpuscle or corpuscles)).ti,ab,kf. (34777)

28 (white adj (cell or cells or corpuscle or corpuscles)).ti,ab,kf. (6623)
29 (wbc or wbcs).ti,ab,kf. (19384)
30 (23 or 24) and (25 or 26 or 27 or 28 or 29) (37390)
31 ((leukocyte$ or leucocyte$) and blood$).ti,ab,kf. (59895)
32 (autologous adj6 (patch$ or matrix$ or matric$ or gel or gels or gelat$ or dressing$)).ti,ab,kf. (2161)
33 (blood$ adj6 (patch$ or matrix$ or matric$ or gel or gels or gelat$ or dressing$)).ti,ab,kf. (6856)
34 bloodpatch$.ti,ab,kf. (7)
35 or/30-34 (97781)
36 11 and (22 or 35) (602)
37 (3c adj4 patch$).ti,ab,kf. (0)
38 (3c adj (system$2 or device$)).ti,ab,kf. (6)
39 (3cpatch$ or 3csystem$2 or 3cdevice$).ti,ab,kf. (0)
40 (leucopatch$ or leuco-patch$).ti,ab,kf. (8)
41 (leukopatch$ or leuko-patch$).ti,ab,kf. (0)
42 reapplix$.ti,ab,kf,in. (3)
43 or/37-42 (15)
44 36 or 43 (613)
45 exp animals/ not humans/ (4809908)
46 (news or editorial or case reports).pt. or case report.ti. (2980288)
47 44 not (45 or 46) (481)
48 limit 47 to english language (425)
49 limit 48 to yr="2009 -Current" (324)

A.2: Source: Embase

Interface / URL: OvidSP
Database coverage dates: 1974 to 2021 April 09
Search date: 13/04/2021
Retrieved records: 875
Search strategy:

1 diabetic foot/ (16763)
2 foot ulcer/ (5409)
3 exp diabetes mellitus/ and (ulcer/ or leg ulcer/ or skin ulcer/ or foot disease/ or wound healing/ or ulcer healing/) (16265)
4 ((diabet$ or dm or dm1 or t1dm or t1d or t1-d or iddm or dm2 or t2dm or t2d or t2-d or niddm or iidm) adj6 (foot or feet or plantar or pedis)).ti,ab,kw,dq. (17542)
5 ((diabet$ or dm or dm1 or t1dm or t1d or t1-d or iddm or dm2 or t2dm or t2d or t2-d or niddm or iidm) and (ulcer$ or ulcus)).ti,ab,kw,dq. (21366)

6 ((diabet$ or dm or dm1 or t1dm or t1d or t1-d or iddm or dm2 or t2dm or t2d or t2-d or niddm or iidm) and wound$).ti,ab,kw,dq. (19351)
7 ((diabet$ or dm or dm1 or t1dm or t1d or t1-d or iddm or dm2 or t2dm or t2d or t2-d or niddm or iidm) and sore$).ti,ab,kw,dq. (867)
8 ((foot or feet or plantar or pedis) adj6 (ulcer$ or ulcus)).ti,ab,kw,dq. (11948)
9 ((foot or feet or plantar or pedis) adj6 wound$).ti,ab,kw,dq. (3113)
10 ((foot or feet or plantar or pedis) adj6 sore$).ti,ab,kw,dq. (180)
11 or/1-10 (51883)
12 thrombocyte rich plasma/ (13281)
13 platelet-rich fibrin/ (1049)
14 fibrin/ (24736)
15 fibrin$.ti,ab,kw,tn,dq,my. (143173)
16 (antithrombin i or anti-thrombin i or antithrombin 1 or anti-thrombin 1 or antithrombini or anti-thrombini or antithrombin1 or anti-thrombin1).ti,ab,kw,rn,tn,dq,dy,my. (11172)
17 (factor ia or factor 1a or factoria or factor1a).ti,ab,kw,rn,tn,dq,dy,my. (2225)
18 (9001-31-4 or 232-597-0 or aq4k8i4r6f).ti,ab,kw,rn,tn,dq,dy,my. (20149)
19 (platelet-rich or thrombocyte-rich).ti,ab,kw,dq,my. (17485)
20 (prp or prf).ti,ab,kw,dq,my. (28506)
21 (lprp or lprf).ti,ab,kw,dq,my. (37)
22 or/12-21 (193021)
23 thrombocyte/ (109302)
24 (platelet$ or thrombocyte$).ti,ab,kw,dq,my. (333496)
25 exp leukocyte/ (1259900)
26 (leukocyte$ or leucocyte$).ti,ab,kw,dq,my. (231221)
27 (white blood adj (cell or cells or corpuscle or corpuscles)).ti,ab,kw,dq,my. (52407)
28 (white adj (cell or cells or corpuscle or corpuscles)).ti,ab,kw,dq,my. (10537)
29 (wbc or wbcs).ti,ab,kw,dq,my. (42374)
30 (23 or 24) and (25 or 26 or 27 or 28 or 29) (69199)
31 ((leukocyte$ or leucocyte$) and blood$).ti,ab,kw,dq,my. (82656)
32 (autologous adj6 (patch$ or matrix$ or matric$ or gel or gels or gelat$ or dressing$)).ti,ab,kw,dq,my. (2916)
33 blood patch/ or (blood$ adj6 (patch$ or matrix$ or matric$ or gel or gels or gelat$ or dressing$)).ti,ab,kw,dq,my. (9977)
34 bloodpatch$.ti,ab,kw,dq,my. (16)
35 or/30-34 (150829)
36 11 and (22 or 35) (1228)

37 (3c adj4 patch$).ti,ab,kw,in,dq,dv,my,dm. (2)
38 (3c adj (system$2 or device$)).ti,ab,kw,in,dq,dv,my,dm. (39)
39 (3cpatch$ or 3csystem$2 or 3cdevice$).ti,ab,kw,in,dq,dv,my,dm. (0)
40 (leucopatch$ or leuco-patch$).ti,ab,kw,in,dq,dv,my,dm. (15)
41 (leukopatch$ or leuko-patch$).ti,ab,kw,in,dq,dv,my,dm. (1)
42 reapplix$.ti,ab,kw,in,dq,dv,my,dm,in. (7)
43 or/37-42 (59)
44 36 or 43 (1275)
45 (animal/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/) not exp human/ (6260150)
46 editorial.pt. or case report.ti. (1015720)
47 44 not (45 or 46) (1125)
48 limit 47 to english language (1027)
49 limit 48 to yr="2009 -Current" (875)

A.3: Source: Cochrane Central Register of Controlled Trials

Interface / URL: Cochrane Library / Wiley
Database coverage dates: Information not found. Issue searched: Issue 3 of 12, March 2021
Search date: 13/04/2021
Retrieved records: 243
Search strategy:

#1 [mh ^"Diabetic Foot"] 1014
#2 [mh ^"foot ulcer"] 474
#3 [mh "Diabetes Mellitus"] AND ([mh ^Ulcer] OR [mh ^"leg ulcer"] OR [mh ^"Skin Ulcer"] OR [mh ^"Foot Diseases"] OR [mh ^"Wound Healing"]) 694
#4 ((diabet* or dm or dm1 or t1dm or t1d or "t1-d" or iddm or dm2 or t2dm or t2d or "t2-d" or niddm or iidm) near/6 (foot or feet or plantar or pedis)) 3174
#5 ((diabet* or dm or dm1 or t1dm or t1d or "t1-d" or iddm or dm2 or t2dm or t2d or "t2-d" or niddm or iidm) and (ulcer* or ulcus)) 3881
#6 ((diabet* or dm or dm1 or t1dm or t1d or "t1-d" or iddm or dm2 or t2dm or t2d or "t2-d" or niddm or iidm) and wound*) 4271
#7 ((diabet* or dm or dm1 or t1dm or t1d or "t1-d" or iddm or dm2 or t2dm or t2d or "t2-d" or niddm or iidm) and sore*) 756
#8 ((foot or feet or plantar or pedis) near/6 (ulcer* or ulcus)) 2245
#9 ((foot or feet or plantar or pedis) near/6 wound*) 645
#10 ((foot or feet or plantar or pedis) near/6 sore*) 42
#11 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 7705

#12 [mh ^"platelet-rich plasma"] 432
#13 [mh ^"platelet-rich fibrin"] 101
#14 [mh Fibrin] 1302
#15 fibrin* 14279
#16 ("antithrombin i" or "anti-thrombin i" or "antithrombin 1" or "anti-thrombin 1" or antithrombini or "anti-thrombini" or antithrombin1 or "anti-thrombin1") 3
#17 ("factor ia" or "factor 1a" or factoria or factor1a) 36
#18 ("9001-31-4" or "232-597-0" or aq4k8i4r6f) 2
#19 ("platelet-rich" or "thrombocyte-rich") 2929
#20 (prp or prf) 3436
#21 (lprp or lprf) 119
#22 #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 17798
#23 [mh ^"Blood Platelets"] 1981
#24 (platelet* or thrombocyte*) 31219
#25 [mh Leukocytes] 9517
#26 (leukocyte* or leucocyte*) 14570
#27 ("white blood" next (cell or cells or corpuscle or corpuscles))4654
#28 (white next (cell or cells or corpuscle or corpuscles)) 866
#29 (wbc or wbcs) 4501
#30 (#23 or #24) and (#25 or #26 or #27 or #28 or #29) 5483
#31 ((leukocyte* or leucocyte*) and blood*) 9600
#32 (autologous near/6 (patch* or matrix* or matric* or gel or gels or gelat* or dressing*)) 312
#33 (blood* near/6 (patch* or matrix* or matric* or gel or gels or gelat* or dressing*)) 1119
#34 bloodpatch* 9
#35 #30 OR #31 OR #32 OR #33 OR #34 14285
#36 #11 and (#22 or #35) 500
#37 (3c near/4 patch*) 2
#38 (3c next (system* or device*)) 11
#39 (3cpatch* or 3csystem* or 3cdevice*) 0
#40 (leucopatch* or leuco next patch*) 10
#41 (leukopatch* or leuko next patch*) 0
#42 reapplix* 3
#43 #37 OR #38 OR #39 OR #40 OR #41 OR #42 24
#44 #36 or #43 515
#45 #44 with Publication Year from 2009 to 2021, in Trials 243

A.4: Source: Cochrane Database of Systematic Reviews

Interface / URL: Cochrane Library / Wiley

Database coverage dates: Information not found. Issue searched: Issue 4 of 12, April 2021
Search date: 13/04/2021
Retrieved records: 6
Search strategy:

#1 [mh ^"Diabetic Foot"] 1014
#2 [mh ^"foot ulcer"] 474
#3 [mh "Diabetes Mellitus"] AND ([mh ^Ulcer] OR [mh ^"leg ulcer"] OR [mh ^"Skin Ulcer"] OR [mh ^"Foot Diseases"] OR [mh ^"Wound Healing"]) 694
#4 ((diabet* or dm or dm1 or t1dm or t1d or "t1-d" or iddm or dm2 or t2dm or t2d or "t2-d" or niddm or iidm) near/6 (foot or feet or plantar or pedis)):ti,ab,kw 3045
#5 ((diabet* or dm or dm1 or t1dm or t1d or "t1-d" or iddm or dm2 or t2dm or t2d or "t2-d" or niddm or iidm) and (ulcer* or ulcus)):ti,ab,kw 3192
#6 ((diabet* or dm or dm1 or t1dm or t1d or "t1-d" or iddm or dm2 or t2dm or t2d or "t2-d" or niddm or iidm) and wound*):ti,ab,kw 2872
#7 ((diabet* or dm or dm1 or t1dm or t1d or "t1-d" or iddm or dm2 or t2dm or t2d or "t2-d" or niddm or iidm) and sore*):ti,ab,kw 251
#8 ((foot or feet or plantar or pedis) near/6 (ulcer* or ulcus)):ti,ab,kw 2142
#9 ((foot or feet or plantar or pedis) near/6 wound*):ti,ab,kw 518
#10 ((foot or feet or plantar or pedis) near/6 sore*):ti,ab,kw 35
#11 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 5920
#12 [mh ^"platelet-rich plasma"] 432
#13 [mh ^"platelet-rich fibrin"] 101
#14 [mh Fibrin] 1302
#15 fibrin*:ti,ab,kw 13733
#16 ("antithrombin i" or "anti-thrombin i" or "antithrombin 1" or "anti-thrombin 1" or antithrombini or "anti-thrombini" or antithrombin1 or "anti-thrombin1"):ti,ab,kw 2
#17 ("factor ia" or "factor 1a" or factoria or factor1a):ti,ab,kw 15
#18 ("9001-31-4" or "232-597-0" or aq4k8i4r6f):ti,ab,kw 2
#19 ("platelet-rich" or "thrombocyte-rich"):ti,ab,kw 2797
#20 (prp or prf):ti,ab,kw3287
#21 (lprp or lprf):ti,ab,kw 113
#22 #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 17148
#23 [mh ^"Blood Platelets"] 1981

#24 (platelet* or thrombocyte*):ti,ab,kw 30353
#25 [mh Leukocytes] 9517
#26 (leukocyte* or leucocyte*):ti,ab,kw 14147
#27 ("white blood" next (cell or cells or corpuscle or corpuscles)):ti,ab,kw 4260
#28 (white next (cell or cells or corpuscle or corpuscles)):ti,ab,kw 724
#29 (wbc or wbcs):ti,ab,kw 4418
#30 (#23 or #24) and (#25 or #26 or #27 or #28 or #29) 5223
#31 ((leukocyte* or leucocyte*) and blood*):ti,ab,kw 9124
#32 (autologous near/6 (patch* or matrix* or matric* or gel or gels or gelat* or dressing*)):ti,ab,kw 277
#33 (blood* near/6 (patch* or matrix* or matric* or gel or gels or gelat* or dressing*)):ti,ab,kw 1106
#34 bloodpatch*:ti,ab,kw 7
#35 #30 OR #31 OR #32 OR #33 OR #34 13692
#36 #11 and (#22 or #35) 272
#37 (3c near/4 patch*) 2
#38 (3c next (system* or device*)) 11
#39 (3cpatch* or 3csystem* or 3cdevice*) 0
#40 (leucopatch* or leuco next patch*) 10
#41 (leukopatch* or leuko next patch*) 0
#42 reapplix* 3
#43 #37 OR #38 OR #39 OR #40 OR #41 OR #42 24
#44 #36 or #43 287
#45 #44 with Cochrane Library publication date Between Jan 2009 and Dec 2021, in Cochrane Reviews, Cochrane Protocols 6

A.5: Source: HTA Database

Interface / URL: https://database.inahta.org/
Database coverage dates: Information not found. The former database was produced by the CRD until March 2018, at which time the addition of records was stopped as INAHTA was in the process of rebuilding the new database platform. In July 2019, the database records were exported from the CRD platform and imported into the new platform that was developed by INAHTA. The rebuild of the new platform was launched in June 2020.
Search date: 13/04/2021
Retrieved records: 29
Search strategy:
50 #49 AND #48 29
49 * FROM 2009 TO 2021 9627
48 #47 OR #4141
47 #46 OR #45 OR #44 OR #43 OR #42 25

46	reapplix*	0
45	(leukopatch* OR "leuko-patch" OR "leuko-patchR" OR "leuko-patchTM")	0
44	(leucopatch* OR "leuco-patch" OR "leuco-patchR" OR "leuco-patchTM")	0
43	(3cpatch* OR 3csystem* OR 3cdevice*)	0
42	(patch OR patchR OR patchTM)	25
41	#40 OR #39	16
40	#38 AND #11	5
39	#22 AND #11	11
38	#37 OR #36 OR #35 OR #34 OR #33 OR #32	58
37	bloodpatch*	0
36	(blood* AND (patch* OR matrix* OR matric* OR gel OR gels OR gelat* OR dressing*))	22
35	(autologous AND (patch* OR matrix* OR matric* OR gel OR gels OR gelat* OR dressing*))	14
34	(autologous AND (patch* OR matrix* OR matric* OR gel OR gels OR gelat* OR dressing*))	14
33	((leukocyte* OR leucocyte*) AND blood*)	16
32	#31 AND #30	11
31	#29 OR #28 OR #27 OR #26 OR #25	87
30	#24 OR #23	95
29	(wbc OR wbcs)	2
28	(white AND (cell OR cells OR corpuscle OR corpuscles))	51
27	("white blood" AND (cell OR cells OR corpuscle OR corpuscles))	37
26	(leukocyte* OR leucocyte*)	30
25	"Leukocytes"[mhe]	13
24	(platelet* OR thrombocyte*)	95
23	"Blood Platelets"[mh]	5
22	#21 OR #20 OR #19 OR #18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12	493
21	(lprp OR lprf)	0
20	(prp OR prf)	11
19	("platelet-rich" OR "thrombocyte-rich")	18
18	("9001-31-4" OR "232-597-0" OR aq4k8i4r6f)	0
17	(factor OR factoria OR factor1a)	421
16	(antithrombin* OR "anti-thrombin" OR antithrombini OR "anti-thrombini" OR antithrombin1 OR "anti-thrombin1")	3
15	fibrin*	36
14	"Fibrin"[mhe]	33
13	"Platelet-Rich Fibrin"[mh]	0
12	"Platelet-Rich Plasma"[mh]	12

11	#10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1	107
10	((foot OR feet OR plantar OR pedis) AND sore*)	11
9	((foot OR feet OR plantar OR pedis) AND wound*)	46
8	((foot OR feet OR plantar OR pedis) AND (ulcer* OR ulcus))	64
7	((diabet* OR dm OR dm1 OR t1dm OR t1d OR "t1-d" OR iddm OR dm2 OR t2dm OR t2d OR "t2-d" OR niddm OR iidm) AND sore*)	14
6	((diabet* OR dm OR dm1 OR t1dm OR t1d OR "t1-d" OR iddm OR dm2 OR t2dm OR t2d OR "t2-d" OR niddm OR iidm) AND wound*)	55
5	((diabet* OR dm OR dm1 OR t1dm OR t1d OR "t1-d" OR iddm OR dm2 OR t2dm OR t2d OR "t2-d" OR niddm OR iidm) AND (ulcer* OR ulcus))	79
4	((diabet* OR dm OR dm1 OR t1dm OR t1d OR "t1-d" OR iddm OR dm2 OR t2dm OR t2d OR "t2-d" OR niddm OR iidm) AND (foot OR feet OR plantar OR pedis))	73
3	"Diabetes Mellitus"[mhe] AND ("Ulcer"[mh] OR "Leg Ulcer"[mh] OR "Skin Ulcer"[mh] OR "Foot Diseases"[mh] OR "Wound Healing"[mh])	26
2	"Foot Ulcer"[mh]	10
1	"Diabetic Foot"[mh]	34

Search note:

It is not possible to search on the term *3c* in the HTA Database. Searching on the term *3c* results in the following message: "Sorry please make your search terms a minimum of 3 characters"

The MEDLINE search line *(3c adj4 patch$).ti,ab,kf.* was therefore translated in the HTA Database as *(patch OR patchR OR patchTM)* – search line 42.

It is not possible to search on the terms *(3c AND (system* OR device*))* – the interface just searches on the term *(system* OR device*)* - ignoring the *3C.* The MEDLINE search line *(system$2 or device$)).ti,ab,kf.* was therefore not translated for the HTA Database.

A.6: Source: Conference Proceedings Citation Index - Science (CPCI-S)

Interface / URL: Web of Science
Database coverage dates: 1990 - present
Search date: 13/04/2021
Retrieved records: 31
Search strategy:

All lines except #37: Indexes=CPCI-S Timespan=1900-2021

# 37	31	(#36) AND LANGUAGE: (English) Indexes=CPCI-S Timespan=2009-2021
# 36	51	#35 OR #28
# 35	7	#34 OR #33 OR #32 OR #31 OR #30 OR #29
# 34	1	ALL FIELDS: (reapplix*)
# 33	0	TS=(leukopatch* or "leuko-patch*")
# 32	2	TS=(leucopatch* or "leuco-patch*")
# 31	0	TS=(3cpatch* or 3csystem* or 3cdevice*)
# 30	5	TS=("3c" near/0 (system* or device*))
# 29	0	TS=("3c" near/4 patch*)
# 28	44	#8 and (#16 or #27)
# 27	5,076	#26 OR #25 OR #24 OR #23 OR #22
# 26	0	TS=bloodpatch*
# 25	588	TS=(blood* near/6 (patch* or matrix* or matric* or "gel" or "gels" or gelat* or dressing*))
# 24	169	TS=("autologous" near/6 (patch* or matrix* or matric* or "gel" or "gels" or gelat* or dressing*))
# 23	3,368	TS=((leukocyte* or leucocyte*) and blood*)
# 22	1,453	#17 AND (#18 or #19 or #20 or #21)
# 21	1,081	TS=("wbc" or "wbcs")
# 20	401	TS=("white" near/0 ("cell" or "cells" or "corpuscle" or "corpuscles"))
# 19	2,102	TS=("white blood" near/0 ("cell" or "cells" or "corpuscle" or "corpuscles"))
# 18	12,325	TS=(leukocyte* or leucocyte*)
# 17	24,917	TS=(platelet* or thrombocyte*)
# 16	11,351	#15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9
# 15	19	TS=("lprp" or "lprf")
# 14	2,514	TS=("prp" or "prf")
# 13	713	TS=("platelet-rich" or "thrombocyte-rich")
# 12	0	TS=("9001-31-4" or "232-597-0" or "aq4k8i4r6f")
# 11	76	TS=("factor ia" or "factor 1a" or "factoria" or "factor1a")
# 10	3	TS=("antithrombin i" or "anti-thrombin i" or "antithrombin 1" or "anti-thrombin 1" or "antithrombini" or "anti-thrombini" or "antithrombin1" or "anti-thrombin1")
# 9	8,307	TS=fibrin*
# 8	2,796	#7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
# 7	11	TS=(("foot" or "feet" or "plantar" or "pedis") near/6 sore*)
# 6	187	TS=(("foot" or "feet" or "plantar" or "pedis") near/6 wound*)

5 823 TS=(("foot" or "feet" or "plantar" or "pedis") near/6 (ulcer* or "ulcus"))

4 41 TS=((diabet* or "dm" or "dm1" or "t1dm" or "t1d" or "t1-d" or "iddm" or "dm2" or "t2dm" or "t2d" or "t2-d" or "niddm" or "iidm") and sore*)

3 1,183 TS=((diabet* or "dm" or "dm1" or "t1dm" or "t1d" or "t1-d" or "iddm" or "dm2" or "t2dm" or "t2d" or "t2-d" or "niddm" or "iidm") and wound*)

2 1,162 TS=((diabet* or "dm" or "dm1" or "t1dm" or "t1d" or "t1-d" or "iddm" or "dm2" or "t2dm" or "t2d" or "t2-d" or "niddm" or "iidm") and (ulcer* or "ulcus"))

1 1,390 TS=((diabet* or "dm" or "dm1" or "t1dm" or "t1d" or "t1-d" or "iddm" or "dm2" or "t2dm" or "t2d" or "t2-d" or "niddm" or "iidm") near/6 ("foot" or "feet" or "plantar" or "pedis"))

A.7: Source: CINAHL Complete

Interface / URL: EBSCOhost
Database coverage dates: 1937 to date
Search date: 14/04/2021
Retrieved records: 131
Search strategy:

All lines:
Expanders - Apply equivalent subjects
Search modes - Boolean/Phrase

S46 S36 OR S43 Limiters - Published Date: 20090101-20211231 Narrow by Language: - english 131

S45 S36 OR S43 Narrow by Language: - english 158

S44 S36 OR S43 162

S43 S37 OR S38 OR S39 OR S40 OR S41 OR S42 22

S42 TX reapplix*9

S41 TX (leukopatch* OR "leuko-patch*") 0

S40 TX (leucopatch* OR "leuco-patch*") 7

S39 TX (3cpatch* OR 3csystem* OR 3cdevice*) 0

S38 TX (3c W0 (system* OR device*)) 3

S37 TX (3c N4 patch*)

S36 S11 AND (S22 OR S35) 145

S35 S30 OR S31 OR S32 OR S33 OR S34 9,212

S34 TI bloodpatch* OR AB bloodpatch* 1

S33 TI ((blood* N6 (patch* OR matrix* OR matric* OR gel OR gels OR gelat* OR dressing*))) OR AB ((blood* N6 (patch* OR matrix* OR matric* OR gel OR gels OR gelat* OR dressing*))) 1,176

S32 TI ((autologous N6 (patch* OR matrix* OR matric* OR gel OR gels OR gelat* OR dressing*))) OR AB ((autologous N6 (patch* OR matrix* OR matric* OR gel OR gels OR gelat* OR dressing*))) 581

S31 TI (((leukocyte* OR leucocyte*) AND blood*)) OR AB (((leukocyte* OR leucocyte*) AND blood*)) 4,302

S30 (S23 OR S24) AND (S25 OR S26 OR S27 OR S28 OR S29) 3,870

S29 TI ((wbc OR wbcs)) OR AB ((wbc OR wbcs)) 2,975

S28 TI ((white W0 (cell OR cells OR corpuscle OR corpuscles))) OR AB ((white W0 (cell OR cells OR corpuscle OR corpuscles))) 873

S27 TI (("white blood" W0 (cell OR cells OR corpuscle OR corpuscles))) OR AB (("white blood" W0 (cell OR cells OR corpuscle OR corpuscles))) 5,621

S26 TI ((leukocyte* OR leucocyte*)) OR AB ((leukocyte* OR leucocyte*)) 12,351

S25 (MH "Leukocytes+") 42,992

S24 TI ((platelet* OR thrombocyte*)) OR AB ((platelet* OR thrombocyte*)) 25,187

S23 (MH "Blood Platelets") 6,350

S22 S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 15,670

S21 TI ((lprp OR lprf)) OR AB ((lprp OR lprf)) 6

S20 TI ((prp OR prf)) OR AB ((prp OR prf)) 2,554

S19 TI (("platelet-rich" OR "thrombocyte-rich")) OR AB (("platelet-rich" OR "thrombocyte-rich")) 2,892

S18 TI (("9001-31-4" OR "232-597-0" OR aq4k8i4r6f)) OR AB (("9001-31-4" OR "232-597-0" OR aq4k8i4r6f)) 0

S17 TI (("factor ia" OR "factor 1a" OR factoria OR factor1a)) OR AB (("factor ia" OR "factor 1a" OR factoria OR factor1a)) 40

S16 TI (("antithrombin i" OR "anti-thrombin i" OR "antithrombin 1" OR "anti-thrombin 1" OR antithrombini OR "anti-thrombini" OR antithrombin1 OR "anti-thrombin1")) OR AB (("antithrombin i" OR "anti-thrombin i" OR "antithrombin 1" OR "anti-thrombin 1" OR antithrombini OR "anti-thrombini" OR antithrombin1 OR "anti-thrombin1")) 0

S15 TI fibrin* OR AB fibrin* 10,018

S14 (MH "Fibrin+") 3,580

S13 (MH "Platelet-Rich Fibrin") 81

S12 (MH "Platelet-Rich Plasma") 1,653

S11 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 16,314

S10 TI (((foot OR feet OR plantar OR pedis) N6 sore*)) OR AB (((foot OR feet OR plantar OR pedis) N6 sore*)) 68

S9 TI (((foot OR feet OR plantar OR pedis) N6 wound*)) OR AB (((foot OR feet OR plantar OR pedis) N6 wound*)) 1,325

S8 TI (((foot OR feet OR plantar OR pedis) N6 (ulcer* OR ulcus))) OR AB (((foot OR feet OR plantar OR pedis) N6 (ulcer* OR ulcus))) 4,910

S7 TI (((diabet* OR dm OR dm1 OR t1dm OR t1d OR "t1-d" OR iddm OR dm2 OR t2dm OR t2d OR "t2-d" OR niddm OR iidm) AND sore*)) OR AB (((diabet* OR dm OR dm1 OR t1dm OR t1d OR "t1-d" OR iddm OR dm2 OR t2dm OR t2d OR "t2-d" OR niddm OR iidm) AND sore*)) 157

S6 TI (((diabet* OR dm OR dm1 OR t1dm OR t1d OR "t1-d" OR iddm OR dm2 OR t2dm OR t2d OR "t2-d" OR niddm OR iidm) AND wound*)) OR AB (((diabet* OR dm OR dm1 OR t1dm OR t1d OR "t1-d" OR iddm OR dm2 OR t2dm OR t2d OR "t2-d" OR niddm OR iidm) AND wound*)) 4,489

S5 TI (((diabet* OR dm OR dm1 OR t1dm OR t1d OR "t1-d" OR iddm OR dm2 OR t2dm OR t2d OR "t2-d" OR niddm OR iidm) AND (ulcer* OR ulcus))) OR AB (((diabet* OR dm OR dm1 OR t1dm OR t1d OR "t1-d" OR iddm OR dm2 OR t2dm OR t2d OR "t2-d" OR niddm OR iidm) AND (ulcer* OR ulcus))) 6,197

S4 TI (((diabet* OR dm OR dm1 OR t1dm OR t1d OR "t1-d" OR iddm OR dm2 OR t2dm OR t2d OR "t2-d" OR niddm OR iidm) N6 (foot OR feet OR plantar OR pedis))) OR AB (((diabet* OR dm OR dm1 OR t1dm OR t1d OR "t1-d" OR iddm OR dm2 OR t2dm OR t2d OR "t2-d" OR niddm OR iidm) N6 (foot OR feet OR plantar OR pedis))) 7,934

S3 (MH "Diabetes Mellitus+") AND ((MH "Ulcer") OR (MH "Leg Ulcer") OR (MH "Skin Ulcer") OR (MH "Foot Diseases") OR (MH "Wound Healing")) 3,497

S2 (MH "Foot Ulcer") 1,523

S1 (MH "Diabetic Foot") 9,522

A.8: Source: ClinicalTrials.gov

Interface / URL: https://clinicaltrials.gov/ct2/home

Database coverage dates: Information not found. ClinicalTrials.gov was created as a result of the Food and Drug Administration Modernization Act of 1997 (FDAMA). The site was made available to the public in February 2000.

Search date: 14/04/2021

Retrieved records: 343

Search strategy:

The following 11 searches were conducted separately. All search terms were entered using the Expert search interface.

Two searches retrieved 0 results. The 9 sets of results were imported into an empty EndNote library (650 records). 93 records with a date in the EndNote Year field before 2009 were removed, leaving 557 records. The 557 records were deduplicated using EndNote default de-duplication settings. 214 records were identified as duplicates and removed from the EndNote library. The remaining 343 records were retrieved for assessment.

1. (diabetes OR diabetic OR diabetics OR dm OR dm1 OR t1dm OR t1d OR "t1-d" OR iddm OR dm2 OR t2dm OR t2d OR "t2-d" OR niddm OR iidm) AND (foot OR feet OR plantar OR pedis OR ulcer OR ulcers OR ulcerative OR ulceration OR ulcerations OR ulcus OR wound OR wounds OR woundcare OR sore OR sores) AND (fibrin OR fibrins OR "antithrombin i" OR "anti-thrombin i" OR "antithrombin 1" OR "anti-thrombin 1" OR antithrombini OR "anti-thrombini" OR antithrombin1 OR "anti-thrombin1" OR "factor ia" OR "factor 1a" OR factoria OR factor1a OR "9001-31-4" OR "232-597-0" OR aq4k8i4r6f OR "platelet-rich" OR "thrombocyte-rich" OR prp OR prf OR lprp OR lprf) = 71

2. (foot OR feet OR plantar OR pedis) AND (ulcer OR ulcers OR ulcerative OR ulceration OR ulcerations OR ulcus OR wound OR wounds OR woundcare OR sore OR sores) AND (fibrin OR fibrins OR "antithrombin i" OR "anti-thrombin i" OR "antithrombin 1" OR "anti-thrombin 1" OR antithrombini OR "anti-thrombini" OR antithrombin1 OR "anti-thrombin1" OR "factor ia" OR "factor 1a" OR factoria OR factor1a OR "9001-31-4" OR "232-597-0" OR aq4k8i4r6f OR "platelet-rich" OR "thrombocyte-rich" OR prp OR prf OR lprp OR lprf) = 71

3. (diabetes OR diabetic OR diabetics OR dm OR dm1 OR t1dm OR t1d OR "t1-d" OR iddm OR dm2 OR t2dm OR t2d OR "t2-d" OR niddm OR iidm) AND (foot OR feet OR plantar OR pedis OR ulcer OR ulcers OR ulcerative OR ulceration OR ulcerations OR ulcus OR wound OR wounds OR woundcare OR sore OR sores) AND (platelet OR platelets OR thrombocyte OR thrombocytes) AND (leukocyte OR leukocytes OR leucocyte OR leucocytes OR "white blood cell" OR "white blood cells" OR "white blood corpuscle" OR "white blood corpuscles" OR "white cell" OR "white cells" OR "white corpuscle" OR "white corpuscles" OR wbc OR wbcs) = 52

4. (foot OR feet OR plantar OR pedis) AND (ulcer OR ulcers OR ulcerative OR ulceration OR ulcerations OR ulcus OR wound OR wounds OR woundcare OR sore OR sores) AND (platelet OR platelets OR thrombocyte OR thrombocytes) AND (leukocyte OR leukocytes OR leucocyte OR leucocytes OR "white blood cell" OR "white blood cells" OR "white blood corpuscle" OR "white blood

corpuscles" OR "white cell" OR "white cells" OR "white corpuscle" OR "white corpuscles" OR wbc OR wbcs) = 21

5. (diabetes OR diabetic OR diabetics OR dm OR dm1 OR t1dm OR t1d OR "t1-d" OR iddm OR dm2 OR t2dm OR t2d OR "t2-d" OR niddm OR iidm) AND (foot OR feet OR plantar OR pedis OR ulcer OR ulcers OR ulcerative OR ulceration OR ulcerations OR ulcus OR wound OR wounds OR woundcare OR sore OR sores) AND (leukocyte OR leukocytes OR leucocyte OR leucocytes) AND (blood OR bloods) = 81

6. (foot OR feet OR plantar OR pedis) AND (ulcer OR ulcers OR ulcerative OR ulceration OR ulcerations OR ulcus OR wound OR wounds OR woundcare OR sore OR sores) AND (leukocyte OR leukocytes OR leucocyte OR leucocytes) AND (blood OR bloods) = 37

7. (diabetes OR diabetic OR diabetics OR dm OR dm1 OR t1dm OR t1d OR "t1-d" OR iddm OR dm2 OR t2dm OR t2d OR "t2-d" OR niddm OR iidm) AND (foot OR feet OR plantar OR pedis OR ulcer OR ulcers OR ulcerative OR ulceration OR ulcerations OR ulcus OR wound OR wounds OR woundcare OR sore OR sores) AND (autologous OR blood OR bloods) AND (patch OR patches OR matrix OR matrixes OR matrice OR matrices OR gel OR gels OR gelatine OR gelatines OR gelatinous OR dressing OR dressings) = 155

8. (foot OR feet OR plantar OR pedis) AND (ulcer OR ulcers OR ulcerative OR ulceration OR ulcerations OR ulcus OR wound OR wounds OR woundcare OR sore OR sores) AND (autologous OR blood OR bloods) AND (patch OR patches OR matrix OR matrixes OR matrice OR matrices OR gel OR gels OR gelatine OR gelatines OR gelatinous OR dressing OR dressings) = 157

9. (diabetes OR diabetic OR diabetics OR dm OR dm1 OR t1dm OR t1d OR "t1-d" OR iddm OR dm2 OR t2dm OR t2d OR "t2-d" OR niddm OR iidm) AND (foot OR feet OR plantar OR pedis OR ulcer OR ulcers OR ulcerative OR ulceration OR ulcerations OR ulcus OR wound OR wounds OR woundcare OR sore OR sores) AND (bloodpatch OR bloodpatches) = 0

10. (foot OR feet OR plantar OR pedis) AND (ulcer OR ulcers OR ulcerative OR ulceration OR ulcerations OR ulcus OR wound OR wounds OR woundcare OR sore OR sores) AND (bloodpatch OR bloodpatches) = 0

11. "3c patch" OR "3c patchR" OR "3c patchTM" OR "3c patches" OR "3c patchesR" OR "3c patchesTM" OR "3c system" OR "3c systemR" OR "3c systemTM" OR "3c systems" OR "3c systemsR" OR "3c systemsTM" OR "3c

device" OR "3c deviceR" OR "3c deviceTM" OR "3c devices" OR "3c devicesR" OR "3c devicesTM" OR 3cpatch OR 3csystem OR 3cdevice OR 3cpatchR OR 3csystemR OR 3cdeviceR OR 3cpatchTM OR 3csystemTM OR 3cdeviceTM OR 3cpatches OR 3csystems OR 3cdevices OR 3cpatchesR OR 3csystemsR OR 3cdevicesR OR 3cpatchesTM OR 3csystemsTM OR 3cdevicesTM OR leucopatch OR "leuco-patch" OR leucopatchR OR "leuco-patchR" OR leucopatchTM OR "leuco-patchTM" OR leucopatches OR "leuco-patches" OR leucopatchesR OR "leuco-patchesR" OR leucopatchesTM OR "leuco-patchesTM" OR leukopatch OR "leuko-patch" OR leukopatchR OR "leuko-patchR" OR leukopatchTM OR "leuko-patchTM" OR leukopatches OR "leuko-patches" OR leukopatchesR OR "leuko-patchesR" OR leukopatchesTM OR "leuko-patchesTM" OR reapplix OR reapplixR OR reapplixTM = 5

A.9: Source: WHO International Clinical Trials Registry Portal (ICTRP)

Interface / URL: https://ictrptest.azurewebsites.net/Default.aspx
Database coverage dates: Information not found. Data sets from data providers are updated every Friday evening according to a schedule. On the date of search, files had been imported from data providers between November 2020 and March 2021
Search date: 14/04/2021
Retrieved records: 72
Search strategy:

WHO International Clinical Trials Registry Portal (ICTRP)

The following 11 searches were conducted separately using the search interface at: http://ictrptest.azurewebsites.net/Default.aspx

This interface was described on the ICTRP webpage (https://www.who.int/clinical-trials-registry-platform) as the "new search platform" in a "testing phase" at the time of the search. On 14/04/2021 this was the only interface version available to be used for search via the ICTRP webpage.

Searches were conducted using the notes on the search functionality of the new interface sent to the ICTRP news listserv (ICTRPNEWS@LISTSERV.WHO.INT) by the ICTRP Manager on 15/03/2021. The strategies reflect the following key changes that at the time of the search where not yet reflected on the "Search Tips" section of the ICTRP website:

- phrases should be placed in quotation marks
- truncation works within phrases
- brackets may be used with Boolean

For all searches 'Without synonyms' was selected.

Two searches retrieved 0 results. The 9 sets of results were imported into an empty EndNote library (157 records). 11 records with a date in the EndNote Year field before 2009 were removed, leaving 146 records. The 146 records were deduplicated using EndNote default de-duplication settings. 74 records were identified as duplicates and removed from the EndNote library. The remaining 72 records were retrieved for assessment.

1. (diabet* OR dm OR dm1 OR t1dm OR t1d OR "t1-d" OR iddm OR dm2 OR t2dm OR t2d OR "t2-d" OR niddm OR iidm) AND (foot OR feet OR plantar OR pedis OR ulcer* OR ulcus OR wound* OR sore*) AND (fibrin* OR "antithrombin i" OR "anti-thrombin i" OR "antithrombin 1" OR "anti-thrombin 1" OR antithrombini OR "anti-thrombini" OR antithrombin1 OR "anti-thrombin1" OR "factor ia" OR "factor 1a" OR factoria OR factor1a OR "9001-31-4" OR "232-597-0" OR aq4k8i4r6f OR "platelet-rich" OR "thrombocyte-rich" OR prp OR prf OR lprp OR lprf) = 35 (38 records for 35 trials)

2. (foot OR feet OR plantar OR pedis) AND (ulcer* OR ulcus OR wound* OR sore*) AND (fibrin* OR "antithrombin i" OR "anti-thrombin i" OR "antithrombin 1" OR "anti-thrombin 1" OR antithrombini OR "anti-thrombini" OR antithrombin1 OR "anti-thrombin1" OR "factor ia" OR "factor 1a" OR factoria OR factor1a OR "9001-31-4" OR "232-597-0" OR aq4k8i4r6f OR "platelet-rich" OR "thrombocyte-rich" OR prp OR prf OR lprp OR lprf) = 35 (38 records for 35 trials found)

3. (diabet* OR dm OR dm1 OR t1dm OR t1d OR "t1-d" OR iddm OR dm2 OR t2dm OR t2d OR "t2-d" OR niddm OR iidm) AND (foot OR feet OR plantar OR pedis OR ulcer* OR ulcus OR wound* OR sore*) AND (platelet* OR thrombocyte*) AND (leukocyte* OR leucocyte* OR "white blood cell" OR "white blood cells" OR "white blood corpuscle" OR "white blood corpuscles" OR "white cell" OR "white cells" OR "white corpuscle" OR "white corpuscles" OR wbc OR wbcs) = 3 (3 records for 3 trials found)

4. (foot OR feet OR plantar OR pedis) AND (ulcer* OR ulcus OR wound* OR sore*) AND (platelet* OR thrombocyte*) AND (leukocyte* OR leucocyte* OR "white blood cell" OR "white blood cells" OR "white blood corpuscle" OR "white blood corpuscles" OR "white cell" OR "white cells" OR "white corpuscle" OR "white corpuscles" OR wbc OR wbcs) = 1 (1 trial found)

5. (diabet* OR dm OR dm1 OR t1dm OR t1d OR "t1-d" OR iddm OR dm2 OR t2dm OR t2d OR "t2-d" OR niddm OR iidm) AND (foot OR feet OR plantar OR pedis OR ulcer* OR ulcus OR wound* OR sore*) AND (leukocyte* OR leucocyte*) AND blood* = 1 (1 trial found)

6. (foot OR feet OR plantar OR pedis) AND (ulcer* OR ulcus OR wound* OR sore*) AND (leukocyte* OR leucocyte*) AND blood* = 1 (1 trial found)

7. (diabet* OR dm OR dm1 OR t1dm OR t1d OR "t1-d" OR iddm OR dm2 OR t2dm OR t2d OR "t2-d" OR niddm OR iidm) AND (foot OR feet OR plantar OR pedis OR ulcer* OR ulcus OR wound* OR sore*) AND (autologous OR blood*) AND (patch* OR matrix* OR matric* OR gel OR gels OR gelat* OR dressing*) = 39 (39 records for 39 trials found)

8. (foot OR feet OR plantar OR pedis) AND (ulcer* OR ulcus OR wound* OR sore*) AND (autologous OR blood*) AND (patch* OR matrix* OR matric* OR gel OR gels OR gelat* OR dressing*) = 37 (37 records for 37 trials found)

9. (diabet* OR dm OR dm1 OR t1dm OR t1d OR "t1-d" OR iddm OR dm2 OR t2dm OR t2d OR "t2-d" OR niddm OR iidm) AND (foot OR feet OR plantar OR pedis OR ulcer* OR ulcus OR wound* OR sore*) AND bloodpatch* = 0

10. (foot OR feet OR plantar OR pedis) AND (ulcer* OR ulcus OR wound* OR sore*) AND bloodpatch* = 0

11. "3c patch*" OR "3c system*" OR "3c device*" OR 3cpatch* OR 3csystem* OR 3cdevice* OR leucopatch* OR "leuco-patch*" OR leukopatch* OR "leuko-patch*" OR reapplix* = 5 (6 records for 5 trials found)

A.10: Source: OpenGrey

Interface / URL: http://www.opengrey.eu/
Database coverage dates: Information not found
Search date: 14/04/2021
Retrieved records: 0
Search strategy:

The following device-specific terms were searched on separately using the search interface at: http://www.opengrey.eu/search/

"3c patch" OR "3c patchR" OR "3c patchTM" = 0 results returned

"3c patches" OR "3c patchesR" OR "3c patchesTM" = 0 results returned

"3c system" OR "3c systemR" OR "3c systemTM" = 0 results returned

"3c systems" OR "3c systemsR" OR "3c systemsTM" = 0 results returned

"3c device" OR "3c deviceR" OR "3c deviceTM" = 0 results returned

"3c devices" OR "3c devicesR" OR "3c devicesTM" = 0 results returned

3cpatch* OR 3csystem* OR 3cdevice* = 0 results returned

leucopatch* = 0 results returned

"leuco-patch" OR "leuco-patchR" OR "leuco-patchTM" = 0 results returned

"leuco-patches" OR "leuco-patchesR" OR "leuco-patchesTM" = 0 results returned

leukopatch* = 0 results returned

"leuko-patch" OR "leuko-patchR" OR "leuko-patchTM" = 0 results returned

"leuko-patches" OR "leuko-patchesR" OR "leuko-patchesTM" = 0 results returned

reapplix* = 0 results returned

A.11: Source: Grey Literature Report

Interface / URL: http://www.greylit.org/home
Database coverage dates: Information not found. The report is a publication produced between 1999 - 2016. As of January 2017, the Grey Literature Report website and database has been discontinued and is no longer updated, but the resources are still accessible.
Search date: 14/04/2021
Retrieved records: 0
Search strategy:

The following device-specific terms were searched on separately using the homepage search interface at: http://www.greylit.org/home. Returned results were assessed by the information specialist for potential relevance to the eligible device. Relevant results were retrieved for further assessment

3c = 3 results returned, 0 retrieved
3cpatch = 0 results returned
3csystem = 0 results returned
3cdevice = 0 results returned
leucopatch = 0 results returned
leuco-patch = 0 results returned
leukopatch = 0 results returned
leuko-patch = 0 results returned
reapplix = 0 results returned

Search note:
In Grey Literature Report terms are automatically truncated after six characters

A.12: Source: EconLit

Interface / URL: OvidSP
Database coverage dates: 1886 to April 08, 2021
Search date: 14/04/2021
Retrieved records: 9
Search strategy:

1	fibrin$.af. (6)
2	(antithrombin i or anti-thrombin i or antithrombin 1 or anti-thrombin 1 or antithrombini or anti-thrombini or antithrombin1 or anti-thrombin1).af. (0)
3	(factor ia or factor 1a or factoria or factor1a).af. (2)
4	(9001-31-4 or 232-597-0 or aq4k8i4r6f).af. (0)
5	(platelet-rich or thrombocyte-rich).af. (1)
6	((prp or prf) and (diabet$ or dm or dm1 or t1dm or t1d or t1-d or iddm or dm2 or t2dm or t2d or t2-d or niddm or iidm or foot or feet or plantar or pedis)).af. (0)
7	(lprp or lprf).af. (0)
8	or/1-7 (9)
9	(platelet$ or thrombocyte$).af. (23)
10	(leukocyte$ or leucocyte$).af. (3)
11	(white blood adj (cell or cells or corpuscle or corpuscles)).af. (1)
12	(white adj (cell or cells or corpuscle or corpuscles)).af. (0)
13	(wbc or wbcs).af. (11)
14	9 and (10 or 11 or 12 or 13) (0)
15	((leukocyte$ or leucocyte$) and blood$).af. (1)
16	(autologous adj6 (patch$ or matrix$ or matric$ or gel or gels or gelat$ or dressing$)).af. (0)
17	(blood$ adj6 (patch$ or matrix$ or matric$ or gel or gels or gelat$ or dressing$)).af. (0)
18	bloodpatch$.af. (0)
19	or/14-18 (1)
20	8 or 19 (10)

21 (3c adj4 patch$).af. (0)
22 (3c adj (system$2 or device$)).af. (0)
23 (3cpatch$ or 3csystem$2 or 3cdevice$).af. (0)
24 (leucopatch$ or leuco-patch$).af. (0)
25 (leukopatch$ or leuko-patch$).af. (0)
26 reapplix$.af. (0)
27 or/20-26 (10)
28 limit 27 to yr="2009 -Current" (10)
29 limit 28 to english (9)

A.13: Source: NHS Economic Evaluation Database (NHS EED)

Interface / URL: https://www.crd.york.ac.uk/CRDWeb

Database coverage dates: Information not found. Bibliographic records were published on NHS EED until 31st March 2015. Searches of MEDLINE, Embase, CINAHL, PsycINFO and PubMed were continued until the end of the 2014.

Search date: 14/04/2021

Retrieved records: 4

Search strategy:

1 MeSH DESCRIPTOR Diabetic Foot 139
2 MeSH DESCRIPTOR Foot Ulcer 29
3 MeSH DESCRIPTOR Diabetes Mellitus EXPLODE ALL TREES 2444
4 MeSH DESCRIPTOR Ulcer 24
5 MeSH DESCRIPTOR Leg Ulcer 86
6 MeSH DESCRIPTOR Skin Ulcer21
7 MeSH DESCRIPTOR Foot Diseases 17
8 MeSH DESCRIPTOR Wound Healing 515
9 (#3 AND (#4 OR #5 OR #6 OR #7 OR #8)) 62
10 (diabet* OR dm OR dm1 OR t1dm OR t1d OR t1-d OR iddm OR dm2 OR t2dm OR t2d OR t2-d OR niddm OR iidm) 5018
11 (foot OR feet OR plantar OR pedis) 674
12 #1 OR #2 OR #9 OR #10 OR #11 5399
13 MeSH DESCRIPTOR Platelet-Rich Plasma 55
14 MeSH DESCRIPTOR Platelet-Rich Fibrin 0
15 MeSH DESCRIPTOR Fibrin EXPLODE ALL TREES 90
16 (fibrin*) 574
17 (antithrombin i OR anti-thrombin i OR antithrombin 1 OR anti-thrombin 1 OR antithrombini OR anti-thrombini OR antithrombin1 OR anti-thrombin1) 0
18 (factor ia OR factor 1a OR factoria OR factor1a) 0
19 (9001-31-4 OR 232-597-0 OR aq4k8i4r6f) 0
20 (platelet-rich OR thrombocyte-rich) 77
21 (prp OR prf) 32
22 (lprp OR lprf) 0
23 #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22661
24 MeSH DESCRIPTOR Blood Platelets 30

25 (platelet* OR thrombocyte*) 1013
26 MeSH DESCRIPTOR Leukocytes EXPLODE ALL TREES 129
27 (leukocyte* OR leucocyte*) 216
28 (white blood NEAR1 (cell OR cells OR corpuscle OR corpuscles)) 145
29 ((cell OR cells OR corpuscle OR corpuscles) NEAR1 white blood) 5

30 (white NEAR1 (cell OR cells OR corpuscle OR corpuscles)) 168
31 ((cell OR cells OR corpuscle OR corpuscles) NEAR1 white) 5
32 (wbc OR wbcs) 43
33 ((#24 OR #25) AND (#26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32)) 57
34 ((leukocyte* OR leucocyte*) AND blood*) 111
35 (autologous NEAR6 (patch* OR matrix* OR matric* OR gel OR gels OR gelat* OR dressing*)) 8
36 ((patch* OR matrix* OR matric* OR gel OR gels OR gelat* OR dressing*) NEAR6 autologous) 8
37 (blood* NEAR6 (patch* OR matrix* OR matric* OR gel OR gels OR gelat* OR dressing*)) 20
38 ((patch* OR matrix* OR matric* OR gel OR gels OR gelat* OR dressing*) NEAR6 blood*) 11
39 (bloodpatch*) 0
40 #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 191
41 (#12 AND (#23 OR #40)) 74
42 (3c NEAR4 patch*)0
43 (patch* NEAR4 3c)0
44 (3c NEAR1 (system* OR device*)) 0
45 ((system* OR device*) NEAR1 3c) 0
46 (3cpatch* OR 3csystem* OR 3cdevice*) 0
47 (leucopatch* OR leuco-patch*) 0
48 (leukopatch* OR leuko-patch*) 0
49 (reapplix*) 0
50 #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 0

51 #41 OR #5074
52 (#51) IN NHSEED 16
53 (#52) IN NHSEED FROM 2009 TO 2021 4

A.14: Source: 3C Patch webpages

Interface / URL: https://3cpatch.com/

Database coverage dates: n/a

Search date: 14/04/2021

Retrieved records: 34

Search strategy:

Navigated to the References webpage at: https://3cpatch.com/proven/references/

References listed under the headings 3C PATCH® PUBLICATIONS, 3C PATCH® PRESENTATIONS and 3C PATCH® POSTERS were retrieved and downloaded into a Word document for assessment. References which were duplicates of references already retrieved via other search resources were not retrieved.

34 references were retrieved.

A.15: Source: UK Government Web Archive

Interface / URL: https://webarchive.nationalarchives.gov.uk/search/
Database coverage dates: n/a
Search date: 14/04/2021
Retrieved records: 1
Search strategy:

The following device-specific terms were searched on separately using the homepage search interface at: https://webarchive.nationalarchives.gov.uk/search/. Terms were entered into the search box "all these words or exact phrase". Returned results were assessed by the information specialist for potentially relevant research evidence on the eligible device. Relevant results were retrieved for further assessment

"3c patch" = 1 (138 results returned, 1 retrieved)
"3c patchR" = 0 results returned
"3c patchTM" = 0 results returned
"3c patches" = 0 (2 results returned, 0 retrieved)
"3c patchesR" = 0 results returned
"3c patchesTM" = 0 results returned
"3c system" = 0 (33 results returned, 0 retrieved)
"3c systemR" = 0 results returned
"3c systemTM" = 0 results returned
"3c systems" = 0 results returned
"3c systemsR" = 0 results returned
"3c systemsTM" = 0 results returned
"3c device" = 0 results returned
"3c deviceR" = 0 results returned
"3c deviceTM" = 0 results returned
"3c devices" = 0 (1 result returned, 0 retrieved)
"3c devicesR" = 0 results returned
"3c devicesTM" = 0 results returned
3cpatch = 0 results returned

3csystem = 0 results returned
3cdevice = 0 results returned
3cpatchR = 0 results returned
3csystemR = 0 results returned
3cdeviceR = 0 results returned
3cpatchTM = 0 results returned
3csystemTM = 0 results returned
3cdeviceTM = 0 results returned
3cpatches = 0 results returned
3csystems = 0 results returned
3cdevices = 0 results returned
3cpatchesR = 0 results returned
3csystemsR = 0 results returned
3cdevicesR = 0 results returned
3cpatchesTM = 0 results returned
3csystemsTM = 0 results returned
3cdevicesTM = 0 results returned
leucopatch = 0 (47 results returned, 0 retrieved)
"leuco-patch" = 0 results returned
leucopatchR = 0 results returned
"leuco-patchR" = 0 results returned
leucopatchTM = 0 results returned
"leuco-patchTM" = 0 results returned
leucopatches = 0 results returned
"leuco-patches" = 0 results returned
leucopatchesR = 0 results returned
"leuco-patchesR" = 0 results returned
leucopatchesTM = 0 results returned
"leuco-patchesTM" = 0 results returned
leukopatch = 0 results returned
"leuko-patch" = 0 results returned
leukopatchR = 0 results returned
"leuko-patchR" = 0 results returned
leukopatchTM = 0 results returned
"leuko-patchTM" = 0 results returned
leukopatches = 0 results returned
 "leuko-patches" = 0 results returned
 leukopatchesR = 0 results returned
"leuko-patchesR" = 0 results returned
leukopatchesTM = 0 results returned
"leuko-patchesTM" = 0 results returned
reapplix = 0 (5 results returned, 0 retrieved)

reapplixR = 0 results returned
reapplixTM = 0 results returned

Figure 14.2: Clinical review PRISMA flow diagram

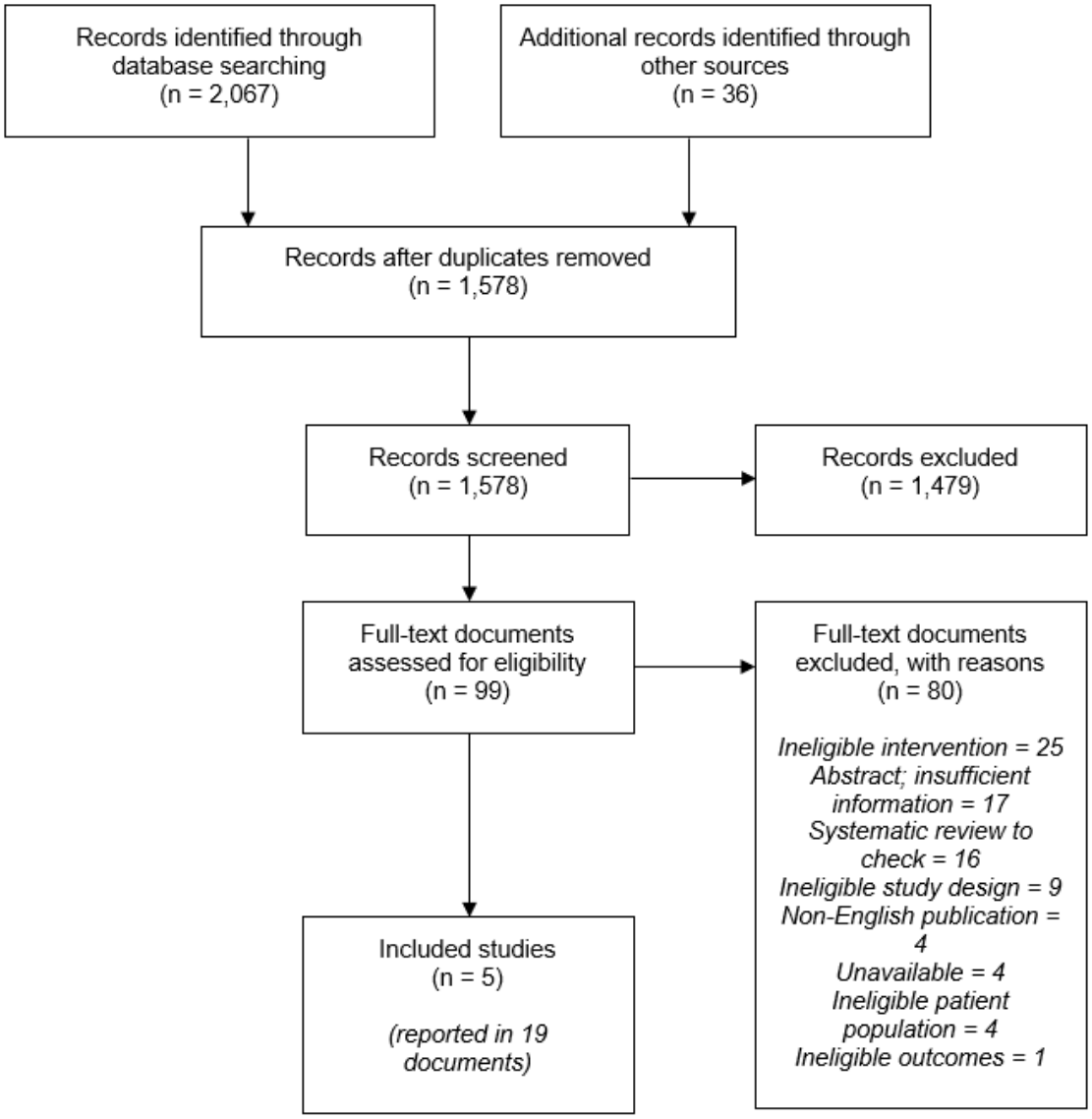
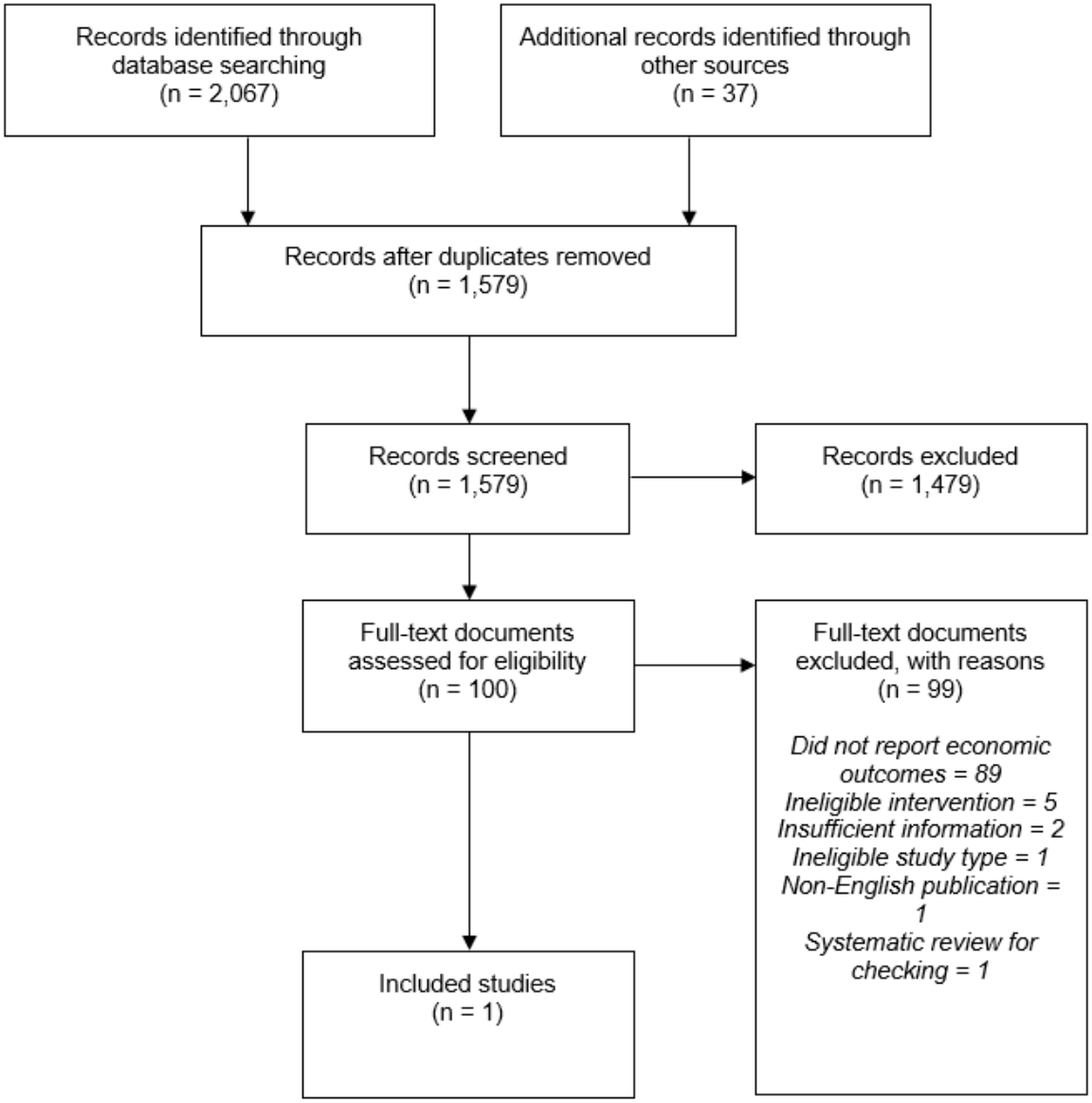


Figure 14.3: Economic review PRISMA flow diagram



14.2 Appendix B: PICO and risk of bias tables; strengths and weaknesses of included studies

Table 14.3: PICO criteria for RCT

Study and type	Population	Intervention	Comparator	Outcomes	Other (follow-up, setting, versions of device etc.)	EAC comment
Game et al. (2018a) RCT	People with DFUs that are not healing despite standard wound care. 32 centres with specialist diabetic foot clinics in the UK, Denmark, and Sweden. 269 randomised (137 to standard care and 132 to 3C). 217 (82%) men, 49 (18%) women. Mean (SD) age 61.9 (11.6) years. 134 participants in the standard care group and 132 in the 3C group were included in the ITT population.	3C Patch (previously known as LeucoPatch) applied weekly until 20 weeks or healing.	Clinical investigators were instructed to manage all eligible ulcers according to the best available standard care (as per International Working Group of the Diabetic Foot guidelines), including offloading.	Healing within 20 weeks Time to healing Proportion healed at 12 and 26 weeks Change in ulcer area at 4, 12, 16, 20, and 26 weeks (vs. week 0) Incidence of secondary infection Number of days of systemic antibiotic therapy for infection of the foot ulcer. Incidence of major (above ankle) amputation affecting the target or contralateral limb Incidence of minor (below ankle) amputation affecting the target or contralateral limb Incidence of new anaemia Quality of life (Short Form-12 and EuroQol 5-dimensions) Pain (visual analogue scale).	If the index ulcer had healed during the intervention period, participants were seen again at 2 weeks and 4 weeks post healing, with a blinded assessment of healing done at the point of healing and at the 4-week post healing visit.	Meets scope Inclusion criteria more restrictive than in the IFU document High quality RCT. The study was funded by the company.
Abbreviations: DFU - diabetic foot ulcer; EAC - External Assessment Centre; IFU - Instructions For Use; ITT - intention-to-treat; RCT - randomised controlled trial; SD - standard deviation						

Table 14.4: Risk of Bias (RoB) - RCTs

Study name (acronym)	Was the method used to generate random allocations adequate?	Was the allocation of treatment adequately concealed?	Were the groups similar at the outset of the study in terms of prognostic factors?	Were the care providers, participants and outcome assessors blind to treatment allocation?	Were there any unexpected imbalances in drop-outs between groups?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	EAC Comments
Game et al. (2018a)	Yes. A computer-generated, web-based, randomisation code was used, with permuted blocks of randomly varying size (two, four, and six), as created by the Nottingham Clinical Trials Unit. Trial participants were allocated with equal probability to each	Yes. Computer-generated and web-based. The randomisation code was stored in the trial coordinating centre, but no procedures for breaking it were defined.	Yes. The groups were well matched.	Partly. Clinical investigators that assessed outcomes were unaware of group assignment throughout the study, as was the study statistician before the clinical database had been cleaned and locked. Participants, caregivers, and site investigators were not	No. The target number of participants were recruited and retention was high, with few dropouts. Reasons for patient withdrawal was documented as similar between groups.	Yes. Most pre-specified outcomes were reported in the main publication; quality of life was reported in a small subgroup in a supplementary publication (abstract only). However, the supplementary protocol also specified cost end-points.	Partly. Primary and secondary outcomes assessed using ITT population (defined as all randomised patients for whom any post-randomization data had been collected); primary outcome also assessed using PP population. Methods used to account for missing data were not described.	High quality RCT. The study was funded by the company. Two investigators had received research funding from the company. The chief investigators had final responsibility for the decision to submit for publication.

Study name (acronym)	Was the method used to generate random allocations adequate?	Was the allocation of treatment adequately concealed?	Were the groups similar at the outset of the study in terms of prognostic factors?	Were the care providers, participants and outcome assessors blind to treatment allocation?	Were there any unexpected imbalances in drop-outs between groups?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	EAC Comments
	treatment group, with stratification by centre and by ulcer area (≤100 mm² vs >100 mm²).			masked to treatment allocation. The use of sham venepuncture was rejected as being unethical, but assessment of the primary outcome was undertaken by an independent and masked observer and backed up with digital imaging. In the event of a disagreement between site investigators and the				The publication reports 96% confidence intervals (EAC assumes this is a typographical error for 95% CI).

Study name (acronym)	Was the method used to generate random allocations adequate?	Was the allocation of treatment adequately concealed?	Were the groups similar at the outset of the study in terms of prognostic factors?	Were the care providers, participants and outcome assessors blind to treatment allocation?	Were there any unexpected imbalances in drop-outs between groups?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	EAC Comments
				masked clinical primary outcome assessor, or if a blinded assessment was not done or was delayed beyond the permitted window described in the protocol, a masked adjudication committee reviewed the digital images.				
Abbreviations: CI – confidence interval; EAC – External Assessment Centre; ITT – intention-to-treat; PP – per protocol; RCT – randomised controlled trial								

Table 14.5: PICO criteria for non-randomised trials

Study and type	Population	Intervention	Comparator	Outcomes	EAC comment
Löndahl et al. (2015) Case series	Patients (older than 18 years) with non-ischaemic Wagner grade 1 or 2 DFUs with a duration of > 6 weeks and a maximal area of 10cm^2, with ≤40% change in ulcer area during the 2-week run-in period. 100% of patients had diabetes.	3C (LeucoPatch) once a week for up to 19 treatments or until the target ulcer was completely epithelised.	None	Ulcer healing at 20 weeks (primary endpoint) and 12 weeks (secondary endpoint). Other secondary endpoints: Time to healing. Change in ulcer area. Safety. Feasibility	Meets scope Small observational pilot study; <50 patients started treatment with <40 in PP population. The study was funded by the company and 2 authors have received consultation fees from the company. One author is a co-inventor of the technology.
Jørgensen et al. (2011) Case series	Patients (older than 18 years) attending the Copenhagen Wound Healing Center, Bispebjerg Hospital with chronic cutaneous ulcers on the lower extremities, chronic DFUs (grade I-II according to the Wagner scale) or amputation wounds, that had been present for at least 2 months and had failed to heal by conventional means	Leucopatch weekly for 6 weeks, or until healing was complete.	None	The primary efficacy outcome was the proportional change in wound area during the 6-week treatment period. Secondary outcome measures were the change in the proportion of granulation tissue within the wound, the proportion of wounds that completely healed and the proportion of wounds showing a significant improvement in wound area during treatment.	Meets scope. Very small pilot study including only 5 patients with diabetes. The study was funded by the company. One author is a co-inventor of the technology.
Katzman et al. (2014) Case series	Patients with non-ischaemic (TcPO2≥ 30 mmHg) DFUs with a duration of at least 6 weeks and a positive probing to bone test.	Leucopatch was applied once weekly for up to 20 weeks	None	Bone covered; healed with complete epithelialization; AE	Meets scope. Small study with only 17 patients. Abstract only; few details
Abbreviations: AE – adverse events; DFU – diabetic foot ulcer; EAC – External Assessment Centre; ITT – intention-to-treat; PP – per protocol; RCT – randomised controlled trial; TcPO2 - transcutaneous oxygen pressure					

Table 14.6: Risk of Bias (RoB) – Observational studies

Study name (acronym)	Was the cohort recruited in an acceptable way?	Was the exposure accurately measured to minimize bias?	Was the outcome accurately measured to minimize bias?	Have the authors identified all important confounding factors?	Have the authors taken account of the confounding factors in the design and/or analysis	Was the follow-up of patients complete?	How precise (for example, in terms of confidence interval and p value) are the results	EAC Comments
Löndahl et al. (2015)	Unclear. Adult patients (>18 years) were treated at secondary or tertiary multidisciplinary diabetic foot clinics in Denmark or Sweden. However, it is unclear how many potentially eligible patients declined to give consent, that is, whether the cohort was representative of the patient group or those treated in the UK NHS.	Yes. Medical records.	Yes. Wounds were debrided and cleaned before being photographed according to a standard procedure. Ulcer edges were drawn on an acetate, and ulcer areas were measured centrally by an independent investigator using ImageJ (free software; http://imagej.en.softonic.com).	Yes. Authors tabulate baseline factors such as BMI, ulcer area, depth and location, HbA1c, Hb, platelets, leucocytes and renal function.	Partly. Data only shown for duration of ulcer. The authors report that neither baseline HbA1c levels nor baseline concentrations of Hb, platelets or leucocytes were associated with either 12 or 20 week healing rates. Healing rates after application were independent of renal function	Yes. No loss to follow up, but 5 patients did not complete treatment.	IQR and p-values only reported for change in ulcer area for PP population at 2 weeks, and healers vs non-healers at 2 and 12 weeks. Only p-values reported for the time to healing according to ulcer duration at baseline.	Small observational pilot study; <50 patients started treatment with <40 in PP population. 60 patients gave signed informed consent, of which 16 were excluded during the run-in period, but the trials registry record reports AEs for the overall 60 patients enrolled (i.e. treated and untreated).

Study name (acronym)	Was the cohort recruited in an acceptable way?	Was the exposure accurately measured to minimize bias?	Was the outcome accurately measured to minimize bias?	Have the authors identified all important confounding factors?	Have the authors taken account of the confounding factors in the design and/or analysis	Was the follow-up of patients complete?	How precise (for example, in terms of confidence interval and p value) are the results	EAC Comments
					in diabetic patients with preserved kidney function. Confounding effects of BMI, ulcer area, depth and location not reported.			The study was funded by the company and 2 authors have received consultation fees from the company. One author is a co-inventor of the technology.
Jørgensen et al. (2011)	Unclear Patients (older than 18 years) attending the Copenhagen Wound Healing Center, Bispebjerg Hospital. Patients with significant medical conditions likely to impede wound healings were excluded. Mixed population of	Yes. Medical records with clinical tests also conducted to establish diagnosis.	Yes. Wounds were cleaned using a protocol that is standard for the clinic and photographed before each treatment. Wound edges were drawn on Visitrak (Smith & Nephew A/S, Hørsholm, Denmark) for	No. None reported	No. None reported	Yes. All patients followed to 6 weeks	Unclear. Percentage reduction in wound area reported for 3 of the 5 patients; the other 2 reported to be reduced to less than 20% of their initial size	Very small pilot study including only 5 patients with diabetes. The study was supported by the company and one author is a co-inventor of the technology.

Study name (acronym)	Was the cohort recruited in an acceptable way?	Was the exposure accurately measured to minimize bias?	Was the outcome accurately measured to minimize bias?	Have the authors identified all important confounding factors?	Have the authors taken account of the confounding factors in the design and/or analysis	Was the follow-up of patients complete?	How precise (for example, in terms of confidence interval and p value) are the results	EAC Comments
	patients with chronic ulcers on the lower extremities or amputation wounds; only 5 patients with diabetes.		estimation of wound size. Estimates were also made of the proportion of granulation tissue in the wound.					
Katzman et al. (2014)	Yes Patients with non-ischaemic (TcPO2≥ 30 mm Hg) DFUs with a duration of at least 6 weeks and a positive probing to bone test recruited consecutively	Yes. Medical records.	Unclear NR	Unclear NR	Unclear NR	Unclear NR	Unclear NR	Abstract only. Small case series study (17 patients). All patients were on oral antibiotic treatment until bone coverage was achieved, and then at physician's discretion.

Abbreviations: DFU - diabetic foot ulcer; EAC – External Assessment Centre; Hb - haemoglobin; HbA1c - glycated haemoglobin; IQR - interquartile range; NHS - National Health Service; NR - not reported; PP - per protocol

Table 14.7: Summary of the strengths and weaknesses of the trial incorporating internal and external validity

Game et al. (2018a)	Strengths	Weaknesses
Study design	Parallel RCT, strongest form of primary evidence providing comparative outcomes with current standard practice. The design and conduct of this study were stated by the authors to have fulfilled the exacting requirements specified for work in this field.	No material weakness found
Patient selection	Well described inclusion and exclusion criteria. Appears to reflect eligible population although not including patients with very large ulcers. The study population was designed to focus on those with hard-to-heal ulcers—the group for which new treatments are most needed. The inclusion and exclusion criteria ensured that the recruited population was representative of a hard-to-heal population; this assumption is reflected in the low overall incidence of healing in the non-intervention group. Recruited from 32 centres with specialist diabetic foot clinics in the UK, Denmark and Sweden. *Low risk of spectrum bias*	Findings may not be generalisable to primary or community care settings or to patients with the largest ulcers. Limiting the study population is reasonable for this first published RCT of 3C. Future trials could extend the eligible population to assess whether the intervention is effective in a wider population which would be more generalisable to the full spectrum of patients seen in a specialist diabetic foot clinic.
Randomisation	Randomisation performed with adequate concealment of allocation. A computer-generated, web-based, randomisation code was used, with permuted blocks of randomly varying size (two, four, and six), as created by the Nottingham Clinical Trials Unit. Trial participants were allocated with equal probability to each treatment group, with stratification by centre and by ulcer area (≤100 mm² vs >100 mm²). The groups were well matched. *Low risk of selection bias*.	No material weakness found
Blinding	Clinical investigators that assessed outcomes were unaware of group assignment throughout the study, as was the study statistician before the clinical database had been cleaned and locked. *Low risk of performance bias.*	Participants, caregivers, and site investigators were not masked to treatment allocation. The use of sham venepuncture was rejected as being unethical, but assessment of the primary outcome was undertaken by an independent and masked observer and backed up with digital imaging. In the event of a disagreement between site investigators and the masked clinical primary outcome assessor, or if a blinded assessment was not done or was delayed

Game et al. (2018a)	Strengths	Weaknesses
		beyond the permitted window described in the protocol, a masked adjudication committee reviewed the digital images.
Patient attrition	The target number of participants were recruited and retention was high, with few dropouts. Reasons for patient withdrawal documented as similar between groups. *Low risk of attrition bias.*	No material weakness found
Reporting of outcomes	All primary and the majority of pre-specified secondary outcomes were reported.	The supplementary protocol also pre-specified cost end-points, which were not mentioned in the main publication. *Unclear potential for selective outcome reporting bias*
Statistical analysis	Power calculation for sample size for primary outcome performed. *Low potential for reporting bias.*	ITT analysis conducted but methods to account for missing data were not reported.
Study company	The other authors declare no competing interests. The chief investigators had final responsibility for the decision to submit for publication.	Study was funded by company. Two authors have received research support from Reapplix ApS.
Abbreviations: ITT – intention-to-treat; RCT – randomised controlled trial		

Table 14.8: Summary of the strengths and weaknesses of non-randomised studies incorporating internal and external validity

Löndahl et al. (2015)	Strengths	Weaknesses
Study design	-	Case series; no comparator
Patient selection	Patients, intervention and outcomes in line with scope. Patients with non-ischaemic Wagner grade 1 or 2 DFUs with a duration of > 6 weeks and a maximal area of 10cm^2, with ≤40% change in ulcer area during the 2-week run-in period. 100% of patients had diabetes. Secondary or tertiary multidisciplinary diabetic foot clinics in Denmark or Sweden.	Recruitment unclear. Patients (older than 18 years) were treated at secondary or tertiary multidisciplinary diabetic foot clinics in Denmark or Sweden.
Intervention	Exposure measured via medical records.	-
Confounding factors	-	Authors tabulated baseline factors such as BMI, ulcer area, depth and location, HbA1c, Hb, platelets, leukocytes and renal function, but data only shown for duration of ulcer as a confounding factor.
Patient attrition	No loss to follow up but 5 patients did not complete treatment.	-
Reporting of outcomes	Measurement of outcome: Wounds were debrided and cleaned before being photographed according to a standard procedure. Ulcer edges were drawn on an acetate, and ulcer areas were measured centrally by an independent investigator using ImageJ (free software; http://imagej.en.softonic.com).	-
Statistical analysis	-	Only p values reported for the time to healing according to ulcer duration at baseline.
Study company	All other authors declare no duality of interest associated with this manuscript.	This study was financed by Reapplix A/S. Two authors have received consultation fees from Reapplix A/S. One author is co-inventor of the Leucopatch technology.
Abbreviation: DFU – diabetic foot ulcer; Hb – haemoglobin; HbA1c – glycated haemoglobin		

Table 14.9: Summary of the strengths and weaknesses of non-randomised studies incorporating internal and external validity

Jørgensen et al. (2011)	Strengths	Weaknesses
Study design	-	Case series; no comparator
Patient selection	-	Recruitment unclear. Patients (older than 18 years) attending the Copenhagen Wound Healing Center, Bispebjerg Hospital. Mixed population with chronic ulcers on the lower extremities and amputation wounds; only 5 patients with diabetes so generalisability unclear
Intervention	Exposure measured via medical records with clinical tests also conducted to establish diagnosis.	-
Confounding factors	-	No confounding factors reported
Patient attrition	All patients followed to 6 weeks.	Follow up short
Reporting of outcomes	Measurement of outcome: Wounds were cleaned using a protocol that is standard for the clinic and photographed before each treatment. Wound edges were drawn on Visitrak (Smith & Nephew A/S, Hørsholm, Denmark) for estimation of wound size. Estimates were also made of the proportion of granulation tissue in the wound.	Outcome reporting unclear. Percentage reduction in wound area reported for 3 of the 5 patients; wound areas in the other 2 patients were reported to be reduced to less than 20% of their initial size.
Statistical analysis	-	None
Study company	-	The study was supported by Reapplix Aps. One author is co-inventor of the LeucoPatch technology.

Table 14.10: Summary of the strengths and weaknesses of non-randomised studies incorporating internal and external validity

Katzman et al. (2014)	Strengths	Weaknesses
Study design	-	Case series; no comparator; abstract only
Patient selection	Patients with non-ischaemic DFUs with a duration of at least 6 weeks and a positive probing to bone test recruited consecutively.	-
Intervention	Exposure measured via medical records.	-
Confounding factors	-	Confounding factors unclear
Patient attrition	-	Follow up unclear
Reporting of outcomes	-	Measurement of outcome and outcome reporting unclear
Statistical analysis	-	None
Study company	Supported by: Lund University	One author is co-inventor of the LeucoPatch technology.
Abbreviations: DFU – diabetic foot ulcers		

14.3 Appendix C: Adverse events

Table 14.11: Outcomes- AEs

	Any AE n (%)	Any SAE n (%)	Device-related AEs n (%)	Patient tolerance and acceptability	Incidence of new anaemia, n (%)	Death n (%) or OR (95% CI)
Game et al. (2018a) (3C plus standard care: ITT)	81 (61%) of 132 [274 reports]	51 (39%) of 132 [98 reports]. The most common SAE was diabetic foot infection; there were 24 events in the 3C group (24% of all SAEs). Of these diabetic foot infections, 16 (67%) in the 3C group (16% of all SAEs) were attributed to the index ulcer.	0 (0%)	NR	13 (10%)	3 (2%)
Game et al. (2018a) (Standard care: ITT)	90 (66%) of 137 [240 reports]	42 (31%) of 137 [74 reports]. The most common SAE was diabetic foot infection; there were 20 events in the standard care group (27% of all SAEs). Of these diabetic foot infections, 12 (60%) in the standard	0 (0%)	NR	11 (8%)	5 (4%)

	Any AE n (%)	Any SAE n (%)	Device-related AEs n (%)	Patient tolerance and acceptability	Incidence of new anaemia, n (%)	Death n (%) or OR (95% CI)
		care group (16% of all SAEs) were attributed to the index ulcer.				
Game et al. (2018a) (comparison between treatments: ITT)	OR 0.93 (95% CI 0.78–1.12), p=0.4607	OR 1.26 (95% CI 0.91–1.76), p=0.1689	NA	NR	OR 1.20 (95% CI 0.56–2.58), p=0.6408	OR 0.60 (95% CI 0.14–2.56), p=0.7221
Löndahl et al. (2015)	33 AEs were reported during the run-in-, treatment- and follow-up phases of the study. None of the AEs were judged related to the 3C treatment.	12 (27.3%) patients during the run-in-, treatment- and follow-up phases of the study	0 (0%)	Three scheduled 3C applications were missed because of difficulties in blood sampling and two because of technical device failure, thus <1% of scheduled treatments were inhibited because of device/treatment-related technical failure.	NR	1 (2.2%)
Jørgensen et al. (2011)	0 (0%)	0 (0%)	0 (0%)	NR	NR	0 (0%)
Katzman et al. (2014)	Tissue infections occurred in 3 patients but resolved with a change in oral antibiotic treatment.	NR	NR	NR	NR	NR
Abbreviations: AE – adverse events; CI – confidence interval; ITT – intention-to-treat; NA – not applicable; NR – not reported; OR – odds ratio; SAE – sever adverse event						

14.4 Appendix D: Ongoing studies

One ongoing study has been identified by the EAC: 3C Patch® Medicare Claims Study. ClinicalTrials.gov Identifier: NCT03997526.

Recruitment Status: Recruiting (at April 8, 2021)

Estimated Study Completion Date: December 31, 2022

Description:

This is a prospective, observational, longitudinal, claims-based study with a historical control group. Data will be collected via claim forms and will be extracted directly from the Centers for Medicare & Medicaid Services (CMS) Medicare Research Identifiable Files (RIFs), which contain all medical claims for 100% of Medicare beneficiaries enrolled in the Medicare fee-for-service program.

Table 14.12: Population and intervention summary

Group/Cohort	Intervention/treatment
Medicare beneficiaries with diabetes and hard-to-heal non-healing ulcers of the foot will receive usual care (that is, care consistent with the IWGDF guidance on use of interventions to enhance the healing of chronic ulcers of the foot in diabetes) supplemented by the application of the 3C Patch (a platelet-rich plasma gel patch comprised of distinct fibrin, platelet, and leukocyte substantially parallel layers, prepared without the use of any added reagents through a two-step centrifugation process)	Device: 3C Patch A platelet-rich plasma gel patch comprised of distinct fibrin, platelet, and leukocyte substantially parallel layers, prepared without the use of any added reagents through a two-step centrifugation process

IWGDF: International Working Group on the Diabetic Foot

Outcome Measures

Primary Outcome Measures:

- Complete healing [Time Frame: within 20 weeks of the first application of the 3C Patch.].
- Rate (%) of complete healing of hard-to-heal DFUs in Medicare beneficiaries following application of the 3C Patch.

Secondary Outcome Measures include:

- Number of 3C Patch treatments administered at 20 weeks.
- Major and minor amputations at 24 weeks.

Inclusion Criteria:

- Medicare beneficiaries diagnosed with DFU and receiving at least one treatment with the 3C Patch System.
- Eligible ulcers will be hard-to-heal, meaning that the cross-sectional area will decrease by less than 50% during a 4-week period prior to the first application of the 3C Patch.
- Eligible ulcer's cross-sectional area will increase by less than 25% during a 4-week period prior to the first application of the 3C Patch.
- The cross-sectional area of the index ulcer will be ≥50 and ≤1000 mm^2 at the end of the 4-week period prior to the first application of the 3C Patch.
- Participants will have the capacity to understand study procedures, and will be able to provide written informed consent.

Exclusion Criteria:

- Presence of sickle-cell anaemia, haemophilia, thrombocytopenia (<100x109/L) or other clinically significant blood dyscrasia.
- Known potential infectivity of blood products, including known HIV and hepatitis.
- Patient on dialysis.
- Clinical signs of infection of the index ulcer or reason to suspect that infection is present.
- Revascularization procedure in the affected limb planned, or undertaken within the 4 weeks prior to the first use of the 3C Patch.
- Current treatment with cytotoxic drugs or with systemically administered glucocorticoids or other immunosuppressants.
- Treatment of foot ulcers with growth factors, stem cells or equivalent preparation within 8 weeks prior to the first use of the 3C Patch.
- The need for continued use of negative pressure wound therapy.
- Likely inability to comply with follow up visits.
- Participation in another interventional clinical foot ulcer-healing trial within the 4 weeks prior to the first application of the 3C Patch.

- Prior enrolment in this study.
- Unable to understand the study procedures or provide informed consent.

Table 14.13: Ongoing studies identified by the company and the EAC assessment

From the company submission:				EAC:	
Date	**Database**	**Terms**	**Results**	**Identification of study**	**Comment**
15/03/2021	www.clinicaltrials.gov (including ICTRP)	Reapplix	4 results:	These studies are:	
			1 study completed with results	LeucoPatch Study A Multicenter Study on the Effect of LeucoPatch in Diabetic Foot Ulcers; NCT01454401 = Löndahl et al. (2015)	Included by EAC already (no new information)
			1 study recruiting	3C Patch® Medicare Claims Study NCT03997526	Identified by the EAC as an ongoing study (see below; no new information)
			1 study withdrawn	LeucoPatch in Nonhealing Wounds With Exposed Bone or Tendon Study (LiNWEX) NCT03370055	Not diabetes so not eligible
			1 study with unknown status	LeucoPatch in Malleoli Ulcer Study (LiDMUS) NCT02958072	Malleoli ulcers not eligible
		Leucopatch	5 results:	The extra one additional to the above is:	
			As above plus 1 study completed	LeucoPatch in the Management of Hard-to-heal Diabetic Foot Ulcers; NCT02224742 = Game et al. (2018a) trial	Included by EAC already (no new information)
		3C patch	4 results:		
			1 recruiting	3C Patch® Medicare Claims Study NCT03997526	Duplicate of one listed

From the company submission:				EAC:	
Date	**Database**	**Terms**	**Results**	**Identification of study**	**Comment**
					above (no new information)
			Another recruiting	OCT vs IVUS vs QCA to Guide Moderate-to-severe Calcified Lesion Stent Implantation; NCT03574636; Other Study ID Numbers: TARGET 3C	Irrelevant topic; only found in search as the study has 3C in its ID
			1 completed with results	A Study of Anti-VEGFR-3 Monoclonal Antibody IMC-3C5 in Subjects With Advanced Solid Tumors; NCT01288989	Irrelevant topic; only has 3C in the title and the name of an antibody intervention
			1 terminated	Glenohumeral Re-centering During Closed Kinetic Chain for Shoulder Physiotherapy. A Prospective and Randomized Study. (SCAPULEO)	Irrelevant topic: "3C Concept" for Centering in a Closed Chain
15/03/2021	ISRCTN	Reapplix	1 result, status completed	ISRCTN27665670 https://doi.org/10.1186/ISRCTN27665670 Leucopatch in the management of hard to heal diabetic foot ulcers; linked to Game et al. (2018a): https://pubmed.ncbi.nlm.nih.gov/30243803/	Included (no new information)
		Leucopatch	1 result, status completed	As above; Game et al. (2018a)	Included (no new information)
		3C patch	2 results:		
			1 completed	ISRCTN14889127 https://doi.org/10.1186/ISRCTN14889127 Pancreatic replacement therapy and glycaemic control in diabetes	Irrelevant topic; excludes patients with

From the company submission:				EAC:	
Date	**Database**	**Terms**	**Results**	**Identification of study**	**Comment**
					Type 3c diabetes
			Another completed	ISRCTN87161129 https://doi.org/10.1186/ISRCTN87161129 Warning Time and Patient Centred Goals with Transdermal Oxybutynin	Irrelevant topic; mentions 3C in the grid reference for the location of the study GRID grid.13097.3c
15/03/2021	PROSPERO	Reapplix	No results	-	-
		Leucopatch	No results	-	-
		3C patch	No results	-	-

EAC: External Assessment Centre

Table 14.14: Grey literature identified by the company and the EAC assessment

From the company submission					
Date	**Database**	**Terms**	**Results**	**Identification of study**	**Comment**
15/03/2021	www.greylit.org	Reapplix Leucopatch 3C Patch	No results	-	-
15/03/2021	www.opengrey.eu	Reapplix	No results	-	-
		Leucopatch	No results	-	-
		3C patch	1 result	Reproductive ecophysiology of the Adelia penguin pair	Irrelevant topic. 3C mentioned as part of a temperature measurement
15/03/2021	http://webarchive.nationalarchives.gov.uk	Reapplix	3 results:		
				The technology, 3C Patch System for treating diabetic foot ulcers - Advice - NICE text/html www.nice.org.uk	This is the Medtech innovation briefing [MIB230] Published: 27 October 2020 (no new information)
				Appointment of Non-Executive Director - RNS - London Stock Exchange text/html www.londonstockexchange.com	Irrelevant topic. A non-executive director has a current directorship of Reapplix Inc
				mia-register-1-january-2020.csv text/csv assets.publishing.service.gov.uk	Master Indemnity Agreement: between NHS and suppliers. DHSC: Reapplix listed as a supplier (no new information)
		Leucopatch	38 results:	Multiple duplicates – unique items listed below:	
			Stomach ulcer - Clinical trial details - NHS Choices text/html www.nhs.uk Peptic-ulcer Clinical trials LeucoPatch	2017 notice of recruitment for the LeucoPatch in the Management of Hard-to-heal Diabetic Foot Ulcers trial = Game et al. (2018a)	Included (no new information)

From the company submission					
Date	**Database**	**Terms**	**Results**	**Identification of study**	**Comment**
			Bradford Teaching Hospitals NHS Foundation Trust text/html www.bradfordhospitals.nhs.uk The new Leucopatch is made up of the patient's own platelets and white blood cells which healthcare professionals	2014 news item about recruitment for the Game et al. (2018a) trial	Included (no new information)
			Leucopatch II - Health Research Authority text/html www.hra.nhs.uk Search glossary Leucopatch	2013 Ethics apprvial af Leucopatch in the management of hard-to-heal diabetic foot ulcers Game et al. (2018a) trial	Included (no new information)
			Clinical and technical evidence | 3C Patch System for treating diabetic foot ulcers | Advice | NICE text/html www.nice.org.uk Intervention and comparator Intervention: 3C Patch (previously known as LeucoPatch) and standard	This is the Medtech innovation briefing [MIB230] Published: 27 October 2020	Included (no new information)
			PI%202013-14%20Q4.pdf application/pdf www.rdehospital.nhs.uk 2013 07/10/2013 Yes 34 11/WM/0381 De-ESCALaTE HPV 29/01/2014 Within 70 days 35 13/WM/0202 DRN 819 Leucopatch	2014 Performance in Initiating Clinical Trials The Royal Devon and Exeter NHS Foundation Trust Gave NHS Permission In The Preceeding Twelve Months = Game et al. (2018a) trial had met benchmark target	Included (no new information)
			NICE Guideline Template application/pdf www.nice.org.uk	Diabetic foot problems - guideline development group and declarations of	Included (no new information)

From the company submission					
Date	**Database**	**Terms**	**Results**	**Identification of study**	**Comment**
			CRN adopted trial Proposed future involvement in studies • LeucoPatch Study.	interest: one guideline development group member declared proposed future involvement in the LeucoPatch Study = Game et al. (2018a) trial	
			Research summaries - Health Research Authority text/html www.hra.nhs.uk It is a major healthcare problem … Leucopatch II 24 May 2013	2013 information extracted from the Research Ethics Committee application form about the Game et al. (2018a) trial	Included (no new information)
			Diabetic foot problems: prevention and management - Guidance and guidelines - NICE text/html www.nice.org.uk CRN adopted trial Proposed future involvement in studies • LeucoPatch Study	NICE guideline [NG19] Published date: August 2015 Last updated: January 2016	Included (no new information)
			west-midlands-south-birmingham-annual-report-2013-2014.pdf application/pdf www.hra.nhs.uk Additional Conditions REC Reference Application Short Title Number of Days on Clock 13/WM/0202 Leucopatch	National Research Ethics Service (NRES) Committee West Midlands - South Birmingham Annual Report 01 April 2013 – 31 March 2014 reporting favourable opinion for the Game et al. (2018a) trial	Included (no new information)
			ar-wm-south-birmingham-14-15.pdf application/octet-stream www.hra.nhs.uk Evaluation of PICO dressings in foot and ankle arthrodesis 1 17/01/2015 3 13/WM/0202/AM01 Leucopatch	RES Committee West Midlands - South Birmingham Annual Report 01 April 2014 - 31 March 2015. Ethics amendment Game et al. (2018a) trial	Included (no new information)

From the company submission					
Date	**Database**	**Terms**	**Results**	**Identification of study**	**Comment**
			West_Midlands - South_Birmingham_Annual_Report_2016-2017.pdf application/octet-stream www.hra.nhs.uk 22/04/2016 6 12/WM/0010/AM09 PRiDE Study ver.1 SA#08 21/12/2016 6 13/WM/0202/AM04 Leucopatch	West Midlands - South Birmingham Research Ethics Committee Annual Report 01 April 2016 - 31 March 2017. Ethics amendment Game et al. (2018a) trial	Included (no new information)
			Research, Development & Innovation | Derby Hospitals Foundation Trust text/html www.derbyhospitals.nhs.uk double-blind, European multicentre clinical trial (EXPLORER) Game, Dr Frances 14/01/2013 15/02/2016 14611 Leucopatch	2015: EXPLORER (Edmonds et al. 2018) study currently open to recruitment in Derby Hospitals NHS Foundation Trust.	Included (no new information)
			1 application/pdf www.nice.org.uk ultrasonic simulation • laser therapy • surgical intervention (offloading / biomechanical healing) • leucopatch	This is the review protocol for the NICE guideline: Diabetic foot problems: Inpatient management of diabetic foot problems. Clinical guideline [CG119] Published: 23 March 2011.	This guidance has been updated and replaced by NICE guideline NG19 which has been included (no new information)
		3C Patch	No results	-	-
Abbreviations: CRN – Clinical Research Network; HPV – human papillomavirus; NHS – National Health Service; NICE – National Institute for Health and Care Excellence; NRES – National Research Ethics Service; PICO – Population, Intervention, Comparator, Outcomes; RES – Research ethics Service; RNS – Regulatory News Service					

Table 14.15: Wounds UK website studies identified by the company and the EAC assessment

Company submission			**EAC**	
Wounds UK website:	Terms	Results	Identification	Comment
Database: Best Practice statements	Reapplix, leucopatch, platelet rich fibrin patch, DFU	3 results:		
			Best practice recommendations for the implementation of a DFU treatment pathway. London: Wounds UK, 2018. Available to download from: www.wounds-uk.com	A group of experts met to discuss the burden of DFUs and the challenges facing service delivery of DFU care in the UK; not eligible
			Diabetic foot ulceration: review of best practice 2009	Non-systematic review; not eligible
			Managing diabetic foot ulcers: best practice. 2006	Non-systematic review; not eligible
Database: Consensus documents		No results	-	-
Abbreviations: DFU – diabetic foot ulcer; EAC – External Assessment Centre				

14.5 Appendix E: Economic search strategy

Critique of the company search strategies to identify economic evidence

Appendix A of the company submission contained a description of the search methodology used to retrieve relevant economic evidence.

The extent to which the EAC could assess the company search methods was restricted by limitations in the search reporting. Although the company submission reported some elements of the search methods reasonably clearly (name of resources searched, date span of searches) the overall reporting did not reflect standard requirements for transparent, reproducible reporting (as outlined, for example, in the PRISMA-S (Preferred Reporting Items for Systematic reviews and Meta-Analyses literature search extension) checklist) (Rethlefsen et al. 2021). Key reporting issues included lack of clarity regarding:

- Which platform / interface was used to search each database.
- Whether individual search line(s) in each database search strategy were combined using Boolean, and if so, how.
- Which search line(s) in each database search strategy were used to output results for assessment.
- The total number of records identified from each database and other information sources.

The above issues meant that only limited assessment of the company search methods was possible.

Currency of searches

The searches were conducted between 08/03/2021 and 15/03/2021. The searches therefore had reasonably good currency at the date of submission (27/04/2001).

Search sources

The search sources included a reasonable selection of bibliographic databases containing published journal literature (MEDLINE, PubMed, Embase, CINAHL). The selection of search sources could have been enhanced by including the following resources:

- Cochrane Central Register of Controlled Trials (CENTRAL). CENTRAL includes records for studies reporting on relevant outcomes such as cost-effectiveness.

- Trial register sources such as ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) portal. Both sources include records reporting on relevant outcomes such as cost-effectiveness.

- The HTA Database. The HTA database contains bibliographic information about ongoing and published health technology assessments commissioned or undertaken by HTA organisations from around the world. HTAs may include economic evidence.

- Conference Proceedings Citation Index-Science (CPCI-S). The submission methods do not detail any search for conference abstracts. The resources searched include Embase, which does contain some conference abstracts, but search methods would have been enhanced by including an additional source of abstracts, such as CPCI-S.

- Specialist economics databases containing economic evidence, for example the NHS Economic Evaluation Database (NHS EED). Although a closed database, NHS EED still has value for identifying evidence up to the date of database closure.

Search strategies

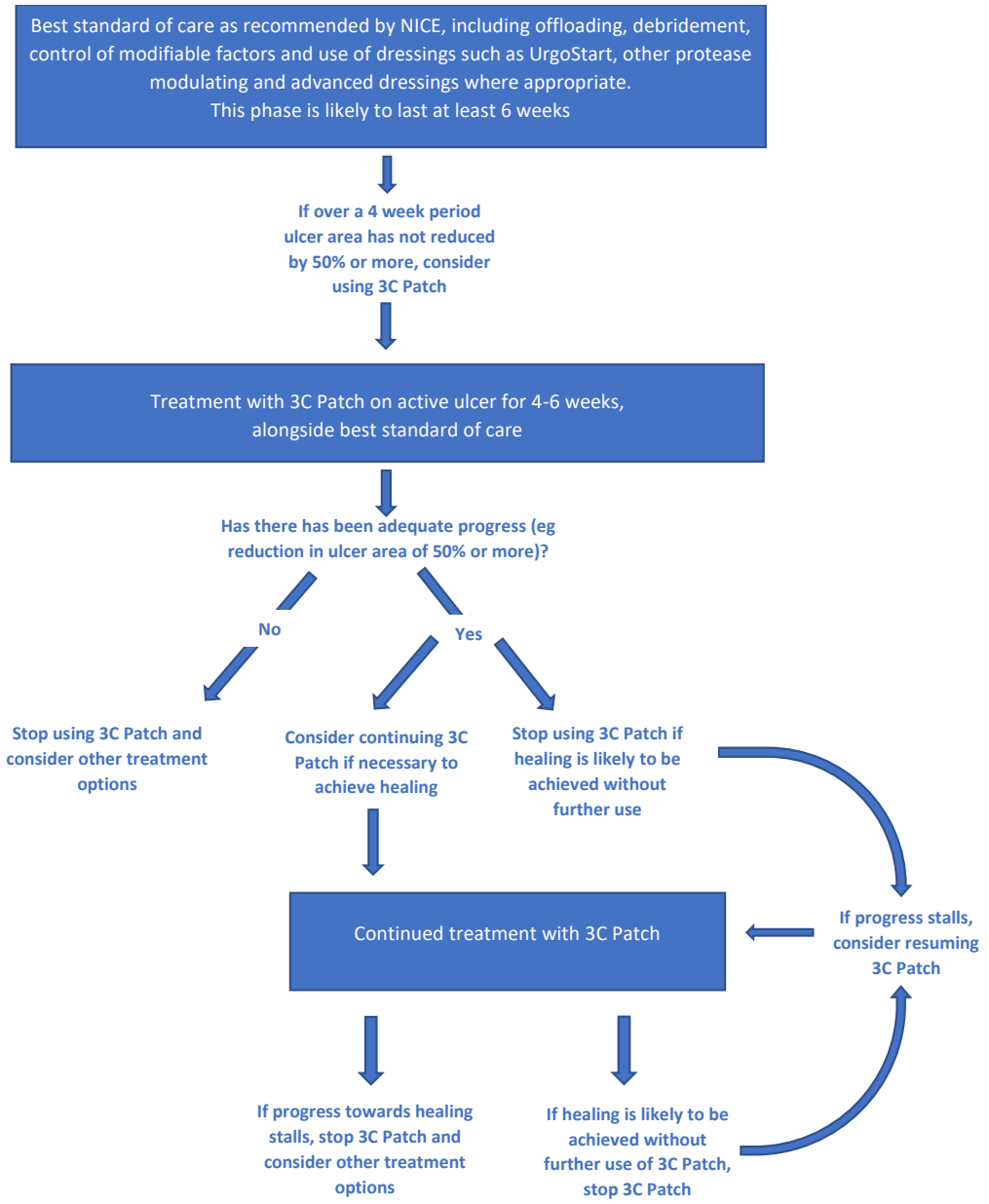
From the reported search strategies for bibliographic databases, it was not possible to know which search lines were used to output results. It was therefore not possible to assess in any detail the search strategy structure, search terms or syntax (for example, using the Peer Review of Electronic Search Strategies (PRESS) Checklist (McGowan et al. 2016)). There appeared to be some limitations that could potentially impact on search sensitivity and the identification of relevant evidence (for example: subject headings searched as major descriptors; restricted range of variant search terms for strategies; syntax reported for some databases, for example, PubMed potentially not being appropriate for use in the database).

The methods stated that the date span of the search was 2000 to present (although no such restrictions were shown in the strategy syntax itself). This date span was appropriate, given the product was first developed as a manual process in 2009 and the initial device was developed in 2010.

Details of EAC de novo searches

The reporting limitations meant the EAC was unable to replicate the search conducted by the company. The EAC therefore conducted a de novo literature search to identify evidence. A single set of searches was conducted to identify clinical and economic evidence. Please see appendix A for details of the EAC de novo searches.

14.6 Appendix F: Clinical pathway proposed by the company



YHEC
York Health Economics Consortium

MT539 External Assessment Centre (EAC) Appendum on Economic Model Cost Updates

The External Assessment Centre made a number of updates to the company's model as described in Section 9 of the Assessment Report. This document details the impact on the model's results of the changes made. The changes made are separated into cost corrections and EAC preferred costs. The changes are shown using the EAC's discontinuation rule in the EAC's model A (without the additional infection health state) and the company's model. Step-by-step comparisons with the EAC's model B are more difficult due to the additional complexity of the change in model structure, hence these results are not presented in this document.

1. Updates using EAC model A

The EAC model A is structured in the same way as the company's model, with the updates to the model and clinical parameters described in Section 9.2 of the Assessment Report. Most notably, this includes discontinuation of 3C patch at 20 weeks or on diabetic foot ulcer (DFU) healing - whichever occurs first with no option to discontinue at 5 weeks.

Table 1 reports the corrections made to the company's cost inputs and Table 2 reports the results of EAC model A with these corrections.

Table 1: EAC corrections to company's cost inputs

#	Model correction	Section in EAC report
1	Absolute rather than relative values for additional NHS provided care for district nurse dressing changes between outpatient consultations – both arms of model.	Table 9.6 (3C Patch) and Table 9.7 (standard care)
2	Outpatient consultation cost (both arms) – removal of cost of district nurse of £20.61 (to avoid double counting)	Table 9.6 (3C Patch) and Table 9.7 (standard care)
3	Application of training cost up front (as opposed to weekly)	Table 9.6

Table 2: EAC model A results with corrected company costs

Per patient costs	3C Patch	Standard care	Incremental cost
Index ulcer (including 3C Patch cost and training cost)	£12,427	£12,010	£417
Regular assessment for patients whose ulcers have healed	£157	£130	£27
Subsequent ulcers	£865	£702	£163
Major amputation	£329	£379	-£50
Minor amputation	£682	£786	-£103
Post amputation costs	£421	£475	-£54
Total	**£14,883**	**£14,483**	**£400**

Correcting the costs specified in Table 1 changes the incremental costs from £168 per patient to £400 per patient (i.e. difference of £232 per patient). This change is primarily driven by correction 1 which reduces the savings assumed by the company from district nurse dressing changes with 3C patch. In this correction, the EAC's district nurse costs (similar between arms) were applied in the absence of any absolute values from the company. Correction 2 also plays a part in that the cost of an unhealed ulcer is reduced and those on standard of care are unhealed for longer hence this lower cost reduces the cost in the standard care arm more than with 3C Patch.

The EAC updated a number of other costs in the model based on EAC preference (rather than correction of an error) as reported in Table 3. The results of EAC model A with these updates (in addition to the corrections made above) are presented in Table 4.

Table 3: EAC preferred cost inputs

#	Model update	Section in EAC report
1	Change outpatient appointment cost to EAC value	Table 9.6
2	Change inpatient cost with 3C patch and standard care to incorporate severe infection and revascularisation based on resource use from RCT	Table 9.6 (3C Patch) and Table 9.7 (standard care)
3	Update of the staff complement required to be trained on 3C patch	Table 9.6
4	Updated antibiotics costs based on resource use from RCT	Table 9.6 (3C Patch) and Table 9.7 (standard care)
5	Change secondary dressing costs to be based on NHS supply chain	Table 9.6 (3C Patch) and Table 9.7 (standard care)
6	Change outpatient appointment with standard care to weekly alternating outpatient appointments and podiatry in the community	Table 9.7
7	Change healed DFU appointment cost to NHS reference cost source	Table 9.8
8	Update to major amputation cost - one off	Table 9.8
9	Update to post major amputation	Table 9.8
10	Update to minor amputation cost - one off	Table 9.8
11	Update to post minor amputation	Table 9.8

Table 4: EAC model A results with corrected company costs and EAC preferred costs

	3C Patch	Standard care	Incremental cost
Index ulcer (including 3C Patch cost and training cost)	£9,339	£7,711	£1,628
Regular assessment for patients whose ulcers have healed	£362	£300	£62
Subsequent ulcers	£556	£451	£105
Major amputation	£341	£392	-£52
Minor amputation	£685	£788	-£104
Post amputation costs	£382	£432	-£49
Total	**£11,664**	**£10,074**	**£1,590**

In order to assess the importance of the change to each of the EAC's preferred cost inputs, in Table 5 the results of the EAC model A with corrected cost inputs and each individual change is presented.

Table 5: Impact of each EAC preferred cost on EAC model A

	Incremental cost
EAC model A with company corrected costs (as per Table 2)	*£400*
1. Change outpatient appointment time to EAC value	£222
2. Change inpatient cost with 3C patch and standard care to incorporate severe infection and revascularisation based on resource use from RCT	£803
3. Update of the staff complement required to be trained annually on 3C patch	£418
4. Updated antibiotics costs based on resource use from RCT	£455
5. Change secondary dressing costs to be based on NHS supply chain	£497
6. Change outpatient appointment with standard care to weekly alternating outpatient appointments and podiatry in the community	£1,166
7. Change healed DFU appointment cost to NHS reference cost source	£435
8. Update to major amputation cost - one off	£398
9. Update to post major amputation	£393
10. Update to minor amputation cost - one off	£400
11. Update to post minor amputation	£403

2. Updates using Company's model

The company's model includes discontinuation after 5 weeks for those with inadequate healing, that is, reduction in DFU area of less than 50% and estimates cost savings of £191 per patient. The results of the company's model with the EAC cost corrections are shown in Table 6. Note that the training cost could not be applied upfront within the company's model structure, hence correction 3 from Table 1 has not been made.

Table 6: Company model results with corrected company costs

Per patient costs	3C Patch	Standard care	Incremental cost
Total	**£14,969**	**£15,056**	**-£87**

In Table 7, the results of the Company model using the EAC corrected and preferred costs are presented. Again, these results do not include application of staff training up front.

Table 7: Company model results with corrected company costs and EAC preferred costs

	3C Patch	Standard care	Incremental cost
Total	**£11,268**	**£10,576**	**£692**

In order to assess the importance of the change to each of the EAC's preferred cost inputs, in Table 8 the results of the Company's model with corrected cost inputs and each individual change is presented.

Table 8: Impact of each EAC preferred cost on Company's model

	Incremental cost
EAC model A with company corrected costs (as per Table 6)	*-£87*
1. Change outpatient appointment time to EAC value	-£188
2. Change inpatient cost with 3C patch and standard care to incorporate severe infection and revascularisation based on resource use from RCT	£196
3. Update of the staff complement required to be trained annually on 3C patch	-£79
4. Updated antibiotics costs based on resource use from RCT	-£49
5. Change secondary dressing costs to be based on NHS supply chain	-£27
6. Change outpatient appointment with standard care to weekly alternating outpatient appointments and podiatry in the community	£386
7. Change healed DFU appointment cost to NHS reference cost source	-£65
8. Update to major amputation cost - one off	-£89
9. Update to post major amputation	-£93
10. Update to minor amputation cost - one off	-£88
11. Update to post minor amputation	-£87

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance

Assessment report overview

3C Patch for treating diabetic foot ulcers

This assessment report overview has been prepared by the Medical Technologies Evaluation Programme team to highlight the significant findings of the External Assessment Centre (EAC) report. It includes **brief** descriptions of the key features of the evidence base and the cost analysis, any additional analysis carried out, and additional information, uncertainties and key issues the Committee may wish to discuss. It should be read along with the company submission of evidence and with the EAC assessment report. The overview forms part of the information received by the Medical Technologies Advisory Committee when it develops its recommendations on the technology.

Key issues for consideration by the Committee are described in section 6, following the brief summaries of the clinical and cost evidence.

This report contains information that has been supplied in confidence and will be redacted before publication. This information is highlighted in [redacted]. This overview also contains:

- Appendix A: Sources of evidence
- Appendix B: Comments from professional bodies
- Appendix C: Comments from patient organisations

1 The technology

3C Patch (Reapplix APS) is a single-use medical device that is used as part of wound care for foot ulcers in people with diabetes. 3C Patch is used in combination the 3CP centrifuge, which is also manufactured by Reapplix APS. Together the device and the centrifuge are referred to as the 3C Patch system.

The system is used to make an individual, biological patch from the patient's own peripheral blood. The patch (a disc-shaped layered matrix of fibrin, leukocytes and platelets) acts as a concentrated source of cells, growth factors and signalling molecules which are thought to promote wound healing.

To create the patch, a blood sample is drawn directly into the 3C Patch device using standard blood draw techniques. The device is then placed in the 3CP centrifuge and spun for about 20 minutes. The centrifuge has optical sensors and uses an automatic pre-specified programme that performs all the steps needed to create the patch.

The patch is applied directly to the ulcer and kept in place with a non-adhesive primary dressing. A separate secondary dressing can also be used to manage exudate. After 7 days, patch material that has not integrated in or been absorbed by the wound, is removed and the treatment can be repeated. The company recommends that the 3C Patch is used for 4-6 weeks initially. The company states that the patch can be used for up to 20 weeks.

3C Patch device received a CE mark in December 2009 (updated in December 2019) as a Class IIa device indicated for use in the treatment of recalcitrant wounds. The 3CP centrifuge is CE marked as a laboratory centrifuge.

Each 3C Patch device is sold as part of a kit that contains one each of the following:

- 3C Patch device

- 3C Patch needle holder
- winged blood sampling set (G21) with protector
- primary cover dressing (Tricotex)
- alcohol swab (for disinfection of the skin before needle insertion)
- post blood sample adhesive bandage
- ruler with adhesive

The price per kit is £150. The 3CP centrifuge is provided on loan by the company free of charge. Servicing and maintenance of the 3CP centrifuge is also free of charge and the expected lifespan of the centrifuge is at least 7 years. A non-sterile 3CP counterbalance is also needed for balancing the centrifuge.

2 Proposed use of the technology

2.1 Disease or condition

As noted above, 3C Patch is used as part of wound care for foot ulcers in people with diabetes. The GIRFT Programme National Specialty Report on Diabetes (2020) states that people with diabetes are at higher risk of footcare problems because high blood glucose levels over time lead to nerve and blood vessel damage. Even small cuts and burns can lead to chronic and non-healing ulcers, which can end in an amputation. Diabetes is the most common cause of non-traumatic limb amputation, with diabetic foot ulcers preceding more than 80% of amputations in people with diabetes. After a first amputation, people with diabetes are twice as likely to have a subsequent amputation as people without diabetes (NICE's guideline on preventing and managing diabetic foot problems). Ulceration and amputation can substantially reduce quality of life.

A diabetic foot ulcer is defined as a localised injury to the skin and or underlying tissue, below the ankle, in a person with diabetes. Some foot

ulcers are categorised as hard-to-heal. This is often considered as those that have not shown substantial healing (reduction in size by 50% or more) after 4 weeks of treatment.

The cost of health care for ulceration and amputation in diabetes in 2014 to 2015 is estimated at between £837 million and £962 million (0.8% to 0.9% of the NHS budget for England). Ulceration equated to 90% of expenditure, and data suggests it is associated with increased length of hospital stay (by around 8 days) compared to that for diabetes-related admissions without ulceration (Kerr et al. 2019).

2.2 Patient group

It is estimated that more than 4.9 million people are living with a diagnosis of diabetes in the UK (Diabetes UK, 2021). According to Diabetes UK, it is estimated that 1 in 20 people with diabetes will develop a foot ulcer each year, and of these, more than 1 in 10 will ultimately need amputation. Even after the resolution of a foot ulcer, subsequent foot ulcers are common. Roughly 40% of people with a foot ulcer will have a recurrence within 1 year after ulcer healing, almost 60% within 3 years, and 65% within 5 years (Armstrong et al. 2017).

2.3 Current management

The aims of treatment for diabetic foot ulcers are to dress and protect the ulcer, to prevent or treat any infection and to promote healing. NICE's guideline on the prevention and management of diabetic foot problems recommends that diabetic foot ulcers are assessed by a healthcare professional, who should record the size, depth and position of the ulcer and refer the person to a diabetic foot protection team for assessment of the wound.

The guideline recommends that one or more of the following is offered to people as standard care for treating diabetic foot ulcers:

- Offloading (interventions to reduce the amount of weight placed on the foot)
- Control of foot infection
- Control of ischaemia (for example, surgery to bypass the blocked blood vessels to restore blood circulation to the affected area)
- Wound debridement (removal of dead or infected tissue or foreign objects from the wound)
- Wound dressings

The guideline states that negative pressure wound therapy may also be considered after surgical debridement for diabetic foot ulcers, on the advice of the multidisciplinary foot care service. It also recommends that clinical assessment and patient preference should inform dressing choices but that healthcare professionals should choose the lowest cost dressing that is likely to achieve the desired results. The overall health of the person with diabetes, how healing has progressed, and any deterioration should be considered when deciding the frequency of follow-up as part of the treatment plan.

NICE's medical technologies guidance on UrgoStart for treating diabetic foot ulcers and leg ulcers recommends that UrgoStart dressings should be considered as an option for people with diabetic foot ulcers after any modifiable factors such as infection have been treated.

NICE advice on wound care products states that there is not enough evidence to determine if advanced dressings (such as alginate, film, foam, hydrocolloid and hydrogel dressings) are more clinically effective than conventional dressings for treating wounds. It also states that there is not currently robust evidence supporting the use of antimicrobial dressings (such as silver, iodine or honey) over non-medicated dressings for treating chronic wounds. Patients with diabetic foot ulcers are treated in community, hospital and primary care settings.

A national wound care strategy programme has been commissioned by NHS England and Improvement to improve the prevention and care of pressure

ulcers, lower limb ulcers. Their recommendations for people with confirmed or suspected diabetic foot ulceration are to refer the individual to a diabetic foot team and provide care in line NICE guidelines. The also recommend reviewing the ulcer at each dressing change and at weekly intervals, monitoring healing at 4-week intervals (or more frequently if concerned) and reassessing if the ulcer remains unhealed at 12 weeks.

2.4 Proposed management with new technology

The company's value proposition is based on the use of 3C Patch for the treatment of hard-to-heal diabetic foot ulcers (DFUs). Specifically, the company propose it is used in people with DFUs where best standard of care as recommended by NICE (including offloading, debridement, control of modifiable factors, and use of dressings such as UrgoStart and other protease modulating and advanced dressings where appropriate) have failed to promote ulcer healing as measured by a reduction in ulcer area of 50% or more over a 4-week period.

It also suggests that when selecting people for 3C Patch treatment, clinicians should consider the current lack of clinical effectiveness evidence for use in those with severe comorbidities such as severe ischaemia (ankle-brachial pressure index less than 0.5) and severe renal disease (renal replacement therapy or estimated glomerular filtration rate less than 20).

The company states that 3C Patch should be used alongside best standard of care for 4 to 6 weeks. The ulcer should then be reviewed to see if adequate progress in healing has been made, such as by measuring if there has been a 50% or more reduction in ulcer area. 3C patch treatment should be stopped and replaced with other treatment options if adequate progress has not happened. If adequate progress has been made, clinicians should continue to use the patch if clinically appropriate. If they think the ulcer will heal without further 3C Patch use, they should stop using it. Thereafter, clinicians should continually review the ulcer and stop using 3C Patch when further healing is likely without its use, or if healing progress stalls. If healing stalls, other treatment options should be considered.

Clinical experts made the following comments regarding the use of 3C patch and the proposed position in the treatment pathway:

- clinical experts agreed with the proposed overall structure of the clinical pathway and the positioning of 3C Patch as a treatment option when other advanced dressings had failed
- the company's definition of hard-to-heal DFU reflects the definition used in the key trial of 3C patch
- in the trial, eligibility was determined by response to standard care during the 4-week run-in period; in practice lack of response to standard care can be judged from a patient's history
- measuring reductions in ulcer area accurately requires specialist equipment that is not available in most settings, so this is likely to be a practical barrier to implementing the 50% threshold for starting or continuing 3C Patch treatment in practice. Other factors would also inform clinical judgement about wound improvement including:
    - changes in ulcer volume or depth
    - improvement in granulation tissue formation
    - greater improvement being seen with the patch compared with previous treatments (but less than the 50% cut off)
- patients may have concerns about discontinuing treatment that is leading to some improvement but not enough to meet the 50% cut-off
- a patient's willingness and or ability to provide blood weekly will also inform clinical judgement
- weekly visits could be challenging for services, with fortnightly visits being used for standard care

- 3C Patch would need to be done in a secondary care setting to access the device and practitioners able to do venepuncture. Currently, many services do not have this skill set and would need to expand their interdisciplinary working.

3 Company claimed benefits and the decision problem

These are described in the scope in Appendix D. Table 1 describes the company's proposed changes to the decision problem.

Decision problem	Variation proposed by company	EAC view of the variation
People with diabetic foot ulcers that are not healing despite standard wound care	People with diabetic foot ulcers that are not healing despite standard wound care including the use of advanced dressings where appropriate	Variation is reasonable as the patient population with hard-to-heal ulcers could have an advanced dressing in the pathway prior to using 3C Patch. The company submission stated that 85% of patients had an advanced dressing in the run-in period in the Game et al. (2018a) RCT. The clinical experts stated that the dressings used in the 4-week run-in period were not particularly advanced (most were iodine or foam, and none were UrgoStart [an advanced dressing with proven efficacy]) (EAC correspondence log 2021). The EAC notes that about 1% of patients in the control arm of Game et al. (2018a) used this dressing for at least 1 week. The experts confirmed that UrgoStart was not part of standard care when recruitment for the Game et al. (2018a) RCT was undertaken. The company defined hard-to-heal ulcers as those with less than 50% progress towards healing during a

		4-week run-in period in which best standard of care is provided. The experts advised that in clinical practice there would be no equivalent to the 4-week run in and they would not apply a 50% rule on change in ulcer size from baseline to determine which patients might benefit from a 3C Patch. Rather, the clinician would be able to tell from the patient's history that their wound had not progressed with previous treatment.

4 The evidence

4.1 Summary of evidence of clinical benefit

The company presented evidence from 6 studies in its clinical evidence submission. The EAC were unable to replicate and re-run the company's searches so undertook its own literature search (see section 4.1 and Appendix A of the assessment report). The EAC identified all 6 studies submitted by the company but only included 4 of them in its review. The EAC did not identify any additional clinical studies. Of the 4 studies included by the EAC, multiple publications were found for each. The EAC identified the main publications for each of the included studies. The full list of publications is listed in 4.2 of the EAC's assessment report. Table 1 summarises the studies included by the company and EAC respectively.

Table 1: Studies included by the company and EAC

Study	Design	Publication type	Included by company	Included by EAC	EAC reason for exclusion
Game et al. (2018)	RCT	Published full text	Yes	Yes	NA
Londahl et al. (2015)	Case Series	Published full text	Yes	Yes	NA
Jorgensen et al. (2011)	Case Series	Published full text	Yes	Yes	NA
Zink et al. (2021)	Clinical pathway consensus document	Unpublished full text	Yes	No	[redacted]
Hogh et al. (2019)	Case series	Abstract	Yes	No	Mixed population and

					outcomes were not reported separately for the patients with diabetes (n=4 out of 26 patients).
Katzman et al. (2014)	Case Series	Abstract	Yes	Yes	NA
Abbreviations: NA – not applicable Source: adapted from EAC report table 4.2					

Table 2: Characteristics of studies included by both the company and EAC

Author & setting	Sample size & population	Intervention	Comparator	Key baseline characteristics	Primary outcome
Game et al. (2018) Specialist diabetic foot clinics in the UK, Denmark, and Sweden	N=266 (ITT) people with hard-to-heal DFUs (cross-sectional area decrease by less than 50%) with cross-sectional area of the index ulcer between 50–1000 mm² at the end of the 4-week run-in period. Key exclusion criteria: • clinical infection or suspected infection of the index ulcer • revascularisation in the 4 weeks prior to baseline visit • HbA1c >12% • Hb <105 g/L • haemophilia, sickle cell anaemia, leukaemia or blood dyscrasias • ongoing dialysis • expected poor adherence.	Weekly 3C Patch with standard care	Standard care	• Ulcer duration not recorded • 217 (82%) men, 49 (18%) women • Mean age 61.9 (SD: 11.6) years • HbA1c: 8.2% (IQR:7.2–9.2)	Proportion of ulcers healed within 20 weeks
Londahl et al. (2015) Secondary or tertiary multidisciplinary diabetic foot clinics in Denmark or Sweden	N=44 people with non-ischaemic (Wagner grade 1 or 2) DFUs with 6 weeks or more duration, maximal area of 10cm², ≤40% change in ulcer area during 2-week run-in period. Key exclusion criteria: • inability to tolerate venesection • Hb<105 g/L • HbA1c >12.0% • ongoing dialysis • haemophilia, sickle cell anaemia, leukaemia or blood dyscrasias	Weekly 3C Patch. Patients also got oral antibiotic treatment until bone coverage was achieved, and thereafter at the discretion of the physician	None	• Median ulcer duration 35 (IQR:16-60) weeks • Median age 63 (IQR: 58–73) years • 35 (79.5%) were men • HbA1c: 8.1 (IQR:7.2-9.4)	Ulcer healing at 20 weeks

	• expected poor adherence • vascular reconstruction in the lower limbs within 4 weeks before the study.				
Jørgensen et al. (2011) Outpatient clinic in Demark	N=5 people with chronic DFUs (grade I-II on Wagner scale), lasting at least 2 months which have failed to heal. Key exclusion criteria: • clinical signs of infection or osteomyelitis • significant medical conditions likely to impede wound healing • wound necrosis • ischaemia needing vascular reconstruction or amputation • haemophilia, sickle cell anaemia, thrombocytopenia, and leukaemia or blood dyscrasia • HbA1c >10%).	Weekly 3C Patch	None	• Age 47-65 years • All participants were male • Ulcer duration 3 to 72 months • HbA1c not reported	Proportional change in wound area during the 6-week treatment period.
Katzman et al. (2014) Sweden (setting NR)	N=17 people with 21 non-ischaemic DFUs with a duration of at least 6 weeks and a positive probing to bone test.	Weekly 3C Patch	None	NR	Bone covered and ulcer healing with complete epithelialization (follow up timescale not stated but treatment duration was up to 20 weeks and median ulcer duration was 27 weeks)
Abbreviations: DFU- diabetic foot ulcer; HbA1c-haemoglobulin A1c; Hb-haemoglobin; ITT-intension to treat; NA – not applicable; NR- not recorded; SD-standard deviation Source: adapted from EAC report table 4.4					

The EAC's full critical appraisal of the included studies can be found in section 5.2 and appendix B of the assessment report.

In summary, the EAC considered that the Game et al. (2018) study provided the best quality evidence for 3C patch but, given that only one RCT was available, it decided to report the efficacy and safety results from the uncontrolled case series for completeness (see section 5.3 of the assessment report).

Game et al. (2018)

The RCT compared 3C Patch with standard care versus standard care only. It was done at multiple sites in the UK (22 centres) with a minority of centres in Denmark and Sweden.

The EAC assessed the company's RCT as high quality with a low risk of bias (good internal validity). It noted that in the trial, the group that received 3C Patch had better wound healing outcomes than those who received standard care and the differences between the groups were statistically significant. The study showed that at the 20-week follow-up, 34% of ulcers were healed in the 3C Patch group versus 22% in standard care (p=0.0235). Time to complete healing (the most clinically important outcome) was also shorter in the 3C Patch group compared with standard care (p=0.0246). The odds ratios for the numbers of amputations, infections and days on antibiotic therapy all favoured 3C Patch versus standard care alone, but none were statistically significantly different (the RCT, however, was not powered to detect differences in these outcomes). The results are reported in full in section 5.3 of the EAC report and table 3 below.

The EAC's main concerns about the evidence related to the external validity of the findings observed in the Game et al. (2018) study. The considerations about the generalisability of the trial results are complex because, as the EAC notes, there is disagreement between the company and clinical experts about how the intervention will be used in practice and the IFUs are also more

permissive than both the company's and the experts' proposed use of 3C patch.

Key differences between the Game et al. (2018) study and the IFU highlighted by the EAC

People with a baseline HbA1c above 12%, large ulcers (greater than 1000 mm^2) or ulcers increasing in size (greater than or equal to 25%) during the 4-week run-in period were excluded from the study. People with actively infected wounds at the start of the study were also excluded (although participants did not stop 3C Patch use if an infection developed during the trial). None of these criteria are reflected in the IFU indications for use or contraindications. Also, in the trial patients continued treatment until complete healing or 20 weeks (whichever occurred first), whereas the IFU does not define a maximum treatment duration.

Overall, the clinical experts agreed that the population in the Game et al. (2018) RCT is broadly representative of the population which would receive 3C Patch if it were to be used in the UK NHS. However, clinical experts noted that in practice it would be challenging to restrict 3C Patch use by HbA1c level and they had differing opinions on whether they would continue 3C Patch use if an infection develops. As discussed in section 2.4, measuring reductions in ulcer area accurately, to judge the 50% threshold for starting or continuing 3C Patch use, requires specialist equipment that is not available in most settings making it a practical barrier. Clinical experts also stated that they would continue 3C Patch use based on other clinical parameters such as changes in ulcer volume or depth and improvement in granulation tissue formation. The EAC note that the Game et al. (2018) RCT is generally more closely aligned with the US IFU in which wounds greater than $10cm^2$, certain blood conditions (haemoglobin less than 10g/dl, platelet count less than $100x10^9$/L, and serum albumin level less than 2.5g/dl) and renal failure on haemodialysis are contraindicated. The US IFU also lists a maximum treatment duration of 20 weeks.

Key differences between the Game et al. (2018) study and the company's proposed treatment pathway highlighted by the EAC

In the company's proposed pathway, clinicians are expected to use UrgoStart before 3C Patch. The dressings used in the 4-week run-in period in the RCT were mostly iodine or foam, although 40% did receive protease-modulating-matrix dressings for at least 1 week in the run-in period. The company confirmed that UrgoStart was used in 1% and other protease modulation dressings in 60% of those in the comparator arm for at least 1 week of treatment.

The company states that 3C Patch should be used alongside best standard of care for 4 to 6 weeks and if no adequate progress in healing has been made, such a 50% or more reduction in ulcer area, then 3C Patch use should be stopped. The company also note that in the Game et al. (2018) study most ulcers which healed by week 20 demonstrated a significant reduction in ulcer area by weeks 4 to 6, and that 78% of ulcers which healed by week 20 had a 50% reduction in ulcer area by week 5. However, as noted above, in the trial all patients continued treatment until healing or 20 weeks regardless of response to treatment (the mean treatment period was 17.1 weeks in the Game et al. (2018) trial).

EAC interpretation of the clinical evidence

Overall, the EAC agrees with the company claims that 3C Patch reduces the time to complete healing and increased the number of healed ulcers compared to standard care, based on evidence published in the Game et al. (2018) study. The uncontrolled pilot studies (Londahl et al. 2015 and Jorgensen et al. 2011) also showed that 3C Patch was an effective treatment for hard-to-heal ulcers, some of which were of a long duration. However, the EAC concludes that there is insufficient direct trial evidence to support the other claimed benefits included in the company submission. This includes 3C Patch helping to avoid wound-related complications (including amputation and infection) and reducing the need for further treatment.

The EAC also concluded that while the population in trial was reasonable for this first RCT of the intervention, there are considerable uncertainties about generalising the findings from the RCT to UK clinical practice. In particular, the EAC believes that in practice 3C Patch may be offered to a wider population than was included in the RCT. It also believes that the Game et al. (2018) study does not provide evidence on using 3C Patch in accordance with the company's proposed model of care, which includes as stopping rule based on treatment response.

The EAC states that further high-quality research is needed to assess whether the RCT findings are generalisable to a greater proportion of people with hard-to-heal diabetic foot ulcers.

Table 3: Studies considered pivotal to the clinical and economic analysis

Study and design	Participants/ population	Intervention & comparator	Outcome measures and follow up	Results	Withdrawals	Funding	Comments
Game et al. (2018) Randomised controlled trial	269 randomised (137 to standard care and 132 to 3C). 82% men,18% women. Mean (SD) age 61.9 (11.6) years.	20 weeks of prespecified good standard care alone or care plus weekly application of 3C Patch.	Primary outcome: Proportion of ulcers that healed within 20 weeks (defined as complete epithelialisation without drainage, confirmed by a trained observer masked to randomisation group, and remained healed for 4 weeks). Secondary ulcer-related outcomes: • Time to healing • Proportion of healed ulcers at 12 and 26 weeks • Change in ulcer area at 4, 12, 16, 20, and 26 weeks (compared to week 0; assessed from digital images of acetate tracings) • Incidence of secondary infection • Number of days of systemic antibiotic therapy administered for infection of the foot ulcer during the 20 weeks after randomisation.	Primary outcome: In the ITT population, healing within 20 weeks in 34% of the intervention group versus 22% in the standard care group: OR 1.58 (95% CI 1.04-2.40), p=0.0235. Secondary outcomes: In ITT population time to healing in intervention group compared to standard care group: hazard ratio 1.709 (95% CI 1.071-2.728); p=0.0246. See figure 5.1 in the assessment report. In subgroup of those with a healed ulcer within 20 weeks: median time to healing 72 days (IQR 56–103) in the intervention group (n=45) and 84 days (IQR 64-98) in the standard care group (n=29; p=0.0343). Change in ulcer areas (in ITT population) significantly	In the standard care group: 1 lost to follow-up, 1 withdrawal of consent and 1 randomised in error. No withdrawals in 3C Patch group.	Company funded	High quality, multi-centre, RCT mostly done in the UK. The inclusion criteria were more restrictive than in the instructions for use document. This includes participants having a baseline HbA1c of 12% (108 mmol/mol) or less. The study was funded by the company and 2 investigators had also received research funding from them.

			<u>Secondary patient-related outcomes:</u> • Amputation incidence (major or minor affecting the target limb or contralateral limb by 12, 20, and 26 weeks) • Quality of life measured using Short Form-12 and EQ-5D at baseline, week 12, and week 20 • Pain measured by a visual analogue scale.	better in 3C patch group (p=0.0168). See figure 5.2 in assessment report. No significant difference in the rates of infections, antibiotic therapy, amputations, revascularisations, pain reduction, AEs or serious AEs between the groups HRQoL in subgroup of 18 people with ulcer extending into tendons (reported in Londahl et al, 2019). 20-week follow-up visit, 4 (40%) of the participants in 3C Patch group improved at least one level in the EQ-5D dimension of "usual activities" (p=0.046) and 3 (30%) at least one level in "mobility" (not significant) compared to baseline. No improvements in any of the five EQ-5D health-related quality of life dimensions in control group.			
Abbreviations used: CI - confidence interval; EQ-5D - EuroQol 5 dimensions; HbA1c - glycated haemoglobin; HRQoL – health related quality of life; IQR - interquartile range; ITT - intention-to-treat; OR - odds ratio; RCT - randomised controlled trial; SD – standard deviation Source: adapted from EAC report table 5.2 and 5.3							

4.2 Summary of economic evidence

The company conducted a systematic literature review and included 1 study within its economic review. This was the RCT published by Game et al. (2018). The EAC does not agree with the inclusion of this study as it does not report any cost or economic outcomes. The EAC was unable to replicate the searches conducted by the company. They conducted their own literature search to identify evidence. No economic studies met the EAC's inclusion criteria.

The trial protocol for the RCT published by Game et al. (2017) reports a plan to undertake a cost-effectiveness and cost-utility analysis. The EAC obtained a copy of the associated unpublished health economic report (Farr et al., Unpublished). The report meets the EAC's selection criteria and was included.

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De novo analysis

The company's economic analysis is based on a Markov model which estimates costs and quality-adjusted life years associated with the use of 3C Patch plus standard care versus standard care alone. The analysis takes account of the impact of each treatment option on the likelihood of healing, re-ulceration, major amputation, minor amputation and death over a 2-year time horizon. The population included in the model is people with hard-to-heal ulcers that have not responded to standard care, including advanced

dressings where appropriate. The comparator is standard wound care which includes conventional and advanced wound dressings. The model cycle length is 1 week with no half cycle corrections. There is a weekly probability of remaining in a state or moving to a different state.

A diagram of the company's model structure is shown below (figure 1) which is also presented in the company's submission (appendix B). The EAC judged the diagrams presented by the company to accurately reflect the model submitted, however, notes that the arrows denoting patients being able to remain in health states have been missed from the diagram. People can remain in all health states with the exception of minor and major amputation which are tunnel states.

For each of the health states, cost and utility values are assigned and applied to the proportion of people in that state each week.

A number of key assumptions are made in the model, these include:

- only those whose ulcers have reduced in area by 50% or more after 5 weeks continue to receive 3C Patch. If they continue with 3C Patch, it would be until healing or up to 20 weeks if healing does not happen.
- those having 3C Patch have weekly clinic visits (as opposed to fortnightly visits in the standard care arm) where clinicians decide whether to apply a new patch.
- if 3C Patch treatment is stopped, good standard care is given, as for those in the standard care arm of the model.

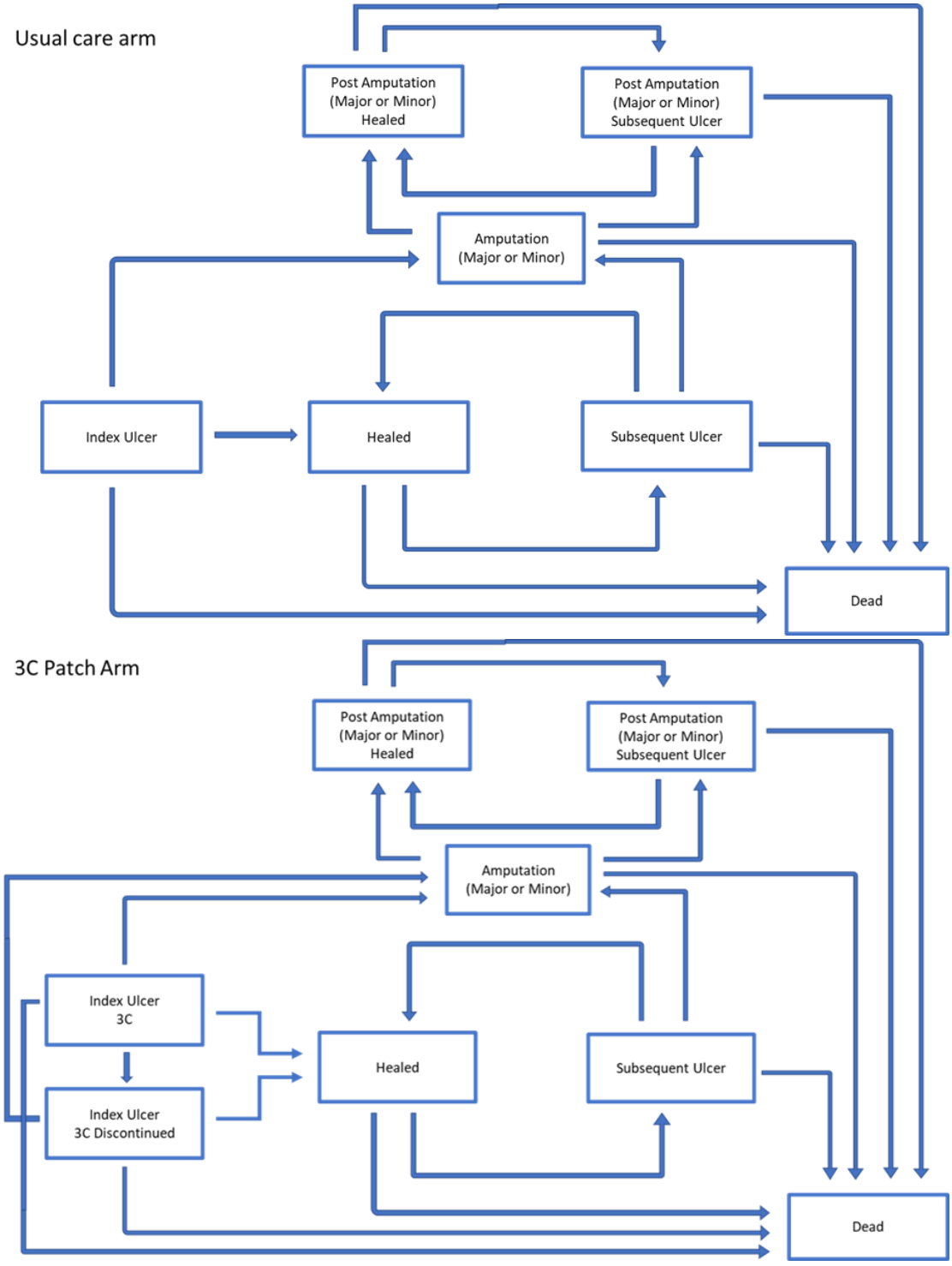
Overall, the EAC judge the company's model structure to be appropriate. However, they identified that the company's stopping rule was problematic because of the issues highlighted by clinical experts regarding implementation of such a precise cut off (discussed in section 2.4) and because the rule was not used in the Game et al. (2018) RCT. The EAC note that in the company model, an unplanned post hoc analysis of the trial data was used to calculate the proportion of people with less than 50% reduction in ulcer area at 5 weeks

and it assumed these people (around 58% of those entering the model) would discontinue use of 3C Patch and receive standard dressings. The EAC highlighted that there is currently no evidence available that shows what would happen to such a cohort of patients (i.e. patients that do not see a more than 50% reduction in ulcer area and then discontinue use of the 3C Patch). As a result, the EAC base case assumes that everyone in the treatment arm continues 3C Patch treatment until healing or for 20 weeks. The EAC has, however, retained the structural functionality to vary the discontinuation rates used in the model and tested the impact of using different discontinuation rates with sensitivity analysis.

The EAC also highlighted that no health state for infection was included in the model, although costs of antibiotics were included. This meant that those with an infection during 3C Patch use would continue using the patch. There were conflicting views on whether this reflects clinical practice. In the Game et al. (2018) RCT, those with an infection continued to receive 3C Patch. Two clinical experts agreed with this. However, 5 clinical experts stated that they would stop 3C Patch use, with 1 expert saying it would depend on the extent of infection and that they would discontinue if the infection was moderate or severe. The UK IFU for 3C Patch states that there is no evidence on the use of 3C Patch in those with an actively infected wound. Further to this, the EAC judged that additional costs would be incurred as a result of an infected ulcer, such as additional appointments, which may not be fully captured within the company's model. As a result, the EAC made a second version of its model with a revised structure (EAC model version B) that included a 'moderate or severe infection' health state. This allowed the EAC to model a pathway where people with moderate or severe infections discontinue use of the 3C Patch whilst their ulcer is infected. The EAC used the total number of days of antibiotics reported as a proxy for the number of days infected. The same probability of an infected ulcer becoming uninfected was applied to both treatment groups.

The EAC also applied a half cycle correction in their model, although they state that this change would have had negligible impact on the results.

Figure 1: Company model structure



Clinical parameters

The EAC assessed the clinical parameters used by the company and made a number of changes to the values used in the economic model. The key changes are listed in table 4 with a full table (table 9.5) in the assessment report.

Overall, the EAC disagrees with the high 3C Patch discontinuation rate used in the company's model. They acknowledge that clinical judgement will likely determine whether 3C Patch treatment is continued. However, the published trial data did not include discontinuation of the patch. As a result, the EAC has aligned its base case model with the trial data (0% discontinuation) and explores various discontinuation rates in sensitivity analysis.

Additionally, the EAC had concerns about the company's use of a post hoc analysis of the Game et al. (2018) RCT to calculate different probabilities of healing for weeks 1 to 5, weeks 6 to 20 and week 21 onwards. The EAC noted that the probability of healing with 3C Patch in weeks 6 to 20 is a key driver in the company model and a fairly small reduction (approximately 0.6%) could result in the direction of the results changing in their model. As a result, the EAC revised the model to use healing probabilities based on the published RCT data. The transition probabilities were still applied for weeks 0 to 5, weeks 6 to 20 and week 21 onwards in line with the company's model structure.

The EAC have also calculated probabilities associated with the additional infection health state included in its model based on the Game et al. (2018) trial, using data on serious adverse events and the number of antibiotic days reported.

Table 4: Clinical parameters used in the company's model and EAC changes

Variable	Company value	EAC value
Discontinuation of 3C Patch at 5 weeks	57.9%	0%
Weekly probability of healing with 3C Patch	Weeks 0 to 5: 0.6% Weeks 6 to 20: 5.7% Week 21 onwards: 1.3%	**Model A** Weeks 0 to 5: 0.8% Weeks 6 to 20: 2.7% Week 21 onwards: 1.3% **Model B**

Variable	Company value	EAC value
		Weeks 0 to 5: 0.8% Weeks 6 to 20: 3.0% Week 21 onwards: 1.3%
Weekly probability of healing with standard care	Weeks 0 to 5: 0.8% Weeks 6 to 20: 1.4% Week 21 onwards: 1.3%	**Model A** Weeks 0 to 5: 0.6% Weeks 6 to 20: 1.5% Week 21 onwards: 1.3% **Model B** Weeks 0 to 5: 0.6% Weeks 6 to 20: 1.7% Week 21 onwards: 1.3%
Weekly probability of healing with 3C Patch discontinued	Weeks 6 to 20: 0.7% Week 21 onwards: 1.3%	Not used in base case. Assumed equal to standard care for sensitivity analysis.
Weekly probability of moderate/severe infection with 3C Patch	NA	**Model B only** 1.99%
Weekly probability of infection with standard care	NA	**Model B only** 1.49%
Weekly probability of infected ulcer becoming uninfected	NA	**Model B only** 9.5%
Abbreviations: NA- not applicable Source: adapted from EAC report table 9.5		

Costs and resource use

The EAC reviewed the company costs and changed almost all of them, including changing the costs of dressings from BNF prices to supply chain costs and adjusting number and length of visits as well as the proportion of people in which procedures are applied. The EAC's changes fell into two categories (a) necessary corrections of mathematical errors, and (b) updates to specific inputs to reflect the EAC's preferred sources of cost data. In terms of the changes that fall into category b, the EAC's costs are largely informed by the unpublished Farr et al. study that it identified in its literature review (see 4.2), whereas the company's inputs were mostly informed by a different study (Kerr et al. 2019).

The full list of changes can be found in tables 9.6 to 9.8 of the assessment report. The changes the EAC made affect both arms of the model. The costs that differ the most across the company and EAC models are those that relate to inpatient costs, infection costs and outpatient costs and consequently the costs for the unhealed ulcer state

- The company costs for unhealed ulcer state are £346.94 (3C Patch); £176.65 (standard care); difference £170.29.

- The EAC costs for the unhealed ulcer state are: £358.22 (3C Patch) and £250.65 (standard care); difference £107.

The changes made by the EAC, particularly the uplifted unhealed ulcer standard care arm costs, have a substantive effect on the results of the analysis.

Health-related quality of life

The EAC thought that utility values used by the company (from Ragnarson Tennvall and Apelqvist, 2000) have several limitations. Specifically, relatively few people had an amputation and the respondents were older (mean age of 67 at diagnosis of a DFU) than those included in Game et al. (2018; mean age of 62 years). The study population was in Sweden, which could limit the validity and generalisability to the UK population. The EAC identified a study by Redekop et al. (2004) which had 13 health states based on the presence or absence of DFU and amputation as well as reporting utility scores for infected and non-infected health states. These reported values were adopted in the modelling informing the NICE guideline (NG19) for DFUs. The EAC therefore used the utility values from this study in their evaluation

Results

The company's base case results show cost savings of £191 per person over 2 years when 3C Patch is used instead of standard care (table 5). Conversely, the EAC's base case results show that 3C Patch is cost incurring compared with standard care by £1,590 per patient over 2 years when modelled without an infection state (model A) and £1,993 when modelled with an infection state (model B).

The EAC note that the difference in the estimates derived from the EAC model compared with the company model can largely be attributed to:

- the EAC's preferred healing rate and lack of discontinuation with 3C Patch (in line with the RCT)

- the more modest difference in weekly cost of an unhealed ulcer with 3C Patch versus standard care (which was significantly affected by the changes the EAC made to the standard care arm costs).

The EAC changes to the cost inputs led to an increase in the overall cost of 3C Patch of around £800 in EAC model A. The impact of specific cost changes, with and without corresponding changes to the clinical parameters, are shown in an addendum to the EAC report. Further to this, changing the discontinuation and healing rates to align with the Game et al. (2018) RCT data increased the cost of 3C Patch by around £370 (EAC model A).

The company base case estimates that using 3C Patch will result in a QALYs gain of 0.0155 over the same time horizon. The EAC's estimates of the QALY gain of 0.018 and 0.013 in model A and B respectively.

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Table 5: 3C Patch compared to standard care

Cost category	Company's base-case				EAC's base-case (model A: without infection state)			EAC's base-case (model B: with infection state)		
	Device	Comparator	Difference*		Device	Comparator	Difference*	Device	Comparator	Difference*
Index ulcer (includes 3C Patch cost)	£11,144	£11,331	£187		£9,339	£7,711	-£1,628	£7,258	£6,046	-£1,212
Regular assessment for those whose ulcers have healed	£148	£128	-£20		£362	£300	-£62	£344	£289	-£55
Subsequent ulcers	£971	£867	-£103		£556	£451	-£105	£450	£371	-£80
Infection	Not applicable				Not applicable			£1,417	£741	-£676
Major amputation	£376	£411	£34		£341	£392	£52	£440	£454	£14
Minor amputation	£779	£851	£71		£685	£788	£104	£858	£886	£28
Post amputation costs	£255	£278	£22		£382	£432	£49	£450	£437	-£13
Total	£13,674	£13,865	£191		£11,664	£10,074	-£1,590	£11,217	£9,225	-£1,993
QALYS	0.8958	0.8803	0.0155		1.326	1.308	0.018	1.313	1.300	0.013

** A minus sign indicates device is more expensive than the comparator in this cost category.*

Sensitivity analysis

The company presented 4 scenario analyses, which were predominantly associated with cost changes. These included:

- varying the weekly quantity of 3C Patches by 10%
- increasing staff costs from band 4 to band 6 for those undertaking phlebotomy and centrifuge operation
- decreasing district nurse visits to 0 for those on 3C Patch
- increasing the weekly probability of healing for those who have discontinued 3C Patch to account for some benefit with the 3C Patch prior to discontinuation.

In all the scenarios presented 3C Patch remained cost saving, with savings ranging from £82 (10% more patches per week of treatment) to £360 (0.5 mean district nurse dressing change visits per week for 3C Patch). The EAC judged that the scenarios were appropriate but noted that none of the scenarios varied the probability of discontinuation or healing with 3C Patch. They thought that this would have been appropriate given the uncertainty in the reduced trial data used in the economic model. The company also presented probabilistic sensitivity analysis for 10,000 iterations of the model, which reported mean probabilistic cost savings of £192 per patient over a 2-year time horizon. Whilst the EAC judged the distributions to be appropriate, they could not assess the sources used for the measures of variation.

The EAC conducted its own sensitivity analyses. Their deterministic sensitivity analysis found that the probability of discontinuing 3C Patch and the cost of index ulcers for both 3C Patch and standard care or 3C Patch discontinued were key drivers of the analysis in both model A and B.

The EAC did threshold analysis on the key cost drivers to estimate the change in these inputs required to change the direction of the results in the model. The results are shown in table 9.14 of the assessment report. Overall, the

EAC deemed that in order for 3C Patch to be cost saving, 3C Patch would have to save a significant amount on inpatient and outpatient care in relation to standard care or for the patch to be considerably cheaper to purchase. For model B, the cost of 3C Patch would need to be negative due to the increase in resources, particularly outpatient appointments, needed with the use of 3C Patch.

The EAC also conducted probabilistic sensitivity analysis. Their model was run for 2,000 iterations and resulted in an average cost increase per person of £1,459 in model A (without infection health state) and £1,858 in model B (with infection health state). There is an estimated probability that the intervention is cost saving is 31% in model A and 25% in model B.

The EAC conducted 2 two-way sensitivity analyses that simultaneously varied healing rates and treatment discontinuation rates. This was to reflect the fact that these are some of the most uncertain parameters in the EAC model and there is likely to be interaction between them. These analyses suggest that if clinicians continue with 3C Patch when weekly healing rates are under 4.5%, then 3C Patch will be cost increasing. This is thrice the healing rate observed with standard care (1.5%). Some clinicians have indicated they will continue with 3C Patch if *any* improvement on standard care rates is observed.

These analyses also demonstrated that when the company assumptions on discontinuation and healing rates were used in the EAC model, 3C Patch was cost incurring (figures 9.4 to 9.7 of the assessment report). This means that the costs changed by the EAC were sufficient to change the direction of predicted cost savings. At NICE's request, the EAC also assessed the impact of using the company costs with the EAC's preferred discontinuation and healing rates. The EAC confirmed in correspondence with NICE that 3C patch remains cost incurring (by £168 per person) in this scenario.

Overall, the EAC note that the key uncertainties with the economic model reflect the uncertainties in the clinical evidence. These uncertainties relate to how 3C Patch will be used in practice. Specifically, the proportion of people who will continue with the 3C Patch after 5 weeks, which factors would

determine 3C Patch discontinuation, and what the subsequent probability of healing will be with or without 3C Patch use.

5 Ongoing research

The company and the EAC identified 1 ongoing study (NCT03997526) in which the population, intervention, comparator and outcomes meet the scope. This study is a prospective observational study of 2680 people with hard-to-heal diabetic foot ulcers compared to a historical control group being done in the US. Further details are listed in appendix D of the EAC's assessment report.

6 Issues for consideration by the Committee

Clinical evidence

Proposed use of the technology

1. Clinical experts have raised concerns about the assumptions the company have made about how 3C Patch will be used in practice. The concerns relate to how people are selected for treatment, the feasibility of implementing any hard stopping rules for treatment based on level of response, and practical challenges (need for weekly blood sampling, more frequent and longer appointments). Therefore, is the clinical pathway suggested by the company appropriate? How is 3C Patch likely to be used in practice? The committee should consider:

    - the clinical characteristics (ulcer size, ulcer duration, disease status, comorbidity status, infection status etc.) of people who could be offered treatment with 3C Patch in the NHS

    - what other treatments people in this group are currently receiving (and will continue to receive if 3C Patch is not recommended)

    - how long people should be treated with 3C Patch in practice and what should inform the decision to stop treatment.

Evidence of clinical effectiveness:

2. The main evidence presented by the company on the clinical effectiveness of 3C Patch comes from the Game et al. (2018) RCT. This study was predominantly done in the UK and is at low risk of bias. However, the EAC have raised concerns about the generalisability of the study results to NHS practice (see section 4.1). Taking account that the current standard of care in the NHS now includes UrgoStart, and that the clinical experts state that UrgoStart would always be used prior to commencing 3C Patch, does the Game et al. (2018) trial provide an accurate estimate of the clinical effectiveness of 3C Patch? The committee should consider:

    - The clinical characteristics of the people included or excluded from the trial
    - The percentage of people who received UrgoStart in the run-in period for at least 1 week (0.2%)
    - The percentage of people in the comparator arm that had UrgoStart for at least 1 week of treatment (1%)
    - The treatment continuation in people who had infections
    - Treatment continuation until healing or up to 20 weeks

3. Does the committee believe the benefits observed are clinically significant?

4. The EAC concluded that the current direct trial evidence partially supports the claimed benefits included in the company submission but believes that further high-quality research is needed to assess whether the RCT findings are generalisable to a greater proportion of people with hard-to-heal diabetic foot ulcers. Does the committee agree with these conclusions? If further research is needed to explore the clinical effectiveness of 3C patch, what would be the key components of the study design?

Cost evidence

5. The company model does not include an infection health state. The EAC recognise that there is some diversity of clinical opinion about whether 3C Patch should be used on actively infected wounds. For this reason it has provided 2 base case models, one without an infection state (EAC model A) and one with (EAC model B). The company model and EAC model A both assume that patients will continue treatment with 3C Patch if an infection occurs. Conversely EAC model B effectively assumes that all patients with moderate to severe infection discontinue treatment with 3C Patch until the infection resolves. Taking account of its response to consideration 1 above and the EAC's comments, does the committee believe that EAC model B provides a more realistic representation of how 3C Patch would be used in practice?

6. The company assumed that 58% of 3C Patch users would discontinue use after 5 weeks. This discontinuation rate was based on the proportion of patients in the Game et al. (2018) trial that did not achieve a 50% or more ulcer area reduction in the first 5 weeks of treatment with 3C Patch. However, in the trial these patients continued to receive treatment (until healing or up to 20 weeks) and expert input has indicated it is unlikely that a strict rule of 50% reduction or more in ulcer area will be adhered to in practice. The EAC changed the discontinuation rate to 0% in both its base case models for consistency with the RCT. Taking account of its response to consideration 1 above and the EAC's comments, does the committee believe it is appropriate for the economic model to include a treatment stopping rule? If it is appropriate, is it appropriate to only use changes in ulcer area as the main criteria for stopping treatment? If not, how should treatment duration be determined?

7. The company used data from an unplanned, post hoc analysis from Game et al. (2018) data to estimate the healing rates used in the

model. The EAC have concerns about the use of this data (see 'clinical parameters' above) and chose to use the published data for the ITT population to inform the healing rates included in its base case. Which is the most appropriate data source for the model healing rates?

8. The EAC also changed various cost parameters, particularly for inpatient and outpatient costs. It's approach to costing involved (a) correcting mathematical errors in the company's model and (b) updating specific inputs to reflect the EAC's preferred sources of cost data. Does the committee accept the both the corrected and preferred costs?

9. The company and EAC have reached fundamentally different conclusions about the best way to model the cost impact of using 3C Patch. As a result of this, the results from the EAC and company models differ greatly with the company predicting cost savings, whereas the EAC assert that 3C Patch treatment is likely to be cost incurring. Taking account of its response to considerations 1 to 8 above, does the committee consider estimates of cost savings derived from the company model to be robust?

10. The EAC's model adjusted some cost parameters and adopted the efficacy data reported in the RCT. It found 3C Patch to be cost incurring even with the discontinuation rates adopted by the company, meaning it's changes to the costs alone are enough to change the direction of the results. The EAC acknowledge that neither the EAC or the company model can claim to be representative of expected clinical practice but assert that the PSA results using the EAC's values suggest that there is a lot of uncertainty around the economic case and these do not support the case for adopting 3C Patch. Does the committee agree with this conclusion?

7 Authors

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NICE Medical Technologies Evaluation Programme

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Appendix A: Sources of evidence considered in the preparation of the overview

A Details of assessment report:

- Green M et al. 3C Patch System for treating diabetic foot ulcers, May 2021.

B Submissions from the following sponsors:

- Reapplix APS

C Related NICE guidance

- Diabetic foot problems: prevention and management NICE guideline NG19 (2019). Available from https://www.nice.org.uk/guidance/ng19
- V.A.C. VERAFLO Therapy System for acute infected or chronic wounds that are failing to heal. NICE medical technologies guidance MTG54 (2020). Available from https://www.nice.org.uk/guidance/MTG54
- Leg ulcer infection: antimicrobial prescribing. NICE guideline NG152 (2020). Available from https://www.nice.org.uk/guidance/ng152
- UrgoStart for treating diabetic foot ulcers and leg ulcers. NICE medical technologies guidance MTG4 (2019). Available from https://www.nice.org.uk/guidance/mtg42
- The MIST Therapy system for the promotion of wound healing. NICE medical technologies guidance MTG5 (2011). Available from https://www.nice.org.uk/guidance/mtg5

D References

AHSN Network. (2019) National Wound Care Strategy Programme [Online]. Available: https://www.ahsnnetwork.com/about-academic-health-science-networks/national-programmes-priorities/national-wound-care-strategy-programme [Accessed 20th May 2021].

Armstrong, D. G., Boulton, M. D. & Bus, S. A. (2017) Diabetic foot ulcers and their recurrence. NEJM, 376, 2367-75.

BNF. (2021) BNF [Online]. NICE. Available: https://bnf.nice.org.uk/ [Accessed].

Curtis, L. & Burns, A. (2020) Unit costs of health & social care 2020. Kent: PSSRU, University of Kent.

Diabetes.co.uk (2019) Foot Ulcers [Online]. Available: https://www.diabetes.co.uk/diabetes-complications/diabetic-foot-ulcers.html [Accessed 20th May 2021].

EAC correspondence log (2021). Correspondence log for MT539 3C Patch System for treating DFUs.

[redacted]

Game, F., Jeffcoate, W., Tarnow, L., Day, F., Fitzsimmons, D. & Jacobsen, J. (2017) The LeucoPatch system in the management of hard-to-heal diabetic foot ulcers: study protocol for a randomised controlled trial. Trials, 18, 469.

Game, F., Jeffcoate, W., Tarnow, L., Jacobsen, J. L., Whitham, D. J., Harrison, E. F., Ellender, S. J., Fitzsimmons, D., Löndahl, M. & LeucoPatch I. I. trial team. (2018) LeucoPatch system for the management of hard-to-heal diabetic foot ulcers in the UK, Denmark, and Sweden: an observer-masked, randomised controlled trial. The Lancet Diabetes & Endocrinology, 6, 870-878.

Hogh, A., Andersen, J. W. & Dashnaw, B. (2019) The effect of autologous blood patch treatment among patients with hard-to-heal wounds; a clinical perspective. European Journal of Vascular and Endovascular Surgery, 58, e751-e752.

Jørgensen, B., Karlsmark, T., Vogensen, H., Haase, L. & Lundquist, R. (2011) A pilot study to evaluate the safety and clinical performance of Leucopatch, an autologous, additive-free, platelet-rich fibrin for the treatment of recalcitrant chronic wounds. International Journal of Lower Extremity Wounds, 10, 218-23.

Katzman, P., Fagher, K., Lundquist, R. & Löndahl, M. (2014) Treatment of hard-to-heal diabetic foot ulcers probing to bone with leucopatch, a leukocytes and platelet rich fibrin patch. Diabetes, 63, A581.

Kerr, M., Barron, E., Chadwick, P., Evans, T., Kong, W. M., Rayman, G., Sutton-Smith, M., Todd, G., Young, B. & Jeffcoate, W. J. (2019) The cost of

diabetic foot ulcers and amputations to the National Health Service in England. Diabetic Medicine, 36, 995-1002.

Kerr, M., Rayman, G. & Jeffcoate, W. J. (2014) Cost of diabetic foot disease to the National Health Service in England. Diabet Med, 31, 1498-1504.

Löndahl, M., Tarnow, L., Karlsmark, T., Lundquist, R., Nielsen, A. M., Michelsen, M., Nilsson, A., Zakrzewski, M. & Jørgensen, B. (2015) Use of an autologous leucocyte and platelet-rich fibrin patch on hard-to-heal DFUs: a pilot study. Journal of Wound Care, 24, 172-4, 176-8.

National Institute for Health and Care Excellence (2015a) Diabetic foot problems: prevention and management NICE guideline. London. www.nice.org.uk/guidance/ng19

National Institute for Health and Care Excellence (2015c) Wound care products. London. https://www.nice.org.uk/advice/ktt14

National Institute for Health and Care Excellence (2019) UrgoStart for treating diabetic foot ulcers and leg ulcers. London. https://www.nice.org.uk/guidance/mtg42

NHS Business Services Authority. (2021) Drug tariff [Online]. Available: https://www.nhsbsa.nhs.uk/pharmacies-gp-practices-and-appliance-contractors/drug-tariff [Accessed].NHS England. (2019) National cost collection for the NHS [Online]. Available: https://www.england.nhs.uk/national-cost-collection/ [Accessed 21st May 2021].

NHS Supply Chain. (2021) NHS Supply Chain [Online]. Available: https://www.supplychain.nhs.uk/ [Accessed].

Ragnarson Tennvall, G. & Apelqvist, J. (2000) Health-related quality of life in patients with diabetes mellitus and foot ulcers. Journal of Diabetes & its Complications, 14, 235-41.

[redacted]

Redekop, W. K., Stolk, E. A., Kok, E., Lovas, K., Kalo, Z. & Busschback, J. J. V. (2004) Diabetic foot ulcers and amputations: estimates of health utility for use in cost-effectiveness analyses of new treatments. Diabetes Metab, 30, 549-56.

[redacted]

Appendix B: Comments from professional bodies

Expert advice was sought from experts who have been nominated or ratified by their Specialist Society, Royal College or Professional Body. The advice received is their individual opinion and does not represent the view of the society.

Mrs Joanne Thorpe
Lead Diabetes and Endocrinology Research Nurse, Bradford Teaching Hospitals NHS Trust

Ms Alison Musgrove
Advanced Podiatrist (Diabetes), Nottingham University Hospitals NHS Trust

Prof Andrew J M Boulton
Consultant Physician (Diabetes), Manchester Royal Infirmary and Professor of Medicine, University of Manchester

Prof Frances Game
Consultant Diabetologist and Director of R&D, Royal Derby Hospital, University Hospitals of Derby and Burton NHS FT

Ms Elaine Ricci
Clinical Specialist, South Tyneside and Sunderland NHS Trust

Mr David Russell
Associate Professor and Honorary Consultant Vascular Surgeon, University of Leeds

Ms Rachel Berrington
Senior Diabetes Nurse Specialist, University Hospitals of Leicester NHS Trust

Dr Paul Chadwick
Podiatrist, Salford Royal Infirmary, Salford Royal NHS Foundation Trust, Clinical Director Royal College of Podiatry, and Visiting Professor Birmingham City University

Professor Edward Jude
Consultant in Diabetes & Endocrinology at Tameside Hospital NHS Foundation Trust

Please see the clinical expert statements included in the pack for full details

Appendix C: Comments from patient organisations

Advice and information was sought from patient and carer organisations.

The following patient organisations were contacted and no response was received.

- British Skin Foundation (BSF)
- Leg Ulcer Charity
- Pressure Ulcers UK
- Leonard Cheshire disability
- Diabetes UK
- Foot in Diabetes UK
- MRSA Action UK
- The Lindsay Leg Club Foundation
- Juvenile Diabetes Research Foundation
- Diabetes Research & Wellness Foundation
- InDependent Diabetes Trust
- Limbless Association
- The Circulation Foundation

Appendix D: decision problem from scope

Population	People with diabetic foot ulcers that are not healing despite standard wound care
Intervention	3C Patch
Comparator(s)	Standard conventional and advanced wound dressings for diabetic foot ulcers, including UrgoStart. Standard care is likely to vary depending on the characteristics of the wound (size, depth, and position) and stage of healing.

Outcomes	The outcome measures to consider include:
	• measures of treatment effectiveness and wound healing, for example:
	  ○ proportion of people with complete epithelialisation or healing
	  ○ time to complete epithelialisation or healing
	  ○ change in ulcer area
	• complications related to non-healing wounds, for example:
	  ○ incidence of wound-related complications (including new infection)
	  ○ number of new amputations
	  ○ pain at ulcer location
	  ○ frequency and amounts of antibiotic or pain medication requirements
	• device-related adverse events
	• patient-reported outcomes, for example:
	  ○ patient tolerance and acceptability
	  ○ health related quality of life
	• measures of resource use
	  ○ total number of 3C Patch treatments needed
	  ○ frequency and total number of secondary dressing changes
	  ○ demand for NHS diabetic foot ulcer care – outpatient, community, primary care and inpatient care

Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be long enough to reflect differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.
Subgroups to be considered	None identified.
Special considerations, including those	3C Patch requires blood to be taken weekly and may not be suitable for people who are unable to provide blood samples, including people with trypanophobia (fear of needles). 3C Patch is

related to equality	intended for people with diabetes. In some cases, diabetes can be considered a disability. People of South Asian, African and African Caribbean family origin are more at risk of diabetes, however there is no evidence that the prevalence of diabetic foot ulceration and amputation is higher in these subgroups than in the general population of people with diabetes in the UK. Disability and race are protected characteristics under the 2010 Equalities Act.	
Special considerations, specifically related to equality	Are there any people with a protected characteristic for whom this device has a particularly disadvantageous impact or for whom this device will have a disproportionate impact on daily living, compared with people without that protected characteristic?	No
	Are there any changes that need to be considered in the scope to eliminate unlawful discrimination and to promote equality?	No
	Is there anything specific that needs to be done now to ensure the Medical Technologies Advisory Committee will have relevant information to consider equality issues when developing guidance?	No
Any other special considerations	Not applicable.	

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technology guidance scope

3C Patch for treating diabetic foot ulcers

1 Technology

1.1 Description of the technology

3C Patch (Reapplix) is a single-use medical device that makes an autologous biological patch from a patient blood sample. The patch is used as part of wound care for foot ulcers in people with diabetes.

Each 3C Patch device is sold as part of a kit that contains one each of the following:

- 3C Patch device
- 3C Patch needle holder
- winged blood sampling set (G21) with protector
- primary cover dressing (Tricotex)
- alcohol swab (for disinfection of the skin before needle insertion)
- post blood sample adhesive bandage
- ruler with adhesive

The 3C Patch device is used in combination with the 3CP centrifuge (together the device and the centrifuge are referred to as the 3C Patch system). The 3CP centrifuge is provided on loan by the company free of charge. Servicing and maintenance of the 3CP centrifuge are also free of charge and the expected lifespan of the centrifuge is at least 7 years.

To make the autologous biological patch, a small sample of the patient's peripheral blood is drawn directly into the 3C Patch device. The device is then placed in the 3CP centrifuge and spun for about 20 minutes. This process results in a disc-shaped layered matrix of fibrin, leukocytes and platelets forming without the need for any additional reagents. The patch is applied directly to the ulcer and kept in place with a non-adhesive dressing. A separate secondary dressing can also be used to manage exudate. The treatment lasts 7 days, during which time the patch dissolves. According to the instructions for use, 3C Patch is used once a week for up to 20 weeks, at the discretion of the treating healthcare practitioner. The company recommends using 3C Patches for 4 weeks to 6 weeks initially and then to continue only in those patients who show improvement.

1.2 Relevant diseases and conditions

The 3C Patch is intended to treat hard-to-heal diabetic foot ulcers that have not responded to standard wound care. Hard-to-heal diabetic foot ulcers are often considered as those that have not shown substantial healing (reduction in size by 50% or more) after 4 weeks of treatment.

It is estimated that more than 3.9 million people are living with a diagnosis of diabetes in the UK (2018 to 2019, Diabetes UK). Foot complications such as diabetic foot ulcers are common in people with diabetes. According to Diabetes UK, it is estimated that 1 in 20 people with diabetes will develop a foot ulcer each year, and of these, more than 1 in 10 will ultimately need amputation. Even after the resolution of a foot ulcer, subsequent foot ulcers are common. Roughly 40% of people with a foot ulcer will have a recurrence within 1 year after ulcer healing, almost 60% within 3 years, and 65% within 5 years (Armstrong et al. 2017).

Foot problems in people with diabetes have a significant financial impact on the NHS. A study published in 2019 reported that during 2014 to 2015, between £837 million and £962 million was spent on managing foot ulcers or undertaking amputations in people with diabetes in England, representing 0.8% to 0.9% of the country's NHS budget. Ulceration equated to 90% of

expenditure, and data suggests it is associated with increased length of hospital stay (by around 8 days) compared to that for diabetes-related admissions without ulceration (Kerr et al. 2019).

1.3 Current management

The aims of treatment for diabetic foot ulcers are to dress and protect the ulcer, to prevent or treat any infection and to promote healing. NICE's guideline on the prevention and management of diabetic foot problems recommends that diabetic foot ulcers are assessed by a healthcare professional, who should record the size, depth and position of the ulcer and refer the person to a diabetic foot protection team for assessment of the wound.

The guideline also recommends that one or more of the following is offered to people as standard care for treating diabetic foot ulcers:

- Offloading (interventions to reduce the amount of weight placed on the foot)
- Control of foot infection
- Control of ischaemia (for example, surgery to bypass the blocked blood vessels to restore blood circulation to the affected area)
- Wound debridement (removal of dead or infected tissue or foreign objects from the wound)
- Wound dressings

NICE's medical technologies guidance on UrgoStart for treating diabetic foot ulcers and leg ulcers recommends that UrgoStart dressings should be considered as an option for people with diabetic foot ulcers after any modifiable factors such as infection have been treated.

Negative pressure wound therapy may also be considered after surgical debridement for diabetic foot ulcers, on the advice of the multidisciplinary foot care service. It is also recommended that clinical assessment and patient preference should inform dressing choices but that healthcare professionals should choose the lowest cost dressing that is likely to achieve the desired results.

NICE advice states that there is not enough evidence to determine if advanced dressings (such as alginate, film, foam, hydrocolloid and hydrogel dressings) are more clinically effective than conventional dressings for treating wounds. It also states that there is not currently robust evidence supporting the use of antimicrobial dressings (such as silver, iodine or honey) over non-medicated dressings for treating chronic wounds. Patients with diabetic foot ulcers are treated in community, hospital and primary care settings.

1.4 Regulatory status

3C Patch device received a CE mark in December 2009 (updated in December 2019) as a Class IIa device. The 3CP centrifuge is CE marked as a laboratory centrifuge.

1.5 Claimed benefits

The benefits to patients claimed by the company are:

- Heals more wounds and reduces wound healing time
- Helps to avoid wound-related complications, including amputation and infection, reducing the need for further treatment
- Improved quality of life through reduced ulcer duration and the avoidance of complications, enabling people to return to activities of daily living sooner and avoid long term reduction in quality of life

The benefits to the healthcare system claimed by the company are:

- Reduced demand for ulcer care, across all care settings
- Reduced need for follow-on treatment including amputation and associated rehabilitation
- Reduced overall costs associated with treating hard-to-heal diabetic foot ulcers

2 Decision problem

Population	People with diabetic foot ulcers that are not healing despite standard wound care
Intervention	3C Patch

Comparator(s)	Standard conventional and advanced wound dressings for diabetic foot ulcers, including UrgoStart. Standard care is likely to vary depending on the characteristics of the wound (size, depth, and position) and stage of healing.

Outcomes	The outcome measures to consider include:
	• measures of treatment effectiveness and wound healing, for example:
	  ○ proportion of people with complete epithelialisation or healing
	  ○ time to complete epithelialisation or healing
	  ○ change in ulcer area
	• complications related to non-healing wounds, for example:
	  ○ incidence of wound-related complications (including new infection)
	  ○ number of new amputations
	  ○ pain at ulcer location
	  ○ frequency and amounts of antibiotic or pain medication requirements
	• device-related adverse events
	• patient-reported outcomes, for example:
	  ○ patient tolerance and acceptability
	  ○ health related quality of life
	• measures of resource use
	  ○ total number of 3C Patch treatments needed
	  ○ frequency and total number of secondary dressing changes
	  ○ demand for NHS diabetic foot ulcer care – outpatient, community, primary care and inpatient care

Cost analysis	Costs will be considered from an NHS and personal social services perspective. The time horizon for the cost analysis will be long enough to reflect differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.
Subgroups to be considered	None identified.
Special considerations, including those related to equality	3C Patch requires blood to be taken weekly and may not be suitable for people who are unable to provide blood samples, including people with trypanophobia (fear of needles). 3C Patch is intended for people with diabetes. In some cases, diabetes can be considered a disability. People of South Asian, African and African Caribbean family origin are more at risk of diabetes, however there is no evidence that the prevalence of diabetic foot ulceration and amputation is higher in these subgroups than in the general population of people with diabetes in the UK. Disability and race are protected characteristics under the 2010 Equalities Act.

Special considerations, specifically related to equality	Are there any people with a protected characteristic for whom this device has a particularly disadvantageous impact or for whom this device will have a disproportionate impact on daily living, compared with people without that protected characteristic?	No
	Are there any changes that need to be considered in the scope to eliminate unlawful discrimination and to promote equality?	No
	Is there anything specific that needs to be done now to ensure the Medical Technologies Advisory Committee will have relevant information to consider equality issues when developing guidance?	No
Any other special considerations	Not applicable.	

3 Related NICE guidance

Published

- V.A.C. VERAFLO Therapy System for acute infected or chronic wounds that are failing to heal (2020) NICE medical technologies guidance MTG54
- Leg ulcer infection: antimicrobial prescribing (2020) NICE guideline NG152.
- Diabetic foot problems: prevention and management (2019) NICE guideline NG19.
- UrgoStart for treating diabetic foot ulcers and leg ulcers (2019) NICE medical technologies guidance MTG4.
- The MIST Therapy system for the promotion of wound healing (2011) NICE medical technologies guidance MTG5.

In development

NICE is developing the following guidance:

- Prontosan for acute and chronic wounds NICE medical technology guidance. Publication expected October 2021.

4 External organisations

4.1 Professional

The following organisations have been asked to comment on the draft scope:

- Association of British Clinical Diabetologists
- British Society for Paediatric Endocrinology and Diabetes
- Institute of Chiropodists and Podiatrists
- Primary Care Diabetes Society
- Royal College of Nursing
- Royal College of Physicians
- Royal College of Surgeons
- Society of Chiropodists and Podiatrists
- Society of Vascular Nurses
- The College of Podiatry
- The Welsh Wound Innovation Initiative
- Tissue Viability Society
- Vascular Society of Great Britain & Ireland

4.2 Patient

NICE's Public Involvement Programme contacted the following organisations for patient commentary and asked them to comment on the draft scope:

- British Skin Foundation (BSF)
- Diabetes Research & Wellness Foundation
- Diabetes UK
- Foot in Diabetes UK
- InDependent Diabetes Trust
- Juvenile Diabetes Research Foundation
- Leg Ulcer Charity
- Leonard Cheshire disability
- Limbless Association
- MRSA Action UK
- Pressure Ulcers UK
- The Circulation Foundation
- The Lindsay Leg Club Foundation

NICE National Institute for Health and Care Excellence

Adoption report: MT539 3C Patch System for treating diabetic foot ulcers

Summary

Adoption levers identified by contributors

- Good support for adoption of the 3C patch from consultant clinicians
- Cost not an issue as eligible patient numbers are small
- Could improve wound healing of diabetic foot ulcers
- Could reduce healing time of hard to heal diabetic foot ulcers.

Adoption barriers identified by contributors

- Necessity to take blood from patient
- Only able to use on specific wounds
- Could be more difficult to introduce on a large ward setting
- Training is needed
- Difficulties in using in none fixed settings such as community clinics which can move between different locations.

1 Introduction

The adoption team has collated information from five healthcare professionals working within NHS organisations 3 of whom have experience of using the 3C patch System. It has been developed for the medical technologies advisory committee (MTAC) to provide context from current practice and an insight into the potential levers and barriers to adoption. It does not represent the opinion of NICE or MTAC.

This adoption report includes some of the adoption considerations for the routine NHS use of the technology.

2 Contributors

Details of contributing individuals are listed in the table below.

Job title	Organisation Type	Experience of use
Podiatrist, Clinical Specialist in Diabetes	acute care	Yes
Consultant diabetologist	acute care	Yes
Tissue Viability Nurse	acute care	No
Clinical Lead Podiatrist	acute care	Yes
Podiatry team lead	community care	No

The adoption team spoke to 5 NHS clinicians. All contributors with experience of the technology had been involved in the same clinical trial of the technology. The 3C patch system has subsequently been adopted at 2 of the trial sites. The other user has now left the trial site and was not aware of continued use of the technology.

3 Current practice in clinical area

People with diabetes are at increased risk of developing foot ulcers. Foot ulcer care is usually provided in secondary or community care by podiatrists working as part of or alongside a multidisciplinary team (MDT) foot care service. Contributors reported that treatments offered as standard care for treating diabetic foot ulcers can include offloading, control of foot infection, wound debridement and a range of different wound dressings depending on individual factors. Other considerations when assessing if a wound is hard to heal include diabetes control, vascular supply and adherence to treatment specific information. The choice of treatment, treatment order and consideration of technologies such as the 3C patch are based on ongoing assessment of the wound including infection, size and depth. Most people with diabetic foot ulcers will be required to attend MDT or follow up clinics on a regular basis for assessment and treatment. This can be in an acute or community setting. All the contributors reported clinical practice in line with the NICE guidance on Diabetic foot problems: prevention and management with variations due to local population needs.

4 Use of the 3C patch in practice

Contributors who adopted the 3C patch system into practice, used it with any patients with hard to heal diabetic foot ulcers once other contributing factors (HbA1c

and pressure reduction) had been addressed. They reported low numbers of patients meeting the selection criteria with no more than 3 people receiving this treatment at any one time.

Contributors followed manufacturer instructions and recommendations regarding preparation and use of the 3C patch on appropriate wounds and explained that clinical judgement was needed to ensure appropriate patient selection. Wounds were assessed when the patch was changed and if no improvement was seen, alternative therapies would be considered.

5 Reported benefits

The potential benefits of adopting the 3C patch system, as reported to the adoption team by the healthcare professionals using the technology are:

- Reduction in time to heal of non-healing diabetic foot ulcers. All contributors who used the 3C patch system reported results within a comparatively short time.

6 Insights from the NHS

Phlebotomy

All contributors agreed the main barrier to adoption would be the logistics of getting the blood sample needed to produce the 3C patch in clinic. Contributor locations varied as did the availability of appropriately trained staff.

The small numbers of people eligible for the treatment means that there could be significant cost and time wastage in employing someone specifically for this purpose unless combined with another function within the clinic.

Some contributors reported that obtaining a blood sample can be difficult if there is poor vascular supply. A health care professional experienced in phlebotomy would be needed for this. Contributors reported examples of healthcare staff who would undertake this are Healthcare assistants or Research nurses.

All the podiatrists spoken to either had phlebotomy training or felt they could be upskilled to fulfil this role but had concerns regarding maintaining competency with small numbers of patients and questioned whether all podiatrists would be comfortable taking on this additional role.

Care pathway

All contributors reported the current care pathway to be similar, with an initial focus on ensuring good diabetes control, use of an appropriate dressing, regular review of healing and advice on reducing wound pressure. All reported that if adopted the 3C patch would be an adjunct therapy that would be used either alongside or replacing another technology at the point when the wound had been non-healing for an agreed period. Clinical judgement is needed as diabetic foot ulcers don't progress at the same rate.

Most contributors felt this technology could fit within their current care pathway in a podiatrist led clinic working alongside an MDT.

The tissue viability nurse delivers an inpatient diabetic foot ulcer service, with most people on 1 ward. They considered the introduction of the 3C patch into this environment would be a significant change in practice and a barrier to its use.

Patient selection

All contributors reported that the 3C patch would not be of benefit to all people with diabetic foot ulcers. The contributors who used the 3C patch reported having local patient selection criteria. These were based on company guidance and learning from their experience in the clinical trial, although these were not exclusions in the clinical trial. Some of the additional exclusions reported by the contributors who used the patches included: Not using on ulcers with slough and not using more than 2 patches on one ulcer. The contributors disagreed on whether the 3C patch system was suitable for use on wounds on the heel and between toes. One contributor said it didn't work as well on these areas and another user had not found this to be a problem. It was highlighted that for people taking anti-coagulants, there may be prolonged coagulation times in the centrifuge to make the 3C patch. The impact of

their medication can be managed by altering the time of their appointment to late in the day if they take their medication in the morning.

All contributors reported that to enable adoption in current practice clear criteria and guidance on selection of eligible patients would be beneficial.

Clinician confidence/acceptance

The contributors who had used the 3C patch were confident that it was beneficial to appropriately selected patients. It was noted that a change in care pathway to introduce a technology requiring phlebotomy and centrifugation would be perceived as a barrier to adoption.

Procurement and resource impact

The contributors using the 3C patch had either gained agreement or were in the process of procuring and introducing the 3C patches within routine use. All contributors reported that cost was not considered to be a significant issue as only a small number of patients would be suitable. Savings were anticipated in a reduction of healing time and clinic visits and ultimately in the costs associated with amputation.

Most contributors felt that gaining approval from their internal procurement process would be straightforward if there was sufficient evidence of effectiveness.

Training

All contributors reported that training would be needed on the use of the equipment and patch and the eligibility criteria to successfully introduce into practice.

All contributors with experience of the 3C patch received initial training from the company, in the use of the centrifuge and the patch, which had been sufficient for them to use the 3C patch and that queries were dealt with responsively. The manufacturer training did not cover phlebotomy, and this would need to be provided by the trust.

Reliability

Contributors involved in the clinical trial reported some initial issues with ensuring a useable patch was produced on every occasion, in a timely manner. Following the clinical trial, contributors who had continued to use noted that the centrifuge had been upgraded and further training provided. They reported the upgrade had improved the likelihood of a useable 3C patch being produced.

7 Comparators

There was disagreement between the contributors who had used the 3C patch on whether there was a comparator available. Some users suggested that UrgoStart would be used at the same part of the care pathway whereas the other felt UrgoStart would be used earlier.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technologies guidance

MT539 3C Patch System for treating diabetic foot ulcers

Company evidence submission

Part 1: Decision problem and clinical evidence

Company name	Reapplix APS
Submission date	26th March 2021
Regulatory documents attached	Please list regulatory documents submitted (e.g. CE certificate, instructions for use, etc.) Already submitted: CE certificate for 3C Patch system CE certificate for 3C Patch centrifuge IFU document
Contains confidential information	Yes

Contents

1 Decision problem

	Scope issued by NICE	Variation from scope (if applicable)	Rationale for variation
Population	People with diabetic foot ulcers that are not healing despite standard wound care	People with diabetic foot ulcers that are not healing despite standard wound care including the use of advanced dressings where appropriate	The study by Game (2018b) captured dressing use in the run-in period which is currently unpublished. Analysis of the data indicated that 85% of patients had an advanced dressing in the run-in period (see uploaded document Supplementary Analysis of RCT (Game 2018b) Dataset))
Intervention	3C Patch	None	NA
Comparator(s)	Standard conventional and advanced wound dressings for diabetic foot ulcers, including UrgoStart. Standard care is likely to vary depending on the characteristics of the wound (size, depth, and position) and stage of healing.	None	NA
Outcomes	The outcome measures to consider include: measures of treatment effectiveness and wound healing, for example: • proportion of people with complete epithelialisation or healing • time to complete epithelialisation or healing • change in ulcer	None	NA

	area complications related to non-healing wounds, for example: • incidence of wound-related complications (including new infection) • number of new amputations • pain at ulcer location • frequency and amounts of antibiotic or pain medication requirements device-related adverse events patient-reported outcomes, for example: • patient tolerance and acceptability • health related quality of life measures of resource use • total number of 3C Patch treatments needed • frequency and total number of secondary dressing changes • demand for NHS diabetic foot ulcer care – outpatient, community, primary care and inpatient care		
Cost analysis	Costs will be considered from an NHS and personal social services perspective.	None	NA

	The time horizon for the cost analysis will be long enough to reflect differences in costs and consequences between the technologies being compared. Sensitivity analysis will be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed.		
Subgroups to be considered	None Identified	None	NA
Special considerations, including issues related to equality	3C Patch requires blood to be taken weekly and may not be suitable for people who are unable to provide blood samples, including people with trypanophobia (fear of needles). 3C Patch is intended for people with diabetes. In some cases, diabetes can be considered a disability. People of South Asian, African and African Caribbean family origin are more at risk of diabetes, however there is no evidence that the prevalence of diabetic foot ulceration and amputation is higher in these subgroups than in the general population of people with diabetes in the UK. Disability and race are protected characteristics under the 2010 Equalities	None	NA

	Act.		

2 The technology

Give the brand name, approved name and details of any different versions of the same device (including future versions in development and due to launch). Please also provide links to (or send copies of) the instructions for use for each version of the device.

Brand name	3C Patch
Approved name	3C Patch
CE mark class and date of authorisation	3C patch system, Class IIa medical device, 20-12-2019 Centrifuge, Laboratory centrifuge, 28-12-2020

Version(s)	**Launched**	**Features**
Leucopatch	2011	First device – used for third party lab centrifuge
LeucoPatch	2013	New device lid design – identical outcome
LeucoPatch System	2017	Fully automated centrifuge added to system – Identical device – identical outcome
3C Patch System	2020	New name – Identical system

What are the claimed benefits of using the technology for patients and the NHS?

Claimed benefit	Supporting evidence	Rationale
Patient benefits		
Heals more wounds and reduces wound healing time	Game 2018b Jorgensen 2011 Londahl 2015	In the RCT (Game 2018b) the 3C Patch reduced the time to complete healing and increased the number of healed ulcers compared to standard care and thereby reduced the treatment times and need for continued care. The 2 pilot studies showed that the 3C Patch was an effective treatment for hard-to-heal ulcers some of which were of a long duration.
Helps to avoid wound-related complications, including amputation and infection, reducing the need for further treatment	Game 2018b	Many hard-to-heal ulcers are of very long duration and some never heal. Increased ulcer duration carries increased risk of complications such as amputation, infection and death. In the study by Games 2018b, the 3C Patch reduced the time to heal and increased the number of healed ulcers thereby lowering the risk of wound associated complications. In addition, the number of infections and days on antibiotics were reduced.
Improved quality of life through reduced ulcer duration and the avoidance of complications, enabling people to return	Game 2018b	Multiple studies have indicated that diabetic foot ulcers

to activities of daily living sooner and avoid long term reduction in quality of life		are associated with substantial decrements in quality of life (Tennvall and Apelqvist, 2000). This was also observed in the RCT: EQ5D-3L scores show a mean increase of 0.14 (95% CI 0.05-0.24, p < 0.05) between week 0 and week 20 for patients who became ulcer free during that period.
System benefits		
Reduced demand for ulcer care, across all care settings	Game 2018b	The 3C Patch reduced the time to heal and increased the number of healed ulcers thereby leading to a shorter period of treatment and therefore reduced demand for NHS care across outpatient community, primary and inpatient settings.
Reduced need for follow-on treatment including amputation and associated rehabilitation	Game 2018b	The 3C Patch reduced the time to healing and increased the number of completely healed ulcers which will in turn reduce the risk of ulcer-associated complications including the need for amputation.
Cost benefits		
Reduced overall costs associated with treating hard-to-heal diabetic foot ulcers	Game 2018b Kerr 2019	Increased ulcer healing and reduced ulcer duration will reduce ulcer treatment volumes and complication rates. The weekly outpatient, community and

		primary care costs for ulcer care in 2014/15 was estimated at £162 per ulcerated patient. In addition there are ulcer-related inpatient care and complications such as amputations. The total cost of healthcare for foot ulceration and amputation in diabetes in England was estimated at £837- 962m, 0.8%-0.9% of the total NHS budget.
Sustainability benefits		
Reduced visits	Game 2018b	The 3C Patch reduced ulcer duration and increased the number of healed ulcers thereby leading to a shorter period of treatment and therefore a reduced number of visits.
Reduced numbers of dressings, medication, offloading devices, wheelchairs and single use plastic	Game 2018b	By reducing the need for continued care and thereby lowering the number of complications, the 3C Patch reduced the need for dressings, medications, offloading devices, wheelchairs and single use plastic.

Briefly describe the technology (no more than 1,000 words). Include details on how the technology works, any innovative features, and if the technology must be used alongside another treatment or technology.

The 3C Patch is an autologous biological patch made on site from a person's own blood. The automated process forms a layered matrix of fibrin, leukocytes and platelets, which acts as a concentrated form of cells, growth factors and signalling molecules which actively promotes wound healing. The patch acts to promote healing of the wound through the release of living cells, a plethora of cytokines (including IL-1ra, IL-6, IL-10) and growth factors (including platelet-derived growth factor (PDGF-AB), transforming growth factor B (TGF-β1) and vascular endothelial growth factor (VEGF)). The released cytokines, growth factors and immune cells are known to be involved in immune regulation, an important factor in wound healing. The patch has been shown to promote fibroblast proliferation, endothelial cell growth and keratinocyte growth and migration which contribute to the healing process. Also, in vitro data showed that 3C Patch derived cells are able to develop into collagen producing fibrocytes known to be involved in wound healing (Lundquist 2013, Lundquist 2016). Further, in vitro studies have shown active leukocyte responses from 3C Patch against relevant bacteria (Thomsen 2016). In the 3C Patch RCT, fewer 3C Patch patients than standard care patients developed infections though this difference was not statistically significant (Game 2018b, 39% vs 49%, p=0.2). Infection was also reported in fewer visits for 3C Patch patients than standard care patients (non-significant, p=0.07).

The process of producing a 3C Patch is started by drawing 18ml of a patient's venous blood (using standard blood draw techniques) into the 3C Patch device (a specialised blood collection and processing tube). The tube is placed into the specialised 3C Patch centrifuge and spun for 20 minutes. The innovative 3CP Centrifuge has been developed to further ease the use and clinical implementation of the 3C Patch technology. The centrifuge uses an automatic pre-specified programme that performs all the steps needed to create the patch at the press of a single button. The majority of clinical trials (including Game 2018b) have been done using a manual procedure and a standard lab

centrifuge (specifically an Eppendorf 5702 centrifuge), despite the 3CP Centrifuge being smaller and fully automated the two systems provide identical outcomes (3C Patch).

The 3C Patch is placed leucocyte-side down on the wound, covered with a primary dressing (e.g. Tricotex, Smith and Nephew) and left in place for 7 days to enable the biological factors to interact with the wound. The wound is dressed with a secondary dressing under the discretion of the treating healthcare provider. The secondary dressing can be changed if needed dependent on wound exudate levels. After 7 days, patch material that has not integrated in or been absorbed by the wound and the primary dressing, is removed and the treatment can be repeated. It is recommended that the 3C Patch is used for 4-6 weeks initially to assess its impact on the wound. If there is inadequate improvement in the wound (assessed for example by decrease in wound area), then treatment with the patch should be stopped. For patients whose wounds are responding well, 3C Patch treatment can be continued beyond 4-6 weeks if clinical judgement indicates that this is necessary and likely to result in healing. The IFU states that the patch can be used for up to 20 weeks. However, expert opinion indicates that likely treatment times will be considerably shorter.

Briefly describe the environmental impact of the technology and any sustainability considerations (no more than 1,000 words).

The 3C Patch device is made from precision moulded clinical grade plastic (PET and PP) with very limited environmental footprint when burned as biological hazardous waste after use.

The 3CP centrifuge is a low energy consuming device with an expected lifetime of more than 7 years and is able to generate several patches a day.

As the fully autologous biological construct (e.g. The 3C Patch) is made on site using shelf stable components (kits) there is no temperature or time critical shipments required nor any needed storage facilities (e.g. - 80C freezer).

Therefore, the environmental footprint of implementing 3C Patch is minimal.

Further, the clinical outcome with the use of 3C Patch will lead to fewer treatments overall thereby saving other equipment, and patient travel etc.

3 Clinical context

Describe the clinical care pathway(s) that includes the proposed use of the technology, ideally using a diagram or flowchart. Provide source(s) for any relevant pathways.

NICE Clinical Guideline (NG19) Diabetic Foot Problems: Prevention and Management sets out recommendations for diabetic foot care in the NHS.

Section 1.5.4 of the NICE NG19 guideline recommends that people with DFUs should be offered one or more of the following as standard care:

- Offloading
- Control of foot infection
- Control of ischaemia
- Wound debridement
- Wound dressings.

Wound dressings and offloading should be selected taking into account the clinical assessment of the wound and the person's preferences, and using devices and dressings with the lowest acquisition costs appropriate to the clinical circumstances. NICE has recently recommended that UrgoStart dressings should be considered as an option, after any modifiable factors have been treated (UrgoStart for treating diabetic foot ulcers and leg ulcers, Medical Technologies Guidance MTG42).

A recent outcome blind randomised controlled trial of 3C Patch demonstrated increased healing and reduced time to healing relative to best standard of care, in a cohort of patients with hard-to-heal DFUs (Game 2018b). Hard-to-heal ulcers were identified as those which did not show adequate healing after a 4 week period with best standard of care, including protease modulating and other advanced dressings where appropriate. Ulcers which had not reduced in area by 50% or more were considered hard-to-heal and eligible for randomisation in the trial.

In 2019 the International Working Group on the Diabetic Foot published "IWGDF Guideline on interventions to enhance healing of foot ulcers in persons with diabetes (Rayman 2019). The guideline includes the following recommendation in relation to 3C Patch, "Consider the use of autologous combined leucocyte, platelet and fibrin as an adjunctive treatment, in addition to best standard of care, in non-infected diabetic foot ulcers that are difficult to heal" (recommendation 11).

An unpublished German consensus document provides guidance on the use of 3C Patch, based on clinical experience with the patch in outpatient and inpatient settings (Zink submitted 2021). This guidance is described as a supplement to the IWGDF recommendation.

Proposed pathway

It is proposed that 3C Patch should be considered for hard-to-heal DFUs. Expert opinion, analysis of the data from the Game 2018b RCT, and associated health economic modelling have been used to inform the draft pathway. Expert feedback on the draft pathway is provided with this submission (Clinical Feedback on Draft 3C Patch Pathway). Supplementary analysis of the trial dataset is provided with this submission (Supplementary Analysis of RCT (Game 2018b) Dataset).

It is acknowledged that the unit cost of this product is high relative to dressings in general use, and that in order to generate cost savings for the NHS through reduced ulcer duration and improved healing, it will be important to ensure that the patch is used appropriately. This pathway is designed to support clinical judgement in this area.

The RCT identified hard-to-heal DFUs as those that did not reduce in area by at least 50% over 4 weeks. During this period, patients received best standard of care including a wide range of dressings according to clinical judgement.

It is proposed that 3C Patch should be considered for hard-to-heal DFUs in cases where best standard of care as recommended by NICE (including offloading, debridement, control of modifiable factors, and use of dressings such as UrgoStart and other protease modulating and advanced dressings where appropriate) have failed to promote ulcer healing. It is likely that best standard of care would be tried for at least 6 weeks before 3C Patch is considered. During this time progress towards healing should be reviewed regularly and the patch should only be considered in cases where ulcer area has not reduced by 50% or more during the 4 week period prior to proposed use. This approach is informed by expert opinion.

It should be noted that the RCT excluded patients with severe comorbidities such as severe ischaemia (ABPI < 0.5) and severe renal disease (renal replacement therapy or eGFR <20). In selecting patients for 3C Patch treatment, clinicians should consider the current lack of clinical effectiveness evidence for use in these patient groups. Further inclusion and exclusion criteria from the RCT are shown in Table 3.1.

Table 3.1. Inclusion and exclusion criteria from the RCT (Game 2018b)*

Inclusion criteria
• Eligible ulcers will be below the level of the malleoli, excluding ulcers confined to the interdigital cleft
• Eligible ulcers will be hard to heal, meaning that the cross-sectional area will decrease by less than 50% during a 4-week run-in period
• The cross-sectional area of the index ulcer will be ≥50 and ≤ 1000 mm2 at the end of the 4-week run-in period
• Either the Ankle-brachial Pressure Index (ABPI) in the affected limb will be between 0.50 and 1.40 or the dorsalis pedis pulse and/or the tibialis posterior pulse will be palpable
• Glycosylated haemoglobin (HbA1c) level ≤ 108 mmol/mol at screening
Exclusion criteria
• Increase in cross-sectional area of the index ulcer by ≥ 25% during the 4-week

run-in period, or is either smaller than 50 mm2 or larger than 1000 mm2 at the end of that time
• Clinical signs of infection of the index ulcer or reason to suspect that infection is present
• Treatment of foot ulcers with growth factors, stem cells or equivalent preparation within the 8 weeks prior to screening
• The need for continued use of negative pressure wound therapy
• Haemoglobin concentration < 105 g/L or 6.5 mmol/L at screening
• Presence of sickle-cell anaemia, haemophilia, thrombocytopenia (<100 Å~ 109/L) or other clinically significant blood dyscrasia
• Known potential infectivity of blood products, including known HIV and hepatitis
• Dialysis or an estimated glomerular filtration rate (GFR) (based on cystatin C or serum creatinine) < 20 ml/min/1.73 m2

*Some inclusion and exclusion criteria have been omitted from this table because they are not considered relevant to routine care.

In addition, the IFU document for 3C Patch sets out the following contra-indications:

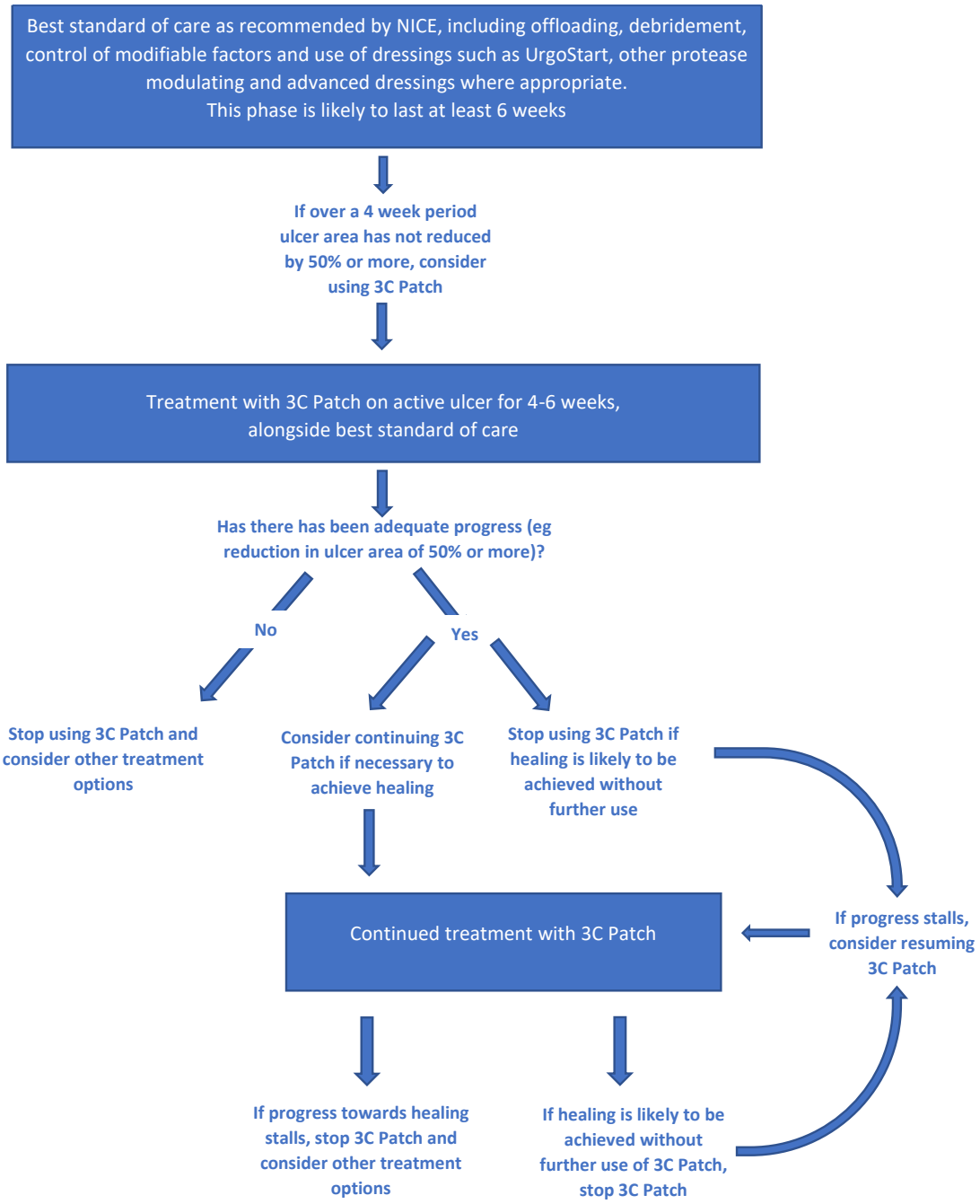
- Actively infected wounds
- Malignant wounds
- Patients with sepsis
- Patients with haemophilia, sickle cell anaemia, thrombocytopenia, leukaemia or other blood dyscrasia.
- Patients being treated for malignant or neoplastic diseases or collagen vascular diseases.

3C Patch should be used in conjunction with the other elements of best standard of care as recommended by NICE NG19. Once 3C Patch treatment has started, clinicians should monitor progress toward healing, and regularly review use of the patch. It is recommended that if there has not been adequate progress toward healing (for example a reduction in ulcer area of 50% or more) during 4-6 weeks of 3C Patch treatment, use of the patch should be discontinued and other treatment options considered. This approach is informed by expert opinion.

In cases where there has been adequate progress during 4-6 weeks of 3C Patch treatment, clinicians should consider continued use if they believe this is necessary to achieve complete healing. Clinicians should continue to monitor progress towards healing and regularly review use of the patch. Use of the patch should be discontinued if clinical judgement indicates that progress towards healing has stalled. Use may also be discontinued in cases where clinical judgement indicates that sufficient progress has been made and healing is likely to be achieved without further use of the patch. In cases where good progress has been made and the patch is discontinued, 3C Patch treatment may be resumed if progress toward healing stalls. This approach is informed by expert opinion.

The draft clinical pathway for 3C Patch is summarised in Figure 3.1.

Figure 3.1. Draft clinical pathway for 3C Patch for hard-to-heal DFUs



Rationale for pathway

4 week run-in period prior to use of 3C Patch

3C Patch is recommended for use on hard-to-heal DFUs. In the recent outcome blind randomised controlled trial of 3C Patch, hard-to-heal ulcers were identified as those which did not reduce in area by 50% or more after a 4 week period with best standard of care (Game 2018b). It is believed that reduction in ulcer area over 4 weeks of best standard of care is a good indicator of the probability of healing; several studies have indicated that an area reduction of less than 50% during 4 weeks of treatment is associated with a lower long-term probability of healing (Coerper 2009, Sheehan 2003, Snyder 2010). Ulcers which do not demonstrate this level of healing over a 4 week period are therefore most likely to be of long duration, and 3C Patch should be considered in addition to best standard of care to increase the likelihood of healing and reduce ulcer duration.

Positioning in pathway

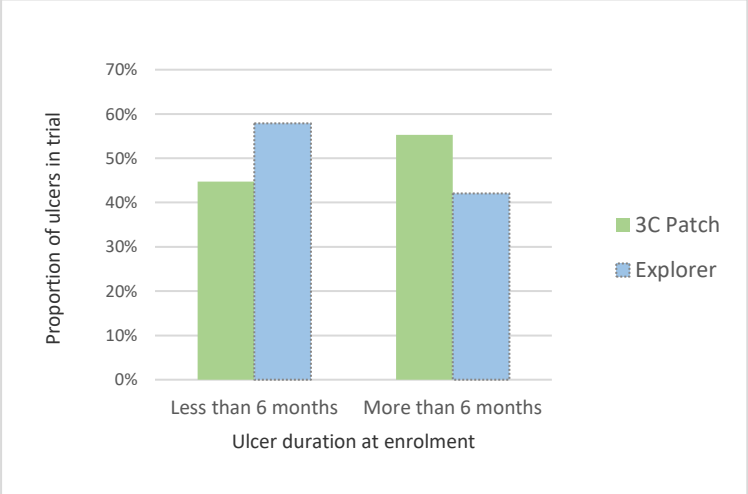
It is likely that in most cases, clinicians will wish to try best standard of care in line with NICE recommendations (NG19) for at least 6 weeks before considering use of 3C Patch (to include the 4 week run-in period described above).

NICE NG19 recommends that wound dressings and offloading should be selected taking into account the clinical assessment of the wound and the person's preferences, and using devices and dressings with the lowest acquisition costs appropriate to the clinical circumstances. NICE has recently recommended that UrgoStart dressings should be considered as an option, after any modifiable factors have been treated (NICE MTG42). 3C Patch is proposed here for harder to heal wounds that have not responded to these treatments.

The ulcers studied in the recent 3C Patch RCT (Game 2018b) were harder to heal than those in the Explorer trial for UrgoStart (Edmonds 2018). This is supported by the following evidence:

- Average ulcer duration at randomisation in the 3C Patch trial was longer than in the Explorer trial for UrgoStart. In the 3C Patch trial, 55% of DFUs were of at least 6 months duration at randomisation, compared with 42% in the Explorer UrgoStart trial (Edmonds 2018) (Figure 3.2). In the 3C Patch trial, 35% of wounds were of at least 12 months duration at randomisation. (The Explorer trial did not provide data on the percentage of wounds with duration of 12 months or more.) Both trials reported that longer wound duration at randomisation was associated with reduced likelihood of healing. The Explorer trial reported that wound duration (≥6 months duration vs <6 months) was associated with reduced likelihood of healing (OR 0.27 95% CI 0.15–0.51). Unpublished data from the 3C Patch trial indicate that wound duration (6 to less than 12 months vs. ≥12 months was associated with increased likelihood of healing (OR 1.943 (95% CI 0.785-4.812). Further details are presented in the attached document, Supplementary Analysis of RCT (Game 2018b) Dataset. This is in line with evidence from other studies that longer wound duration is associated with reduced likelihood of healing (Margolis 2003).

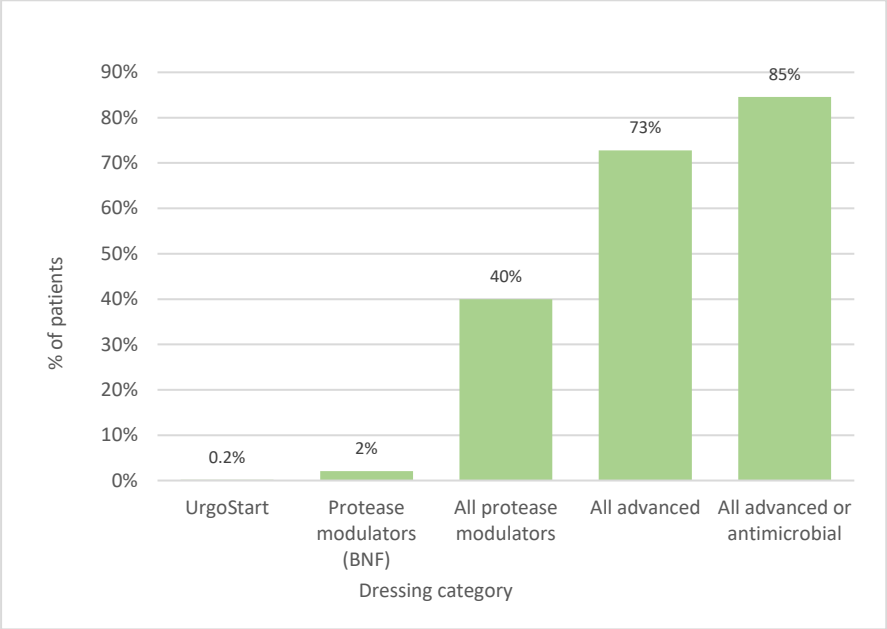
Figure 3.2. Ulcer duration in 3C Patch and Explorer (UrgoStart) studies



- During the 4 week run-in period for the 3C Patch RCT, ulcers were treated with best standard of care, including a wide range of dressings, according to clinical judgement. These included protease modulating dressings such as UrgoStart, and other advanced dressings. In the Explorer trial, all patients in the run-in period received UrgoTul dressings. Protease modulating dressings were not used in the run-in period for the Explorer trial. Dressings used in the 3C Patch trial were classified using BNF categories[1]. It should be noted that the Journal of Wound Care provides an alternative classification of protease modulating dressings[2]. Protease modulating dressing use under both classifications is shown in the charts below. 73% of patients received advanced dressings in the run-in period for the 3 Patch trial, and 40% received protease modulating dressings (JWC classification) (Figure 3.3). Further analysis is presented in the attached document, Supplementary Analysis of RCT (Game 2018b) Dataset.

[1] https://bnf.nice.org.uk/ Last accessed 19/03/21
[2] https://www.woundcarehandbook.com/configuration/categories/wound-care/protease-modulating-dressings/ Last accessed 19/03/21

Figure 3.3. Percentage of patients receiving at least one week of treatment with advanced and antimicrobial dressings in 4 week run-in period (3C Patch RCT)



- After randomisation in the 3C Patch RCT, ulcers in the control group were treated with best standard of care, including a wide range of dressings, according to clinical judgement. These included protease modulating dressings such as UrgoStart, and other advanced dressings. In the Explorer trial, all ulcers in the control group were treated with UrgoTul dressings. Protease modulating dressings were not used in the control group for the Explorer trial. In the 3C Patch control arm 90% of patients received advanced dressings (Figure 3.4). Patients who received protease modulating dressings in the control arm of the 3C Patch trial did not have higher healing rates than other control patients (Figure 3.5). Further analysis is presented in the attached document, Supplementary Analysis of RCT (Game 2018b) Dataset.

Figure 3.4. Percentage of patients receiving at least one week of treatment with advanced and antimicrobial dressings in control arm (3C Patch RCT)

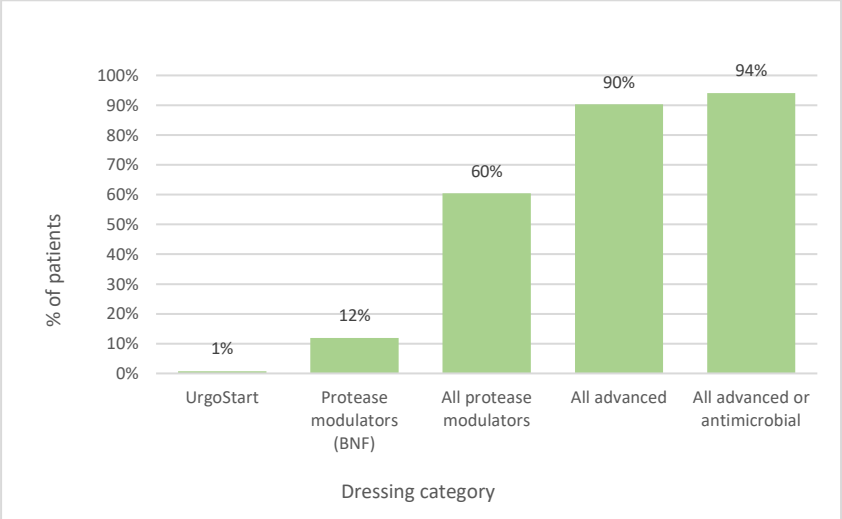
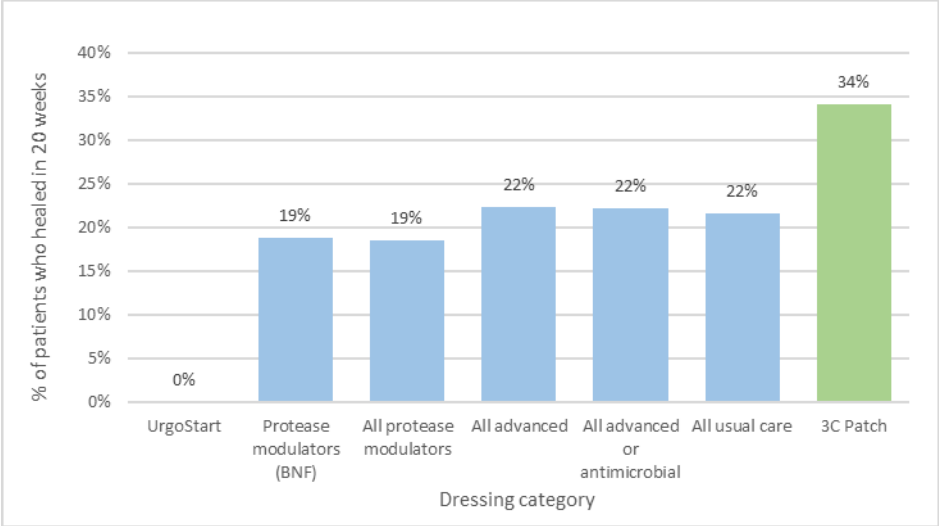
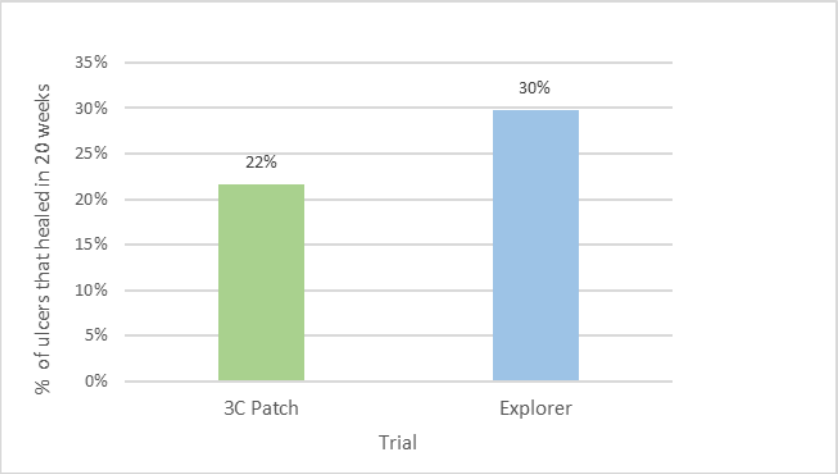


Figure 3.5. 20 week healing rates for patients in control arm who received at least one week of treatment by dressing type, compared with 3C Patch arm



- The control arm in the 3C Patch trial had a lower healing rate (22%) than the control arm in the Explorer (UrgoStart) trial (30%), in spite of best standard of care and widespread use of protease modulating dressings (which were not available to the control group in the Explorer trial) (Figure 3.6).

Figure 3.6. 20 week healing rates in control arms, 3C Patch and Explorer trials

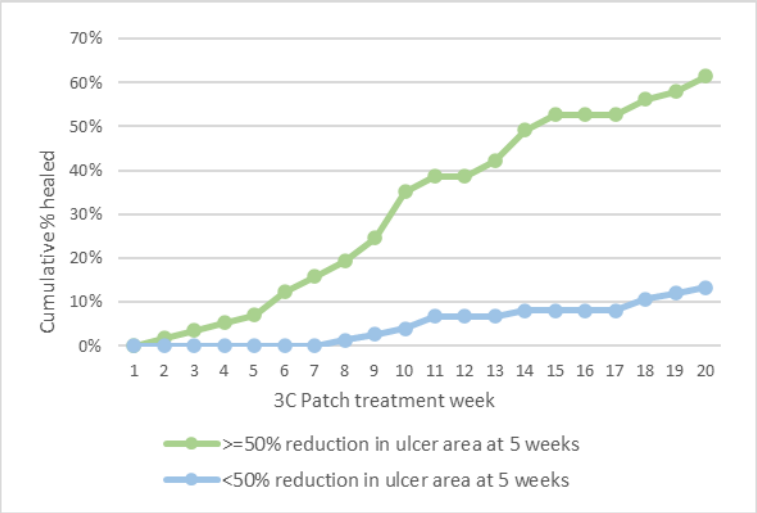


4-6 week review

Analysis of the data from the 3C Patch RCT indicates that most 3C Patch patients who achieved healing by week 20 had a substantial reduction in ulcer area by weeks 4-6. For example, 78% of ulcers that healed by week 20 had a 50% reduction in ulcer area by week 5. Clinicians will exercise judgement on progress towards healing and on whether to continue treatment. As an illustration, if treatment beyond week 5 had been continued in the trial population only for patients whose ulcers had a 50% reduction in ulcer area by week 5, 43% would have continued treatment.

Of those who met this illustrative criterion for continued treatment beyond week 5, 61% healed by week 20. In contrast, of ulcers treated with 3C Patch that had not reduced in area by at least 50% at 5 weeks, 14% healed by week 20 (Figure 3.7).

Figure 3.7. Cumulative healing in 3C Patch cohort, subgroups defined by ulcer area at 5 weeks



Treatment review beyond 4-6 weeks

In the 3C Patch RCT, patients were treated for up to 20 weeks or until healing occurred. Mean treatment duration was 17.1 weeks and the mean number of patches per patient was 14.3. In the illustrative example set out above, if only those whose ulcers had reduced in area by 50% or more at 5 weeks had continued treatment beyond this point, the mean treatment duration would have been 9.0 weeks and the mean number of patches per patient is estimated at 7.6.

Expert opinion (see Clinical Feedback on Draft 3C Patch Pathway) indicates that in routine practice it would be unlikely that treatment with 3C Patch would continue for up to 20 weeks. Clinicians would monitor progress towards healing and regularly review use of the patch. 3C Patch would be discontinued in cases where progress towards healing is judged to have stalled, and also in cases where clinical judgement indicates that sufficient progress has been made and healing is likely to be achieved without further use of the patch.

Expert opinion on the clinical pathway and context was provided by:

Rachel Berrington, Senior Diabetes Specialist Nurse, University Hospitals of Leicester NHS Trust

Hannah Bond, Advanced Podiatrist in Diabetes, Nottingham University Hospitals NHS Trust

Nikki Drake, Lead Podiatrist Diabetes Bristol, Sirona Care and Health CIC

Prof. Fran Game, Consultant Diabetologist and Director of R&D, Royal Derby Hospital

Prof. William Jeffcoate, Clinical Lead in the National Diabetes Foot Care Audit of England and Wales

Prof Gerry Rayman, Consultant Diabetologist, Ipswich Hospital, East Suffolk and North East Essex NHS Foundation Trust

Describe any training (for healthcare professionals and patients) and system changes that would be needed if the NHS were to adopt the technology.

The blood draw uses standard techniques and venous access equipment (supplied as part of the system) therefore no training would be needed for this step of the process. Healthcare workers would need to be familiarised with the process of attaching the system specific 3C Patch Needle holder to the standard needle provided, filling the 3C Patch device by blood collection and start the processing of the filled device in the 3CP Centrifuge.

Training is needed to operate the 3C Patch centrifuge and administer the patch but every effort has been made to make this as intuitive and as easy as possible. Reapplix would deliver the training by a 1 hour introductory training session. In addition, a clinical specialist from Reapplix will participate at the first 2-3 treatments and will be available for continuous sparring/training of any new staff as needed. Reapplix training and service will be provided free of charge.

Staff training numbers will vary depending on the size of the centre and organisational factors. It is estimated that on average, two band 4 nurses and two band 6 podiatrists would be trained. The nurses would typically take the blood and operate the centrifuge, and the podiatrists would administer the patches.

Minimal changes are needed for implementation. The centrifuge has a small foot-print (22cm in diameter) and will fit easily onto a standard bench or table top. It also only requires access to mains electricity via a standard plug.

It is expected that the blood will be taken and the centrifuge operated by a nurse. The centrifuge takes 20 minutes to produce a patch. It is anticipated that on average 10 minutes additional nurse time during the visit will be required for each patch produced. This time requirement is based on the assumption that nurses will perform other tasks while the centrifuge is operating. It is not expected that any additional podiatrist or other healthcare professional time will be required relative to time requirements for administering alternative dressings. However, appointment times for patients will need to be extended to allow for examination of the wound to determine whether a patch is required, followed by patch production and application where necessary. The study by Londahl (2015) looked at time consumption to use the 3C Patch in a routine clinical appointment

and concluded that in the absence of any major problems with the venepuncture, the procedure could be accomplished within a few extra minutes and easily included in routine clinical appointments.

4 Published and unpublished clinical evidence

Identification and selection of studies

Complete the following information about the number of studies identified.

Please provide a detailed description of the search strategy used, and a detailed list of any excluded studies, in appendix A.

Number of studies identified in a systematic search.		320
Number of studies identified as being relevant to the decision problem.		14
Of the relevant studies identified:	Number of published studies (included in table 1).	3
	Number of abstracts (included in table 2).	2
	Number of ongoing studies (included in table 3).	1

List of relevant studies

In the following tables, give brief details of all studies identified as being relevant to the decision problem.

- Summarise details of published studies in table 1.
- Summarise details of abstracts in table 2.
- Summarise details of ongoing and unpublished studies in table 3.
- List the results of all studies (from tables 1, 2 and 3) in table 4.

For any unpublished studies, please provide a structured abstract in appendix A. If a structured abstract is not available, you must provide a statement from the authors to verify the data.

Any data that is submitted in confidence must be correctly highlighted. Please see section 1 of the user guide for how to highlight confidential information. Include any confidential information in appendix C.

Table 1 Summary of all relevant published studies

Data source	Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Main outcomes
PubMed	Game, 2018b UK, Denmark, Sweden	Multinational, observer masked RCT	Adults aged 18 or over with a hard-to-heal diabetic foot ulcer (defined as no reduction in area by less than 50% in a 4 week run-in period), n=266 (ITT) Clinic setting 3 participants lost to follow up/withdrawal	3C Patch used weekly for up to 20 weeks	Best standard of care	Proportion of ulcers healed within 20 weeks. Time to heal Change in ulcer area Incidence of infection and antibiotic usage Amputation Safety and adverse events
Pubmed	Jorgensen, 2011. Denmark and Sweden	Prospective uncontrolled open label pilot study	Adults aged 18 years old or more, with a chronic cutaneous ulcer on lower extremity, chronic diabetic foot ulcer or amputation wound, present for at least 2 months and not healed using conventional means, n=16 Clinical setting	3C Patch used weekly for 6 weeks	None	Proportional change in wound area in 6 week treatment period. Change in the proportion of: granulation tissue, wounds that completely healed and wounds with significant improvement of wound area.

Pubmed	Londahl, 2015 Denmark and Sweden	Prospective, multicentre open, cohort pilot study	Adult patients with at least 1 full-thickness diabetic foot ulcer (Wagner grade 1 or 2) at or below the ankle, with a duration of more than 6 weeks, a reduction in area by less than 40% in a 2 week run-in period and a maximal area of 10cm^2, n=44 (ITT) Clinic setting. None lost to follow up/withdrawal.	3C Patch used weekly for up to 19 treatments	None	Proportion of ulcers healed within 20 weeks. Ulcer healing at 12 weeks Time to heal Change in ulcer area Safety and feasibility

Table 2 Summary of all relevant abstracts

Data source	Author, year and location	Study design	Patient population, setting, and withdrawals/lost to follow up	Intervention	Comparator(s)	Main outcomes
Embase	Hogh, 2019 Denmark	Non-randomised prospective observational study	Population: Mixed patients with hard to-heal wounds (wound duration>6 weeks). DFU n=4, pressure ulcer n=7, surgery incision n=9, venous n=3, other n=3 Setting: multi-disciplinary outpatient clinic specialised in advanced wound treatment. Treatment stopped, n=3/26 (n=1 each: issues with blood draw, infection and amputation)	Blood patch (3C Patch, Reapplix) used weekly for up to 19 treatments	None	• Median pre-treatment time • Mean no blood patches • Median time to heal • Reduction in mean wound size • Pain
Embase	Katzman, 2014	Feasibility study	Population: Patients with at least Wagner grade 3 diabetic foot ulcers i.e. ulcers with positive probing to bone test - non-ischemic (TcPO2≥30 mm Hg) ulcers with a duration of at least 6 weeks, n=17. Setting: Clinic None lost to follow up	Blood patch (3C Patch, Reapplix) used weekly for 20 weeks.	None	Median ulcer duration Median number of treatments Healing/complete epithelialisation Safety

Table 3 Summary of all relevant ongoing or unpublished studies

Data source	Author, year (expected completion) and location	Study Aim	Intended Patient population and setting	Intervention	Comparator(s)	Outcomes
Company	Zink, 2021, [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 4 Results of all relevant studies (from tables 1, 2 and 3)

Study	Results	Company comments
Game, 2018b	**Participants:** 595 patients with hard-to-heal DFU recruited of which 266 were randomised with 134 into standard of care group and 132 into Leucopatch intervention group. Baseline characteristics were well balanced between the 2 groups. **Completely healed ulcer, 20 weeks, ITT** Standard Care: 29/134 (22%) Leucopatch: 45/132 (34%), OR1.58 (96%CI1.04-2.4), p-0.0235) **Completely healed ulcer, 20 weeks, Per Protocol** Standard Care: 28/107 (26%) Leucopatch: 44/114 (39%), OR 1.47 96% CI 0.98-2.23), p=0.0480) **Completely healed ulcer, 12 weeks, ITT** Standard Care: 17/134 (13%) Leucopatch: 27/132 (20%), p=0.0882 **Completely healed ulcer, 26 weeks, ITT** Standard Care: 29/134 (22%)	The study describes a well-designed and robust RCT and includes appropriate details on the overall trial methodology including inclusion/exclusion criteria, randomisation, blinding, treatment regimen, outcomes and data and statistical analysis. Study limitations and confounding factors are discussed. The study was funded by Reapplix. The publication states the following: "The funder of the study had no role in study design, data collection, data analysis, data interpretation or writing of the report."

Leucopatch: 45/132 (34%), OR1.89 (95%CI1.09 – 3.28), p-0.0237)

Median Days to heal, 20 weeks, ITT

Standard Care: 84 days (n=29)

Leucopatch: 72 days (n=45), p=0.0343

Number of patients how developed new infections within 20 weeks, ITT

Standard Care: 63/134 (47%)

Leucopatch: 51/132 (39%), , OR 0.8350 [95%CI 0.63-1.11], p=0.2080

Percentage of visits where infection reported, ITT

Standard Care: 10.1%

Leucopatch: 8.6% , OR 0.8417[95%CI 0.70-1.02], p=0.0728

Healing by ABPI subcategory, n (% in subcategory)

ABPI Subcategory	Standard Care	Leucopatch
0.5-0.79	2/16 (12.5%)	5/14 (35.7%)
0.8-0.99	6/23 (26.0%)	8/30 (26.7%)
1-1.4	14/73 (19.2%)	25/65 (38.4%)
>1.4	7/22 (31.8%)	7/23 (30.4%)

Total number of days of antibiotic therapy

Standard Care: 2822

Leucopatch: 2662, OR 0.92 [95%CI 9.14-7.35], p=0.8314

Amputations

	Index limb, new minor		Index limb, new major		Contralateral limb, new minor		Contralateral limb, new major	
	SoC	Reapplix	SoC	Reapplix	SoC	Reapplix	SoC	Reapplix
12 wks	2	5, p=0.8314	0	0	1	4 P=0.3746	0	0
20 wks	5	8 P=0.4196	2	2 P=1.0	2	7 P=0.1062	1	1 P=1.0
26 wks	9	8 P=1.0	2	2 P=1.0	3	7 P=0.2226	1	1 P=1.0

Reduction in pain (% change VAS), ITT

Control: -45.5% (n=85)

The study protocol used the patch for 20 weeks but it is accepted that this is not how the 3C Patch would be used in reality. Clinicians would be expected to use the patch for 4-6 weeks and to only continue if the wound shows improvement. This is also covered in Section 3. Clinical Context, Zink 2021, submitted manuscript and Clinical Feedback on Draft 3C Patch Pathway document.

<table>
<tr><td></td><td>Leucopatch: -54.5% (n=71), p=0.1194
Revascularisation of index limb, 26 weeks (n, %)
Control: 6 (5%)
Leucopatch: 3 (2%), OR 0.44 (95% CI 0.08-3.31), p=0.49
Death by 26 weeks (n, %)
Control: 5 (4%)
Leucopatch: 3 (2%), OR 0.60 (95% CI 0.14-2.56), p=0.7221</td><td></td></tr>
<tr><td>Jorgensen, 2011</td><td>Participants: 15 patients with 16 wounds (mixed) were recruited and 12 patients (13 wounds) received the full treatment course of 6 treatments (6 weeks) until fully healed and were analysed.
Patch: Made using either the Leucopatch device (n=4 wounds) or in an Eppendorf tube (n=9 wounds)
Wounds: DFU (n=5), Venous Leg Ulcer (n=3), other (n=8)
<table><tr><td>Complete Wound healing at 6 weeks</td><td>4/13 (31%) *</td></tr><tr><td>Patients with wound area reduction</td><td>11/13</td></tr><tr><td>Mean wound area reduction in 6 weeks from baseline</td><td>64.7% (95% CI 45.6-83.3%)
Regression analysis, p>0.0007</td></tr><tr><td>Mean wound size at 6 weeks</td><td>1.8cm^2 (95% CI 0.4-3.3cm^2)</td></tr><tr><td>Median wound size</td><td>0.9cm^2 (95% CI 0-9.6cm^2)</td></tr><tr><td>Eppendorf v Leucopatch device</td><td>No significant difference in rate of healing</td></tr><tr><td>Granulation tissue, %
Baseline
6 weeks</td><td>
33% (95%CI 9-57%)
72% (95%CI 55-90%)
Regression analysis, p-0.0097</td></tr></table>* Further two patients were observed to have healed during routine clinic visits 4 and 8 weeks after the end of treatment respectively.</td><td>The study describes prospective uncontrolled pilot trial and includes appropriate details on the overall study methodology including inclusion/exclusion criteria, treatment regimen, outcomes and data and statistical analysis. Study limitations are discussed.

The study using either patches generating using a standard laboratory Eppendorf tubes or the Leucopatch devices. The primary difference is the size of the patch meaning that more of the Eppendorf tube derived patches need to be produced to cover the same area.

* This was reported in the Karlsmark (2011) abstract as “Of the 13 wounds included in the per-protocol analysis, 6 healed at the 12-week follow-up” but the abstract has not been included in Tables 3 and 4 as it reports the same population of patients as Jorgensen 2011. This was stated as the reason for exclusion in</td></tr>
</table>

<table>
<tr><td></td><td></td><td>Appendix A</td></tr>
<tr><td>Londahl, 2015</td><td>Participants: Adults (>18 years) with at least 1 full thickness diabetic ulcer at or below the ankle, duration> 6weeks, area <10cm^2. 60 people were recruited of which 44 passed the screening criteria (<40% area change in a 2 week run-in) and had at least 1 treatment were included in the ITT analysis and 39 were per-protocol analysis.
Neuropathy: 42/44
Median ulcer duration: 35 weeks (7-490 weeks range)
Median ulcer area: 1.1cm^2 (0.1-10.0cm^2 range)

<table><tr><td></td><td>ITT</td><td>PP</td></tr><tr><td>Complete epithelialisation at 12 weeks</td><td>15/44 (34%)</td><td>36%</td></tr><tr><td>Complete epithelialisation at 20 weeks</td><td>23/44 (52%)</td><td>59%</td></tr></table>Healing rates at 20 weeks was significantly higher in the 1/3 of patients with the shortest ulcer duration (73.3%) compared to the 1/3 of patients with the longest duration (26.7%, p=0.026).
Ulcer area reduction was greatest in healers compared to non-healers at 12 weeks: 53% (47-61%) compared to 26% (13-48%), p<0.01. Patients were classified as healers and non-healers after 20 weeks. During the 2 week run-in period, changes in ulcer area were similar in healers and non-healers and increased in the overall per-protocol population by 2% (-18-27%). In the first 2 weeks of treatment, ulcer area decreased by 36% (14-56%) overall.

Time consumption was included in the results with the authors concluding that in the absence of severe problems with the venepuncture, the procedure could be accomplished within a few extra minutes and easily applied within routine clinical management.</td><td>The study describes prospective uncontrolled pilot trial and includes appropriate details on the overall study methodology including inclusion/exclusion criteria, treatment regimen, outcomes and data and statistical analysis. Study limitations are discussed.</td></tr>
<tr><td>Hogh, 2019</td><td>Participants: Hard-to-heal wounds (wound duration>6 weeks), n=26. The mean age was 65 years (SD 13.6), 58% (n=15) were males.
Wounds: DFU n=4, pressure ulcer n=7, surgery incision n=9, venous n=3, other n=3
Median pre-treatment time before inclusion was 21.5 weeks (IQR 28).</td><td>The study, presented in abstract form, describes a mixed population with hard-to-heal ulcers some of which were DFU (4/26).
The specific outcomes of the DFU</td></tr>
</table>

	Median number of blood patches (Reapplix) treatments was three ranging from 1-19 treatments per patient. **Median time to healing** was 73 days (IQR 156). Healed at less than 20 weeks - 54 %(14/26) Healed at more than 20 weeks - 27%(7/26) Did not heal 19%(5/32) **Reduction in mean wound size**: Start or treatment - 2.75 cm^2 (SD 3.55) (95%CI 1.29;4.22) Completion of treatment - 1.62cm^2 (SD 2.48) (95%CI 0.59;2.64) p=0.0058. **Pain** - In all cases with pain prior to treatment, the patients reported less pain after treatment started.	patients are not known
Katzman, 2011	**Participants**: Patients with non-ischemic ($TcPO2_{\varepsilon}$ ≥30 mm Hg) diabetic foot ulcers with a duration of at least 6 weeks and a positive probing to bone test, n=17 patients with 21 ulcers. Median ulcer duration: 27 weeks Median number of treatments: 9 Healing/complete epithelialisation: 13 healed with complete epithelialisation, bone was covered in 16 ulcers.	The study, presented in abstract form, describes a specific subset of DFU patients that have hard-to-heal wounds.
Zink, submitted, 2021	[redacted]	[redacted]

	[redacted]	

5 Details of relevant studies

Please give details of all relevant studies (all studies in table 4). Copy and paste a new table into the document for each study. Please use 1 table per study.

Game, 2018b	
How are the findings relevant to the decision problem?	The study is a well-designed RCT involving the patient population, the intervention and comparator group as outlined in the decision problem. The comparator in this study was best standard of care (as detailed in the NICE guidelines) which included protease modulating or other advanced dressing for most patients. The outcomes of the study are included in the decision problem but do not cover the patient-reported outcomes (tolerability, acceptability or QoL). The study did collect data on additional secondary outcomes including resource use but the data was not considered to be of an acceptable quality for use. The outcomes data is relevant to the cost analysis as described in the decision problem.
Does this evidence support any of the claimed benefits for the technology? If so, which?	The evidence presented in the paper does support the 3C Patch benefits. The results show that the 3C Patch results in a statistically significant increase in healing and reduction in healing time of hard-to-heal DFUs compared to best standard care. This reduces the need for ulcer care across all NHS settings, and also the risk of complications including amputation and infection. Use of the patch is expected to reduce risks and side effects of complications because the ulcers show improved rates of healing. This in turn leads to an improved quality of life for patients enabling them to return to activities of daily living more quickly than patients receiving standard care. The 3C Patch is anticipated to be cost saving in the longer term due to reduced ulcer duration, fewer complications, and associated reduction in healthcare resource use.
Will any information from this study be used in the economic model?	Yes. The economic model will use the data from the study on clinical effectiveness including healing rates, time to healing, area reduction and infections. It will also use data from the study on dressing use.
What are the limitations of this evidence?	The study is a robust RCT that is considered to be of high quality but there are some limitations regarding the study design and conduct as it was not possible to mask participants or researchers to treatment allocation. This was mitigated in part by using independent, blinded observers (backed up by digital imaging) for the primary outcome assessment as well as the digital images.

	The study recruited a large number of males – 82% rather than the expected 67%. However, this is recognised as a typical feature of large trials in this field as males are more likely to develop a DFU compared to females. The study describes the continuous use of the 3C Patch for 20 weeks but this is not how the patch would be used in the real world. The company states that the patch should be used initially for 4-6 weeks and the ulcer regularly reviewed for progress toward healing. Use of 3C Patch should continue only if adequate progress is being made, and if clinical judgement indicates that continued use is necessary to achieve complete healing. This is supported by expert opinion as set out in the uploaded document Clinical Feedback on Draft 3C Patch Pathway. The 3C Patch can be used for up to 20 weeks safely.
How was the study funded?	The study was funded by Reapplix APS but they had no role in the study design, data collection, data analysis, data interpretation or writing of the report.

Jorgensen, 2011	
How are the findings relevant to the decision problem?	The study involves a population of recalcitrant wounds of mixed etiologies, some of which are included in the population described in the decision problem. The intervention is the 3C Patch and it should be noted that the article describes 2 slightly different methodologies to create that patch relating to the type of device used (Eppendorf tube or 3C Patch device). There is no comparator group. The outcomes of the study are included in the decision problem.
Does this evidence support any of the claimed benefits for the technology? If so, which?	The study data supports the claimed benefits for the 3C Patch although the results for the DFU patients are not separated out from the overall results. The results show that 4 out of 13 wounds healed completely within the 6 week treatment period and that another 2 wound healed within 12 weeks. Although there was no comparator group, none of the healed wounds had healed in the previous 7 months using conventional treatment (duration of healed wounds 7, 24, 24 and 60 months). More rapid healing reduces the need for further treatment and reduces the need for GP, nurse and specialist clinician appointments which lead to an overall cost saving. More rapid healing will also reduce the risks and side effects of complications associated with recalcitrant wounds that are not healing with standard care and improve quality of life for patients.

	Enter text.
Will any information from this study be used in the economic model?	No
What are the limitations of this evidence?	The limitations of the study are discussed within the paper. Specifically, the authors discussed the following: The study was an open pilot design so was neither comparative nor controlled. The small patient population had a mix of wound types but does include those classified as hard-to-heal DFU but also others which are not covered by the scope but all wounds were recalcitrant to conventional treatment. It is difficult to know which of the wounds "would have improved as a result of the additional care and attention the patients would have received as part of the clinical trial. There are many patient-related factors that can influence healing of ulcers, which were not controlled for in this study." The study used two different methods to prepare the patches (laboratory tube-based and commercial device) though subsequent analysis indicated no difference in outcomes between the 2 methods.
How was the study funded?	The study was supported by Reapplix APS.

Londahl, 2015	
How are the findings relevant to the decision problem?	The patient population and intervention is the same as the decision problems although the study uses the Wagner grades to determine the severity and this system is not recommended by NICE. This was an uncontrolled trial so there was no comparator group but the study outcomes were covered by the decision problem.
Does this evidence support any of the claimed benefits for the technology? If so, which?	The study data supports the claimed benefits for the 3C Patch. The study shows that within 2 weeks the 3C Patch resulted in ulcer area reduction and healing in ulcers that had shown no improvement in the previous 2 weeks. More rapid healing reduces the need for further treatment and reduces the need for GP, nurse and specialist clinician appointments which leads to an overall cost saving. More rapid healing will also reduce the risks and side effects of complications associated with recalcitrant wounds that are not healing with standard care and improve quality of life for patients.

Will any information from this study be used in the economic model?	No
What are the limitations of this evidence?	The study was a prospective, open cohort study design so was neither comparative nor controlled. As part of the Discussion, the authors also state that "Interventions such as more frequent visits to diabetic foot clinics and increased attention may affect the outcome, hence our ulcer healing rates must be interpreted with caution. However, treatment strategies including offloading, antibiotics, offloading vascular intervention are the same."
How was the study funded?	The study was supported by Reapplix APS

Hogh 2016	
How are the findings relevant to the decision problem?	The study involves a population of recalcitrant wounds of mixed etiologies, some of which are included in the population described in the decision problem. The intervention is the 3C Patch but there is no comparator group. The outcomes of the study are included in the decision problem
Does this evidence support any of the claimed benefits for the technology? If so, which?	The study data supports the claimed benefits for the 3C Patch although the results for the DFU patients are not separated out from the overall results. Hard-to-heal wounds showed an improvement in wound size and healing times with only 19% not healing within the 20 weeks. This study also describes a reduction in patient pain which will benefit both patients' quality of life as well as reduced costs from pain management and analgesia. More rapid healing reduces the need for further treatment and reduces the need for GP, nurse and specialist clinician appointments which leads to an overall cost saving. More rapid healing will also reduce the risks and side effects of complications associated with recalcitrant wounds that are not healing with standard care and improve quality of life for patients.
Will any information from this study be used in the economic model?	No
What are the limitations of this evidence?	The evidence has several limitations as the data set is small and is presented in abstract form only. In addition, the data is for a mixed patient population and the data for the DFU patients alone is not presented. Additionally there is no comparator group included in the study.

How was the study funded?	The funding is not stated but is assumed to be via Reapplix.

Katzman 2014	
How are the findings relevant to the decision problem?	The patient population, intervention and outcomes are all covered by the decision problem statement. However, it should be noted that the study covers patients with DFU whose ulcers probe to the bone. The study also uses Wagner grades to determine the severity and this system is not recommended by NICE. The study is uncontrolled so there is no comparator group.
Does this evidence support any of the claimed benefits for the technology? If so, which?	The evidence does support the claim that the 3C Patch increases the healing times for hard-to-heal DFU. This in turn reduces the need for further treatment, appointments and reduces the risk of side-effects and complications all of which have a positive impact on the cost savings and quality of life.
Will any information from this study be used in the economic model?	No
What are the limitations of this evidence?	The evidence has several limitations as the data set is small and is presented in abstract form only. Additionally there is no comparator group included in the study. The decision problem states that infected wounds are excluded but in this study the patients received topical antibiotic treatment for 1 week prior to application of the 3C Patch. Several patients also received oral antibiotic treatment due to infection during the study
How was the study funded?	The abstract states that the study was supported by Lund University, Sweden.

Zink, submitted 2021	
How are the findings relevant to the decision problem?	[redacted]
Does this evidence support any of the claimed benefits for the technology? If so, which?	[redacted]
Will any information from this study be used in the economic model?	[redacted]

What are the limitations of this evidence?	[redacted]
How was the study funded?	[redacted]

6 Adverse events

Describe any adverse events and outcomes associated with the technology in national regulatory databases such as those maintained by the MHRA and FDA (Maude). Please provide links and references.

No entries could be identified in either the MHRA, the FDA (MAUDE) or the TGA (DAEN and SARA) databases.

Search strings used:

- Reapplix
- Leucopatch
- Leukopatch
- 3C Patch

Describe any adverse events and outcomes associated with the technology in the clinical evidence.

The potential for the 3C Patch to have an adverse effect on the patient, particularly from repeated blood draws have been considered in all 3 of the clinical studies undertaken with specific safety outcomes data being gathered.

Game, 2018: No adverse events associated with the device were recorded.

	Standard of Care	**Leucopatch**
Incidence of new anaemia	11 (8%)	13 (10%) OR 1.20 (95%CI 0.56-2.58), p=0.6408
Any adverse event, no of participants, n (%)	90 / 137 (66%)	81/132 (61%) OR 0.93 (95% CI 0.78-1.12), p=0.4607
Any adverse event, no of reports	240	274
Device related adverse event	0	0
Any serious adverse event, no of participants, n (%)	42 (31%)	51 (39%) OR 1.26 (95% CI 0.91-1.76), p=0.1689
Any serious adverse event, no of reports	74	98

Jorgensen, 2011 (n=15 patients with 16 wounds)

No. adverse events reported – 2

No. serious adverse events reported – 0

No. AE/SAE judged to be related to the device – 0 (zero)

Londahl 2015 (n=44)

No. adverse events reported – 33

No. serious adverse events reported – 12

No. AE/SAE judged to be related to the device – 0 (zero)

Hogh 2019 (Abstract, n=26)

No specific adverse or serious adverse events reported.
Treatment was stopped ahead of time for 3/26 patients: one because of difficulties obtaining the blood sample, one had an infection and one was amputated

Katzman 2014 (Abstract, n=17 patients with 21 ulcers)
No specific adverse or serious adverse events reported.
Tissue infection, n=3
Bone resection, n=2
Distal phalangeal resection, n=1
Leucopatch seems to be safe to apply to the bone surface

7 Evidence synthesis and meta-analysis

Although evidence synthesis and meta-analyses are not necessary for a submission, they are encouraged if data are available to support such an approach.

If an evidence synthesis is not considered appropriate, please instead complete the section on qualitative review.

If a quantitative evidence synthesis is appropriate, describe the methods used. Include a rationale for the studies selected.

A quantitative review is not appropriate as the 3 clinical studies identified (Game, 2018, Jorgensen 2011, Londahl, 2015) used different patient populations and outcomes and 2 did not include comparators (Jorgensen 2011, Londahl, 2015). In addition the abstracts did not present sufficient information to enable a quantitative review.

Report all relevant results, including diagrams if appropriate.

Enter text.

Explain the main findings and conclusions drawn from the evidence synthesis.

Enter text.

Qualitative review

Please only complete this section if a quantitative evidence synthesis is not appropriate.

Explain why a quantitative review is not appropriate and instead provide a qualitative review. This review should summarise the overall results of the individual studies with reference to their critical appraisal.

A quantitative review is not considered appropriate due to the heterogeneity of the included clinical studies and limited data presented in the abstracts.

The clinical evidence is derived from 1 high-quality multi-centre RCT including UK settings, 2 non-controlled clinical studies and 2 clinical evaluations/case studies presented as abstracts. In addition, there is 1 consensus paper on the patient pathway for the 3C Patch. The RCT provides evidence that the 3C Patch results in significantly higher rates of healing and reduced ulcer duration relative to standard care (including treatment with advanced dressings) in DFU that are classed as hard to heal. There was also a (non-significant) reduction in infections requiring antibiotic treatment relative to standard care. The remaining uncontrolled studies describe healing of previously recalcitrant ulcers in patients receiving 3C Patch. It should be noted that 2 of the studies included a mixed population of recalcitrant wounds i.e. not all were DFU as described in the scope. All studies provide evidence that the 3C Patch is safe to use in the relevant patient population.

8 Summary and interpretation of clinical evidence

Summarise the main clinical evidence, highlighting the clinical benefit and any risks relating to adverse events from the technology.

The RCT was a large multi-centre study, including sites in the UK that recruited 266 patients with hard-to-heal DFU as presented in the scope. The RCT data demonstrated the key clinical benefits of an increased healing rate (34% with 3C Patch v 22% with standard care, p=0.0235) and a reduced time to healing (72 days with 3C Patch v 84 days with standard care, p=0.0343) in those patients with hard-to-heal diabetic foot ulcers treated with the 3C Patch. The study also reported a non-significant reduction in infections and time spent on antibiotics. This data is supported by the additional non-RCT clinical studies where recalcitrant wounds including DFU were treated effectively with the 3C Patch. Diabetic foot ulcers can be of very long duration and some never heal. They entail a substantial reduction in quality of life, and large ongoing costs to the NHS. There is substantial direct benefit to both patients and the NHS from interventions that promote increased healing and reduced ulcer duration. There are also secondary benefits from reduced complications including infection, amputation and death. None of the studies reported any adverse events associated with using the technology.

Briefly discuss the relevance of the evidence base to the scope. This should focus on the claimed benefits described in the scope and the quality and quantity of the included studies.

The evidence presented includes a high quality RCT that supports all benefits presented in the scope. The trial report demonstrates increased healing of hard-to-heal DFUs and reduced time to healing for patients treated with 3C Patch, relative to control. Hard-to-heal DFUs are defined as ulcers that do not reduce in area by 50% or more over a four week period despite best standard of care. The control group received best standard of care, including the use of protease modulating and other advanced dressings as described in the comparator definition in the decision problem. The report also shows a reduction in infections requiring antibiotic treatment, and a reduction in pain, though these did not achieve statistical significance. Unpublished data from the RCT also indicate that patients who became ulcer-free had a significant increase in health-related quality of life (EQ-5D) at week 20 relative to week 0. The RCT report does not

include data on demand for NHS care. However, it is clear that increased healing and reduced ulcer duration directly reduce demand for ongoing ulcer care, and the likelihood of longer-term complications such as amputation that have substantial impacts on quality of life, demand for NHS care and NHS costs.

The potential contribution of 3C Patch to DFU healing is supported by 4 smaller non-controlled studies. It should be noted that 2 of these additional non-RCT studies included mixed patient populations i.e. were not solely DFU as described in the scope.

All studies showed that the 3C Patch was safe to use in the defined patient population.

Identify any factors which might be different between the patients in the submitted studies and patients having routine care in the UK NHS.

The patients in the submitted studies included a large cohort of UK patients and there are no anticipated differences between the patients in the submitted studies and patients receiving care in the UK.

Describe any criteria that would be used in clinical practice to select patients for whom the technology would be most appropriate.

The 3C Patch would deliver the greatest benefit to those patients who have a hard-to-heal DFU that has not improved despite best standard of care including offloading, debridement, control of modifiable factors and use of advanced dressings where appropriate. It is expected that best standard of care would be tried for at least 6 weeks before 3C Patch is considered, as outlined in the draft clinical pathway (see uploaded Final Proposed 3C Patch Clinical Pathway). Additionally, we propose that progress over the 4 week period prior to use of the 3C Patch should be reviewed, and the patch should only be considered in cases where ulcer area has not reduced by 50% or more over this time period. This run-in period and decision rule are in line with the approach used in the RCT. In addition, the RCT excluded patients with severe comorbidities including severe ischaemia and severe renal disease as well as wounds that were greater than 1000mm^2. In selecting patients for whom the technology would be most appropriate, clinicians may wish to consider the lack of clinical effectiveness data for these excluded groups.

Briefly summarise the strengths and limitations of the clinical evidence for the technology.

The main strength of the clinical evidence lies with the RCT that is judged to be of high quality with statistically significant outcomes that are directly relevant to the scope. The supporting evidence, particularly the 2 published papers despite being small uncontrolled studies, are all well reported with suitable analysis and appropriate discussion of confounding factors. The limitations to the evidence lie in the fact that these studies are difficult to blind to device use and the fact that patients participating in such studies may receive better than usual care due to more frequent visits to clinics etc. In addition, some of the evidence base comes from studies that used mixed etiologies of recalcitrant wounds that included patients with hard-to-heal DFU and the results for the different wound types were not separated

out but these studies are not a key part of the evidence base. Another limitation is the fact that the studies by Game (2018b), Londahl (2015), Hogh (2018) and Katzman (2011) used the patch for up to 19 or 20 weeks. The draft clinical pathway proposes that clinicians should monitor progress toward healing, and regularly review use of the patch. It is recommended that if there has not been adequate progress toward healing (for example a reduction in ulcer area 50% or more) during 4-6 weeks of 3C Patch treatment, use of the patch should be discontinued and other treatment options considered. In cases where there has been adequate progress during 4-6 weeks of 3C Patch treatment, clinicians should consider continued use if they believe this is necessary to achieve complete healing. This pathway is supported by additional analysis of some unpublished RCT data as outlined in Section 3. The draft pathway also proposes that clinicians may discontinue use in cases where they feel sufficient progress has been made and healing is likely to be achieved without further use of the patch. In cases where good progress has been made and the patch is discontinued, 3C Patch treatment may be resumed if progress toward healing stalls. The recommendations in the draft clinical pathway are supported by expert opinion from the UK as described in Clinical Feedback on Draft 3C Patch Pathway.	

9 References

Please include all references below using NICE's standard referencing style.

Coerper S, Beckert S, Kuper MA, Jekov M, Konigsrainer A. (2009) Fifty percent area reduction after 4 weeks of treatment is a reliable indicator for healing—analysis of a single centre cohort of 704 diabetic patients. J Diabetes Complications 23: 49–53.

Edmonds M, Lázaro-Martínez JL, Alfayate-García JM, Martini J, 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. Lancet Diabetes Endocrinol. 6(3):186-196. doi: 10.1016/S2213-8587(17)30438-2.
Epub 2017 Dec 20. Erratum in: Lancet Diabetes Endocrinol. 2018 Mar 6; PMID: 29275068.

Game F, Jeffcoate W et al, LeucoPatch II trial team. (2017) The LeucoPatch® system in the management of hard-to-heal diabetic foot ulcers: study protocol for a randomised controlled trial. Trials 18 (1); 469-476

Game F, Jeffcoate W, Tarnow L et al. (2018a) The LeucoPatch system in the management of hard-to-heal diabetic foot ulcers: A multicentre, multinational, observer-blinded, randomised controlled trial. 54th EASD Annual Meeting of the European Association for the Study of Diabetes. Diabetologia 61, 1–620. https://doi.org/10.1007/s00125-018-4693-0 (Abstract)

Game F, Jeffcoate W et al, LeucoPatch II trial team. (2018b) LeucoPatch system for the management of hard-to-heal diabetic foot ulcers in the UK, Denmark, and Sweden: an observer-masked, randomised controlled trial. The lancet. Diabetes & endocrinology 6 (11): 870-878

Hogh A, Andersen JW, Dashnaw B. (2019) The Effect of Autologous Blood Patch Treatment Among Patients With Hard-to-heal Wounds; A Clinical Perspective. European Journal of Vascular and Endovascular Surgery 58 (6, Suppl3): e751-752 (Abstract)

Jecht M. 2018 Das LeucoPatch-System zur Behandlung von schwer therapierbaren diabetischen Fusulzera: Eine randomisierte, kontrollierte BeobachtungsstudieThe LeucoPatch syste for the treatment of hard-to-heal diabetic foot ulcers: A randomized, controlled observational study. Diabetologe 14 (8): 603-604

Jorgensen B, Karlsmark T, Vogensen H et al. (2011) A pilot study to evaluate the safety and clinical performance of Leucopatch, an autologous, additive-free, platelet-rich fibrin for the treatment of recalcitrant chronic wounds. International Journal of Lower Extremity Wounds 10 (4): 218-223

Karlsmark T, Vogensen H, Haase L et al. (2011) In vitro characterization of the autologous platelet rich fibrin leucopatch and its clinical use in the treatment of chronic wounds. Wound Repair and Regeneration 19 (5): 045 (Abstract)

Katzman P, Fagher K, Lundquist R et al. (2014) Treatment of hard-to-heal diabetic foot ulcers probing to bone with leucopatchTM, a leukocytes and platelet rich fibrin patch. Diabetes 63: A581 (2291-PO) (Abstract)

Kerr M, Barron E, Chadwick P et al. (2019). The cost of diabetic foot ulcers and amputation to the National Health Service in England. Diabetic medicine 36 (8): 995-1002

Löndahl M, Tarnow L, Karlsmark T et al. (2015) Use of an autologous leucocyte and platelet-rich fibrin patch on hard-to-heal DFUs: a pilot study. Journal of wound care 24 (4): 172-178

Lundquist R, Holmstrøm K, Clausen C et al. (2013) Characteristics of an autologous leukocyte and platelet-rich fibrin patch intended for the treatment of recalcitrant wounds. Wound repair and regeneration 21 (1): 66-76

Lundquist R. (2016) Autologous cell-rich biomaterial (LeucoPatch) in the treatment of diabetic foot ulcers. In: Ågren MS, ed. Wound Healing Biomaterials. Vol 1. Elsevier; 2016:277-287. doi:10.1016/B978-1-78242-455-0.00011-2

Margolis DJ, Gelfand JM, Hoffstad O, Berlin JA. (2003) Surrogate end points for the treatment of diabetic neuropathic foot ulcers. Diabetes Care 26(6):1696-700. doi: 10.2337/diacare.26.6.1696. PMID: 12766096.

National Diabetes Foot Audit. https://digital.nhs.uk/data-and-information/publications/statistical/national-diabetes-footcare-audit/2014-2018) [online; accessed 15th March 2021]

Nazarko (2020) NICE evaluate 3C Patch System for treating diabetic foot ulcers. Nursing & Residential Care 22 (12): 1-2

NICE Guideline. NG19. Diabetic foot problems: prevention and management https://www.nice.org.uk/guidance/ng19 [online: accessed 15th March 2021]

Rayman G, Vas P, International Working Group on the Diabetic Foot (IWGDF). (2020) Guidelines on use of interventions to enhance healing of chronic foot ulcers in diabetes (IWGDF 2019 update). Diabetes Metab Res Rev. 36 (Suppl1):e3283.

Schmidt JD and Lundquist R. (2019) In vitro study of an autologous leukocyte and platelet-rich fibrin patch for managing diabetic foot ulcers. Wound Repair and Regeneration 27 (3): A1-A40 (Abstract)

Sheehan P, Jones P, Caselli A, Giurini JM, Veves A. (2003) Percent change in wound area of diabetic foot ulcers over a 4-week period is a robust predictor of complete healing in a 12-week prospective trial. Diabetes Care 26(6):1879-82. doi: 10.2337/diacare.26.6.1879. PMID: 12766127.

Snyder RJ, Cardinal M, Dauphinee DM and Stavosky J. (2010) A post-hoc analysis of reduction in diabetic foot ulcer size at 4 weeks as a predictor of healing at 21 weeks. Ostomy Wound Manage 55: 44–50.

Tennvall GR and J Apelqvist. (2000) Health-related quality of life in patients with diabetes mellitus and foot ulcers, Journal of Diabetes and Its Complications 14(5):235-41. doi: 10.1016/s1056-8727(00)00133-1.

Thomsen K, Trostrup H, Christophersen L et al. (2016). The phagocytic fitness of leucopatches may impact the healing of chronic wounds. Clin. Exp. Immunology 84:368-377

Vas P, Rayman G, Dhatariya K et al. (2020) Effectiveness of interventions to enhance healing of chronic foot ulcers in diabetes: a systematic review. Diabetes/metabolism research and reviews; 2020: e3284

Wounds UK, Best practice recommendations for the implementation of a DFU treatment pathway. https://www.wounds-uk.com/resources/details/best-practice-recommendations-for-the-implementation-of-a-dfu-treatment-pathway [online; accessed 15th March 2021]

[redacted]

10 Appendices

Appendix A: Search strategy for clinical evidence

Describe the process and methods used to identify and select the studies relevant to the technology. Include searches for published studies, abstracts and ongoing studies in separate tables as appropriate. See section 2 of the user guide for full details of how to complete this section.

Date search conducted:	8 and 15th March 2021
Date span of search:	2000 to present

List the complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean). List the databases that were searched.

Search strings were drawn from the following phrases or words

Population – "Diabetic foot" and "Foot ulcer, diabetic" from the HDAS Thesauraus as exploded as major Terms

Intervention

- Reapplix OR leucopatch OR leukopatch OR 3C patch
- Patch
- Leucocytes OR leukocytes
- Fibrin
- Platelets

Comparator – Standard wound care, standard care, advanced wound care, urgo

Outcomes

- Non-healing OR nonhealing OR non healing
- Wound healing OR epithelialisation
- Wound-related complications
- Quality of life

Published studies

DATE	DATABASE	TERMS	RESULTS
08/03/2021	Medline	(exp *"DIABETIC FOOT"/ OR exp *"FOOT ULCER"/) AND ((leucocytes OR leukocytes).ti,ab OR (fibrin).ti,ab OR (platelets).ti,ab)	67
		(3C patch OR leucopatch OR leukopatch).ti,ab	20
		(autologous platelet rich fibrin patch).ti,ab	12
		(exp *"DIABETIC FOOT"/ OR exp *"FOOT ULCER"/) AND (autologous platelet rich fibrin patch).ti,ab	2
		(((exp *"DIABETIC FOOT"/ OR exp *"FOOT ULCER"/) AND ((leucocytes OR leukocytes).ti,ab OR (fibrin).ti,ab OR (platelets).ti,ab)) AND ((clinical trial OR RCT OR clinical OR evaluation).ti,ab OR (randomised controlled trial OR randomised clinical trial).ti,ab OR (observation trial).ti,ab)) AND ((wound heal* OR epithelialisation).ti,ab OR (non-healing OR nonhealing OR non healing).ti,ab)	28
		((exp *"DIABETIC FOOT"/ OR exp *"FOOT ULCER"/) AND ((leucocytes OR leukocytes).ti,ab OR (fibrin).ti,ab OR (platelets).ti,ab)) AND (standard of care OR standard	7

		care OR “advanced wound dressing” OR urgostart).ti,a	
		((exp *”DIABETIC FOOT”/ OR exp *”FOOT ULCER”/) AND ((leucocytes OR leukocytes).ti,ab OR (fibrin).ti,ab OR (platelets).ti,ab)) AND (quality of life OR EQ5D OR EuroQOL).ti,ab	5

DATE	DATABASE	TERMS	RESULTS
08/03/2021	PubMed including The Cochrane database of systematic reviews	(diabetic foot OR foot ulcer).ti,ab AND ((leucocytes OR leukocytes).ti,ab OR (fibrin OR platelets).ti,ab)	354
		((diabetic foot OR foot ulcer).ti,ab AND ((leucocytes OR leukocytes).ti,ab OR (fibrin OR platelets).ti,ab)) AND (clinical trial OR RCT OR clinical OR evaluation OR randomised controlled trial OR randomised clinical trial OR observation trial).ti,ab	178
		(3C patch OR leucopatch OR leukopatch).ti,ab	41
		(autologous platelet rich fibrin patch).ti,ab	2
		(diabetic foot OR foot ulcer).ti,ab AND (autologous platelet rich fibrin patch).ti,ab	0
		(clinical trial OR RCT OR clinical OR evaluation OR randomised controlled trial OR randomised clinical trial OR observation trial).ti,ab AND (((diabetic foot OR foot ulcer).ti,ab AND ((leucocytes OR leukocytes).ti,ab OR (fibrin OR platelets).ti,ab)) AND ((non-healing OR nonhealing OR non healing).ti,ab OR (wound heal* OR epithelialisation).ti,ab))	76
		((diabetic foot OR foot ulcer).ti,ab AND ((leucocytes OR leukocytes).ti,ab OR (fibrin OR platelets).ti,ab)) AND (standard of care OR standard care OR “advanced wound dressing” OR urgostart).ti,ab	16
		((diabetic foot OR foot ulcer).ti,ab AND ((leucocytes OR leukocytes).ti,ab OR (fibrin OR platelets).ti,ab)) AND (quality of life OR EQ5D OR EuroQOL).ti,ab	11

DATE	DATABASE	TERMS	RESULTS
08/03/2021	Cinahl	(exp *”DIABETIC FOOT”/ OR exp *”FOOT ULCER”/) AND ((leucocytes OR leukocytes).ti,ab OR (fibrin OR platelets).ti,ab)	93
		(3C patch OR leucopatch OR leukopatch).ti,ab	6
		(autologous platelet rich fibrin patch).ti,ab	5
		(exp *”DIABETIC FOOT”/ OR exp *”FOOT ULCER”/) AND (autologous platelet rich fibrin patch).ti,ab	3
		((clinical trial OR RCT OR clinical OR evaluation OR randomised controlled trial OR randomised clinical trial OR observation trial).ti,ab AND ((exp *”DIABETIC FOOT”/ OR exp *”FOOT ULCER”/) AND ((leucocytes OR leukocytes).ti,ab OR (fibrin OR platelets).ti,ab))) AND ((non-healing OR nonhealing OR non healing).ti,ab OR (wound heal* OR epithelialisation).ti,ab)	36
		((exp *”DIABETIC FOOT”/ OR exp *”FOOT ULCER”/) AND ((leucocytes OR leukocytes).ti,ab OR (fibrin OR platelets).ti,ab)) AND (standard of care OR standard care OR “advanced wound dressing” OR urgostart).ti,ab	11
		(quality of life OR EQ5D OR EuroQOL).ti,ab AND ((exp *”DIABETIC FOOT”/ OR exp *”FOOT ULCER”/) AND ((leucocytes OR leukocytes).ti,ab OR (fibrin OR platelets).ti,ab))	5

DATE	DATABASE	TERMS	RESULTS
08/03/2021	Embase	(exp *”DIABETIC FOOT”/ OR (exp *”FOOT ULCER”/ OR	

		exp *"FOOT ULCER, DIABETIC"/)) AND ((leucocytes OR leukocytes).ti,ab OR (fibrin OR platelets).ti,ab)	110
		(3C patch OR leucopatch OR leukopatch).ti,ab	13
		(autologous platelet rich fibrin patch).ti,ab	2
		(exp *"DIABETIC FOOT"/ OR exp *"FOOT ULCER"/) AND (autologous platelet rich fibrin patch).ti,ab	1
		((clinical trial OR RCT OR clinical OR evaluation OR randomised controlled trial OR randomised clinical trial OR observation trial).ti,ab AND ((exp *"DIABETIC FOOT"/ OR (exp *"FOOT ULCER"/ OR exp *"FOOT ULCER, DIABETIC"/)) AND ((leucocytes OR leukocytes).ti,ab OR (fibrin OR platelets).ti,ab))) AND ((non-healing OR nonhealing OR non healing).ti,ab OR (wound heal* OR epithelialisation).ti,ab)	27
		((exp *"DIABETIC FOOT"/ OR (exp *"FOOT ULCER"/ OR exp *"FOOT ULCER, DIABETIC"/)) AND ((leucocytes OR leukocytes).ti,ab OR (fibrin OR platelets).ti,ab)) AND (standard of care OR standard care OR "advanced wound dressing" OR urgostart).ti,ab	10
		(quality of life OR EQ5D OR EuroQOL).ti,ab AND ((exp *"DIABETIC FOOT"/ OR (exp *"FOOT ULCER"/ OR exp *"FOOT ULCER, DIABETIC"/)) AND ((leucocytes OR leukocytes).ti,ab OR (fibrin OR platelets).ti,ab))	3

Ongoing studies

DATE	DATABASE	TERMS	RESULTS
15/03/2021	www.clinicaltrials.gov (including ICTRP)	Reapplix	4 results 1 study completed with results 1 study recruiting 1 study withdrawn 1 study with unknown status
		Leucopatch	5 results As above plus 1 study completed
		3C patch	4 results 2 recruiting, 1 completed with results, 1 terminated
15/03/2021	ISRCTN	Reapplix	1 result, status completed
		Leucopatch	1 result, status completed
		3C patch	2 results, both completed
15/03/2021	PROSPERO	Reapplix	No results
		Leucopatch	No results
		3C patch	No results

Grey Literature

DATE	DATABASE	TERMS	RESULTS
15/03/2021	www.greylit.org	Reapplix Leucopatch 3C Patch	No results
15/03/2021	www.opengrey.eu	Reapplix	No results
		Leucopatch	No results
		3C patch	1 result
15/03/2021	http://webarchive.nationalarchives.gov.uk	Reapplix	3 results
		Leucopatch	38 results
		3C patch	No results

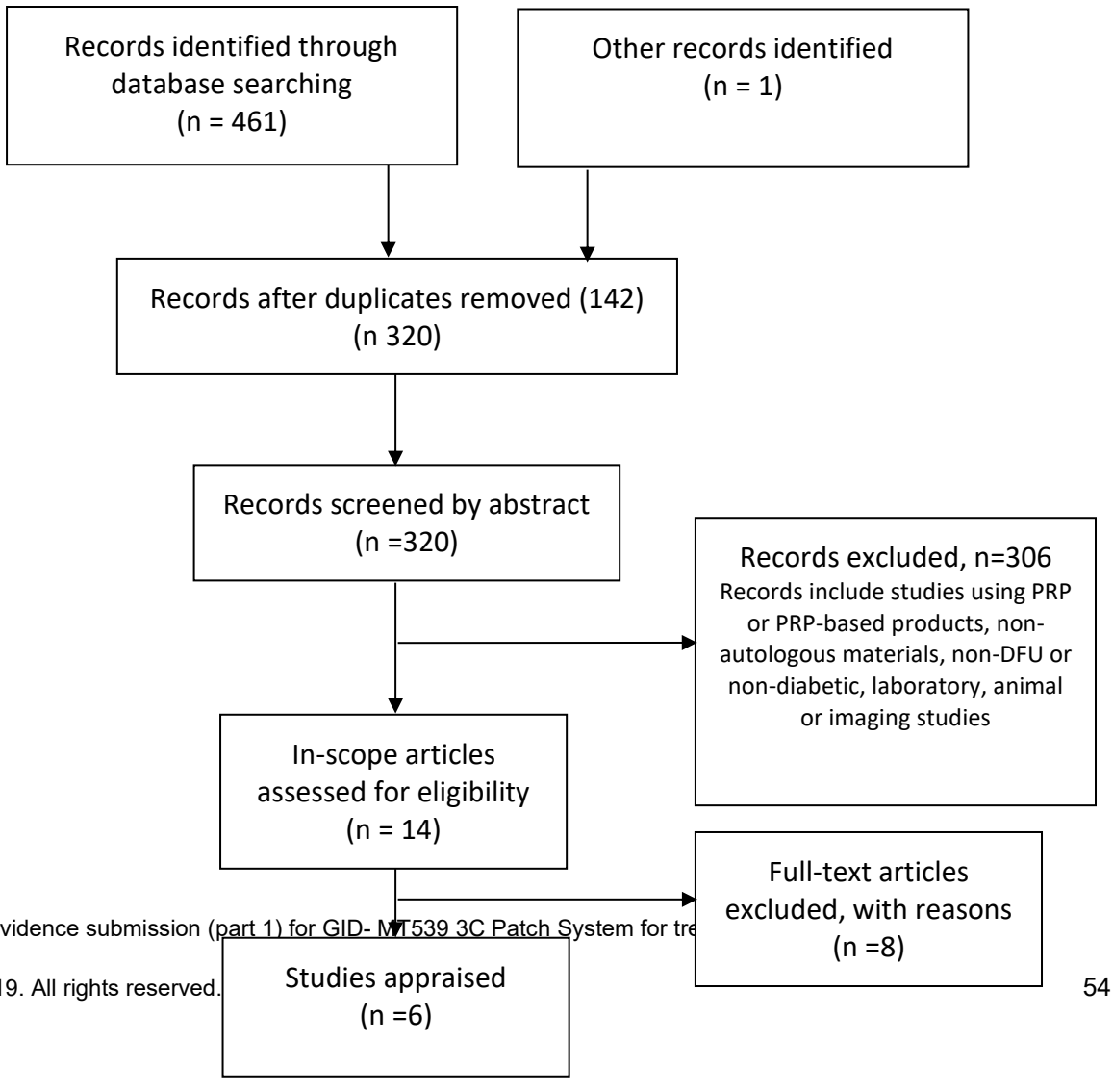
Brief details of any additional searches, such as searches of company or professional organisation databases (include a description of each database):
Wounds UK website Search Terms: Reapplix, leucopatch, platelet rich fibrin patch, DFU Database: Best Practice statements – 3 results Database: Consensus documents– no results
Inclusion and exclusion criteria
Inclusion – Leucopatch, 3C patch, DFU, recalcitrant or heard-to-heal wounds Exclusion – use of platelet-rich plasma products, non-3C Patch products
Data abstraction strategy:
The data from peer-reviewed published articles was abstracted using either the critical appraisal tool for RCT (adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination) or a tool adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence: 12 questions to help you make sense of a cohort study The data abstraction was conducted by Sarah Bolton and reviewed by clinical and product experts at Reapplix.

Excluded studies

List any excluded studies below. These are studies that were initially considered for inclusion at the level of full text review, but were later excluded for specific reasons.

Excluded study	Design and intervention(s)	Rationale for exclusion	Company comments
Game 2017	Protocol publication	Publication of RCT protocol in Trials Journal. Full trial published in Game et al 2018	Text
Game 2018a	Abstract publication	Publication in abstract form, full data set included in Game 2018b.	
Karlsmark 2011	Observational case study	Abstract publication on the same population of patients as described in Jorgenson 2011	Text
Lundquist 2013	Experimental study	Laboratory-based scientific study on the Leucopatch	Text
Nazarko 2020	NA	Commentary on NICE publication of the 3C Patch MIB	Text
Schmidt 2019	NA	Commentary on the Game et al 2018b RCT	Text
Thomsen 2016	Experimental study	Laboratory-based scientific study on the Leucopatch	

Report the numbers of published studies included and excluded at each stage in an appropriate format (e.g. PRISMA flow diagram).



Structured abstracts for unpublished studies – NOT APPLICABLE

Study title and authors
Introduction
Objectives
Methods
Results
Conclusion
Article status and expected publication: Provide details of journal and anticipated publication date

Appendix B: Search strategy for adverse events

Date search conducted:	8th March 2021
Date span of search:	From 2000 onwards

List the complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean). List the databases that were searched.

In addition to searches above, the following search strings were included;

DATE	DATABASE	TERMS	RESULTS
08/03/2021	Medline	((leucocytes OR leukocytes).ti,ab OR (fibrin).ti,ab OR (platelets).ti,ab) AND ((exp *"DIABETIC FOOT"/ OR exp *"FOOT ULCER"/) AND ((wound related complications).ti,ab OR (adverse events).ti,ab OR (infection OR amputation).ti,ab))	30
08/03/2021	PubMed including The Cochrane database of systematic reviews	(clinical trial OR RCT OR clinical OR evaluation OR randomised controlled trial OR randomised clinical trial OR observation trial).ti,ab AND (((diabetic foot OR foot ulcer).ti,ab AND ((leucocytes OR leukocytes).ti,ab OR (fibrin OR platelets).ti,ab)) AND ((adverse events).ti,ab OR (wound related complications).ti,ab OR (infection OR amputation).ti,ab))	106
08/03/2021	Cinahl	((clinical trial OR RCT OR clinical OR evaluation OR randomised controlled trial OR randomised clinical trial OR observation trial).ti,ab AND ((exp *"DIABETIC FOOT"/ OR exp *"FOOT ULCER"/) AND ((leucocytes OR leukocytes).ti,ab OR (fibrin OR platelets).ti,ab))) AND ((adverse events).ti,ab OR (wound related complications).ti,ab OR (infection OR amputation).ti,ab)	30
08/03/2021	Embase	((clinical trial OR RCT OR clinical OR evaluation OR randomised controlled trial OR randomised clinical trial OR observation trial).ti,ab AND ((exp *"DIABETIC FOOT"/ OR exp *"FOOT ULCER"/) AND ((leucocytes OR leukocytes).ti,ab OR (fibrin OR platelets).ti,ab))) AND ((adverse events).ti,ab OR (wound related complications).ti,ab OR (infection OR amputation).ti,ab)	28

Brief details of any additional searches, such as searches of company or professional organisation databases (include a description of each database):

None

Inclusion and exclusion criteria:

Inclusion – Leucopatch, 3C patch, DFU, recalcitrant or heard-to-heal wounds

Exclusion – use of platelet-rich plasma prodcuts, non-3C Patch products

Data abstraction strategy:

The data from peer-reviewed published articles was abstracted using either the critical appraisal tool for RCT (adapted from Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination) or a tool adapted from Critical Appraisal Skills Programme (CASP): Making sense of evidence: 12 questions to help you make sense of a cohort study

The data abstraction was conducted by Sarah Bolton and reviewed by clinical and product experts at Reapplix

Adverse events evidence

List any relevant studies below. If appropriate, further details on relevant evidence can be added to the adverse events section.

No further studies other than those described in Appendix A, clinical evidence, were identified.

Study	Design and intervention(s)	Details of adverse events	Company comments
Text	Text	Text	Text

Report the numbers of published studies included and excluded at each stage in an appropriate format (e.g. PRISMA flow diagram).

See Appendix A

Appendix C: Checklist of confidential information

Please see section 1 of the user guide for instructions on how to complete this section.

Does your submission of evidence contain any confidential information? (please check appropriate box):

No ☐ If no, please proceed to declaration (below)

Yes ☒ If yes, please complete the table below (insert or delete rows as necessary). Ensure that all relevant sections of your submission of evidence are clearly highlighted and underlined in your submission document, and match the information in the table. Please add the referenced confidential content (text, graphs, figures, illustrations, etc.) to which this applies.

Page	Nature of confidential information	Rationale for confidential status	Timeframe of confidentiality restriction
29, 34-35, 40-41	☐ Commercial in confidence ☒ Academic in confidence	Manuscript has been submitted to Wounds International but it has not been accepted for publication yet.	To be communicated when known
Details			
Details			

Confidential information declaration

I confirm that:

- all relevant data pertinent to the development of medical technology guidance (MTG) has been disclosed to NICE

- all confidential sections in the submission have been marked correctly
- if I have attached any publication or other information in support of this notification, I have obtained the appropriate permission or paid the appropriate copyright fee to enable my organisation to share this publication or information with NICE.

Please note that NICE does not accept any responsibility for the disclosure of confidential information through publication of documentation on our website that has not been correctly marked. If a completed checklist is not included then NICE will consider all information contained in your submission of evidence as not confidential.

Signed*: ** Must be Medical Director or equivalent*	[redacted]	**Date:**	25/3/2021
Print:	Rasmus Lundquist	**Role / organisation:**	Chief Scientific Officer
Contact email:	[redacted]		

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Medical technologies guidance

MT539 3C Patch System for treating diabetic foot ulcers

Company evidence submission

Part 2: Economic evidence

Company name	Reapplix APS
Submission date	27th April 2021
Contains confidential information	Yes

Contents

1 Published and unpublished economic evidence

Identification and selection of studies

Complete the following information about the number of studies identified.

Please provide a detailed description of the search strategy used, and a detailed list of any excluded studies, in appendix A.

Number of studies identified in a systematic search.		59
Number of studies identified as being relevant to the decision problem.		1
Of the relevant studies identified:	Number of published studies.	1
	Number of abstracts.	0
	Number of ongoing studies.	0

List of relevant studies

In table 1, provide brief details of any published or unpublished economic studies or abstracts identified as being relevant to the decision problem.

For any unpublished studies, please provide a structured abstract in appendix A. If a structured abstract is not available, you must provide a statement from the authors to verify the data provided.

Any data that is submitted in confidence must be correctly highlighted. Please see section 1 of the user guide for how to highlight confidential information. Include any confidential information in appendix C.

Table 1 Summary of all relevant studies (published and unpublished)

Data source	Author, year and location	Patient population and setting	Intervention and comparator	Unit costs	Outcomes and results	Sensitivity analysis and conclusion
PubMed	Game et al. 2018 UK, Denmark, Sweden	Multinational, observer masked RCT Adults aged 18 or over with a hard-to-heal diabetic foot ulcer (defined as no reduction in area by less than 50% in a 4 week run-in period), n=266 (ITT) Clinic setting 3 participants lost to follow up/withdrawal	3C Patch used weekly for up to 20 weeks Comparator: Best standard of care	Not covered	Proportion of ulcers healed within 20 weeks. Time to heal Change in ulcer area Incidence of infection and antibiotic usage Amputation Safety and adverse events	In the 3C Patch group, 45 (34%) of 132 ulcers healed within 20 weeks versus 29 (22%) of 134 ulcers in the standard care group (odds ratio 1·58, 96% CI 1·04–2·40; p=0·0235) by intention-to-treat analysis. Time to healing was shorter in the LeucoPatch group (p=0·0246) than in the standard care group. No difference in adverse events was seen between the groups.

2 Details of relevant studies

Please give details of all relevant studies (all studies in table 1). Copy and paste a new table into the document for each study. Please use 1 table per study.

Game F, Jeffcoate W et al, LeucoPatch II trial team. (2018b) LeucoPatch system for the management of hard-to-heal diabetic foot ulcers in the UK, Denmark, and Sweden: an observer-masked, randomised controlled trial. The lancet. Diabetes & endocrinology 6 (11): 870-878 (Game et al. 2018)	
What are main differences in resource use and clinical outcomes between the technologies?	The study did not describe the impact on resource use. The main differences in clinical outcomes were increased healing rates and reduced ulcer duration with 3C Patch.
How are the findings relevant to the decision problem?	The study is a well-designed RCT involving the patient population, the intervention and comparator group as outlined in the decision problem. The comparator in this study was best standard of care (as detailed in the NICE guidelines) which included protease modulating or other advanced dressing for most patients. The outcomes of the study are included in the decision problem but do not cover the patient-reported outcomes (tolerability, acceptability or QoL). The outcomes data is relevant to the cost analysis as described in the decision problem.
Does this evidence support any of the claimed benefits for the technology? If so, which?	The evidence presented in the paper does support the 3C Patch benefits. The results show that the 3C Patch results in a statistically significant increase in healing and reduction in healing time of hard-to-heal DFUs compared to best standard care. This reduces the need for ulcer care across all NHS settings, and also the risk of complications including amputation and infection. Use of the patch is expected to improve quality of life through increased healing, enabling patients to return to activities of daily living more quickly than patients receiving standard care. The 3C Patch is anticipated to be cost saving in the longer term due to reduced ulcer duration, fewer complications, and associated reduction in healthcare resource use.
Will any information from this study be used in the economic model?	Yes. The economic model will use the data from the study on clinical effectiveness including healing rates and time to healing. (It will also use unpublished data from the study on area reduction, dressing and antibiotic use, and staff inputs.

What cost analysis was done in the study? Please explain the results.	The study did collect data on additional secondary outcomes including resource use but no cost analysis was included in the published paper. (Data from the trial on resource use including dressings, medications and staff inputs were analysed and used for the economic model for this submission.)
What are the limitations of this evidence?	The study is a robust RCT that is considered to be of high quality but there are some limitations regarding the study design and conduct as it was not possible to mask participants or researchers to treatment allocation. This was mitigated in part by using independent, blinded observers (backed up by digital imaging) for the primary outcome assessment. The study recruited a large number of males – 82% rather than the expected 67%. However, this is recognised as a typical feature of large trials in this field as males are more likely to develop a DFU compared to females. The study describes the continuous use of the 3C Patch for 20 weeks but this is not how the patch would be used in routine clinical practice. The company states that the patch should be used initially for 4-6 weeks and the ulcer regularly reviewed for progress toward healing. Use of 3C Patch should continue only if adequate progress is being made, and if clinical judgement indicates that continued use is necessary to achieve complete healing. This is supported by expert opinion as set out in the document Clinical Feedback on Draft 3C Patch Pathway submitted in Part 1 clinical submission. The 3C Patch can be used for up to 20 weeks safely.
How was the study funded?	The study was funded by Reapplix. The publication states the following: "The funder of the study had no role in study design, data collection, data analysis, data interpretation or writing of the report."

3 Economic model

This section refers to the de novo economic model that you have submitted.

Description

Patients

Describe which patient groups are included in the model.

People with diabetic foot ulcers that are not healing despite standard wound care including the use of advanced dressings where appropriate.

Technology and comparator(s)

State the technology and comparators used in the model. Provide a justification if the comparator used in the model is different to that in the scope.

Technology: 3C Patch. Comparator: Good standard care, including conventional and advanced wound dressings for diabetic foot ulcers, as appropriate.

Model structure

Provide a diagram of the model structure you have chosen in Appendix B.

Justify the chosen structure of the model by referring to the clinical care pathway outlined in part 1, section 3 (Clinical context) of your submission.

The model is a Markov model which estimates the likelihood of healing, re-ulceration, major amputation, minor amputation and death over 2 years, for patients with hard to heal ulcers that have not responded to standard care, including advanced dressings where appropriate. In one arm of the model, patients receive 3C Patch care for up to 20 weeks, and in the other arm patients receive standard care for the same period, including the use of advanced dressings where appropriate, as in the 3C Patch RCT (Game et al. 2018). After the 20-week intervention period, both groups receive standard care

without 3C Patch.

The model is informed by the 3C Patch RCT, and by the clinical care pathway set out in part 1, section 3 of the submission. In the RCT, 3C Patch treatment was continued until healing or for 20 weeks in cases where healing had not occurred. The pathway set out in part 1 section 3 differs from the RCT in recommending that 3C Patch treatment should be stopped before healing in some circumstances. It proposes that:

1. If there has not been adequate progress toward healing (for example a reduction in ulcer area of 50% or more) during 4-6 weeks of 3C Patch treatment, use of the patch should be discontinued and other treatment options considered.
2. Where there has been adequate progress during 4-6 weeks of 3C Patch treatment, clinicians should consider continued use if they believe this is necessary to achieve complete healing. Clinicians should continue to monitor progress towards healing and regularly review use of the patch. Use of the patch should be discontinued if clinical judgement indicates that progress towards healing has stalled.
3. Use may also be discontinued in cases where clinical judgement indicates that sufficient progress has been made and healing is likely to be achieved without further use of the patch. In cases where good progress has been made and the patch is discontinued, 3C Patch treatment may be resumed if progress toward healing stalls.

In the Markov model, it is assumed that after 5 weeks of 3C Patch treatment, progress toward healing is assessed, and only those patients whose ulcers have reduced in area by 50% or more continue to receive 3C Patch. Unpublished data from the RCT on the proportion of patients whose ulcers have reduced by 50% or more during the first five weeks of treatment, and healing outcomes for that patient sub-group, are used to derive probabilities for the model. (The probability of healing for those who discontinue the Patch after 5 weeks is assumed to be the same as that observed in the RCT for patients in the usual care arm whose ulcers have reduced in area by less than 50% during the first 5 weeks.) It is recognised that the pathway proposes that clinical judgment be used along with objective measures of progress to decide whether to continue treatment. However, it was not possible to incorporate the element of judgment in the model.

The second and third pathway proposals on stopping use of the Patch have not been incorporated in the model, as clinical judgement is required, and it was not possible to determine from the dataset which patients would be likely to stop under these criteria. The omission of these two criteria for stopping the patch from the analysis may lead to overestimation of the cost of 3C Patch and underestimation of potential savings, relative to its likely use in the NHS if the clinical pathway is followed.

The model cycle length is one week. The health states in the model are:
Index ulcer with 3C
Index ulcer 3C discontinued
Index ulcer no 3C (for the control arm)
Healed
Major Amputation
Minor Amputation
Subsequent Ulcer
Post Major Amputation healed
Post Minor Amputation healed
Post Major Amputation Subsequent Ulcer
Post Minor Amputation Subsequent Ulcer
Dead

In each health state (apart from dead), patients have a weekly probability of remaining in that state or moving

to a different state. These transitions are shown in diagrams 1 and 2 in Appendix B. Costs and utility values are assigned to each health state and applied to the proportion of patients in that state each week. These are summed at the end of the model to provide an estimate of total cost and QALY impacts in each arm.

Model inputs are derived from the 3C Patch RCT (Game et al. 2018), and from additional analysis of the dataset from that RCT, supplemented by NHS data, evidence from peer reviewed literature and expert opinion where necessary.

The key impacts of 3C Patch in the RCT and in the model are an increase in the proportion of patients who achieve index ulcer healing, and averted weeks of ulcer care for these patients. There are also averted major and minor amputations over time. The model applies the same weekly probability of amputation to both arms while ulcerated; the higher rate of amputations arises because in the standard care arm patients spend longer in the ulcerated state. Once healing has been achieved, it is assumed that patients receive regular assessment in line with NICE guidance. In the healed state patients are at risk of re-ulceration. Amputation can occur only in the ulcerated states and, in the model, patients can only have one amputation. It is recognised that this is a simplification, but it was considered a reasonable assumption in the context of a 2-year model in order to avoid a substantial increase in model complexity.

A number of sensitivity and scenario analyses are provided, to explore the impact of key variables on model outputs.

The base case model runs for 2 years, as data from the 3C Patch RCT indicate that at 52 weeks, 45.8% of 3C Patch patients and 53.7% of standard care patients remain unhealed. (These figures are based on only those patients for whom 52 week follow up data were recorded; data were not available for 11% of 3C Patch patients (7% of those who were unhealed at week 20) and 19% of standard care patients (16% of those unhealed at week 20). It is possible therefore that these figures underestimate the proportion unhealed at week 52, particularly in the standard care arm.) As a major cost driver for these patients is ulcer duration, and it is known that some diabetic foot ulcers never heal, it was considered important to run the model for a second year to capture the full impact of increased healing probability and shorter ulcer duration associated with 3C Patch. The model predicts that at the end of the second year, for 11.8% of 3C Patch patients and 13.6% of usual care patients, the index ulcer remains unhealed. This indicates that there are likely to be further cost and QALY benefits associated with 3C Patch in year 3. It was considered that decision makers would be more interested in a shorter time frame for benefits. However, in supplementary analysis the model is run for 3 years.

Table 2 Assumptions in the model

In this table, list the main assumptions in the model and justify why each has been used.

Assumption	Justification	Source
All patients start with a hard to heal ulcer that is not healing despite standard care including advanced dressings where appropriate	These were the ulcers studied in the 3C Patch RCT and proposed in the draft clinical pathway.	Game et al. 2018, 3C Patch draft clinical pathway
Patients receiving 3C Patch are reviewed after 5 weeks, and 3C Patch is continued only for patients whose ulcers have reduced in area by ≥50%.	This is in line with the draft clinical pathway, though the pathway also stresses the importance of clinical judgement.	3C Patch draft clinical pathway
Patients who continue 3C Patch treatment after 5 weeks continue with 3C Patch until healing or up to 20 weeks if healing does not occur	This is in line with the 3C Patch RCT (though in the RCT it applied to all 3C Patch patients as the protocol did not include provision for stopping at 5 weeks if sufficient progress had not been made). It is also in line with the draft clinical pathway, though the pathway also allows for 3C Patch to be stopped at any point after 5 weeks if clinical judgement indicates either that progress toward healing has stalled, or that healing is likely to be completed without further use of 3C Patch. This is a conservative assumption.	Game et al. 2018, 3C Patch draft clinical pathway
Patients in the 3C Patch arm have weekly clinic visits. At each visit clinicians decide whether to apply a new patch. Each patch lasts one week and is not replaced during that time.	This is in line with the 3C Patch RCT and the draft clinical pathway.	Game et al. 2018, 3C Patch draft clinical pathway
Patients in the standard care arm of the model receive good standard care, including advanced dressings where appropriate. Clinic visits (MDFT or foot protection service) are fortnightly.	The use of good standard care is in line with the 3C Patch RCT. In the RCT, patients in the standard care arm had weekly clinic visits. However, expert opinion indicates that this is not usual practice in the NHS unless ulcers are infected. Conservatively, we adjust the frequency of clinic visits to fortnightly for	Game et al. 2018, Expert opinion

	standard care patients, relative to that observed in the RCT, but we do not adjust healing rates.	
The distribution of severe and less severe index ulcers is as seen in NDFA. (Although these ulcers are hard to heal, they are not considered to be more severe in terms of SINBAD score than average ulcers, and weekly costs of treatment are assumed to be the same as for average ulcers, apart from cost adjustments specific to 3C Patch.)	Conservative assumption.	Expert opinion
When patients stop 3C Patch treatment, they receive good standard care, as for patients in the standard care arm of the model.	Expert opinion indicates that this is likely. It is also an important modelling assumption, to avoid bias in the results.	Expert opinion
After ulcer healing, all patients receive care in line with NICE guidance for those at high risk of developing a diabetic foot problem.	Expert opinion indicates that this is likely.	NICE Guideline NG19 Diabetic Foot Problems: Prevention and Management
Patients who have healed are at risk of re-ulceration. If re-ulceration occurs, the distribution of severe and less severe ulcers, and associated healing rates, are as seen in NDFA. It is not assumed that these subsequent ulcers are hard to heal.	No clinical evidence was found to indicate that subsequent ulcers are more likely than average to be hard to heal in patients who have had a previous hard to heal ulcer. Some studies indicate that subsequent ulcers tend to be less severe than index ulcers in patients who have been treated in a multidisciplinary setting, owing to good quality follow-up and patient education.	Expert opinion, Hicks et al. 2020
Amputations occur only when patients have active ulcers		Expert opinion
A maximum of one amputation occurs in the model	This is considered a reasonable assumption over the 2-year model horizon, to avoid unnecessary complexity in the model. It is a conservative assumption, as additional amputations would be more likely in the standard care arm owing to increased risk of a first amputation in the index ulcer state, owing to increased ulcer duration.	

Table 3 Clinical parameters, patient and carer outcomes and system outcomes used in the model

In this table, describe the clinical parameters, patient and carer outcomes and system outcomes used in the model.

Parameter/outcomes	Source	Relevant results	Range or distribution	How are these values used in the model?
Weeks 1-20 index ulcer healing rate, 3C Patch	Game et al. 2018	34%	N/A	This value is not used, as the 3C cohort is divided into two sub-groups after 5 weeks of care, and separate healing rates are applied to these sub-groups.
Weeks 1-20 index ulcer healing rate, standard care arm	Game et al. 2018	22%	N/A	This value is not used directly in the model. Separate healing rates are calculated for weeks 1-5 and 6-20, to align with the 3C Patch arm. However, overall healing by week 20 for this group is equivalent to the weeks 1-20 healing rate.
% of patients whose index ulcers reduce in area by ≥50% in first 5 weeks of treatment, 3C Patch	Supplementary analysis of 3C Patch RCT dataset	43.2%	N/A	This value is used to derive the percentage of patients in the model who continue with 3C Patch treatment after week 5.
Weeks 1-5 index ulcer healing rate, 3C Patch	Supplementary analysis of 3C Patch RCT dataset	3.0%	N/A	This value is used to derive the weekly probability of healing in weeks 1-5 for 3C Patch patients.
Weeks 1-5 index ulcer healing rate, standard care	Supplementary analysis of 3C Patch RCT dataset	3.7%	N/A	This value is used to derive the weekly probability of healing in weeks 1-5 for standard care patients.
Weeks 6-20 index ulcer healing rate for patients whose ulcers reduce in area by ≥50% in first 5 weeks of treatment, 3C Patch	Supplementary analysis of 3C Patch RCT dataset	58%	N/A	This value is used to derive the weekly probability of healing in weeks 6-20 for patients who continue 3C Patch after week 5.
Weeks 6-20 index ulcer healing rate for patients whose ulcers do not reduce in area by ≥50% in first 5 weeks of treatment, standard care	Supplementary analysis of 3C Patch RCT dataset	9.7%	N/A	This value is used to derive the weekly probability of healing in weeks 6-20 applied in the model to patients who stop 3C Patch treatment after 5 weeks.

Weeks 6-20 index ulcer healing rate, all standard care patients	Supplementary analysis of 3C Patch RCT dataset	18.8%	N/A	This value is used to derive the weekly probability of healing in weeks 6-20 for patients in the standard care arm of the model.
Weeks 21-52 index ulcer healing rate, all patients	Supplementary analysis of 3C Patch RCT dataset	33.7%	N/A	This value is used to derive the weekly probability of index ulcer healing in weeks 21-52 for patients in both arms. There was no significant difference in healing in this period between the two trial arms. This probability is also applied to weeks 53-104.
Weeks 1-26 major amputation rate, all patients	Game et al. 2018, and Supplementary analysis of 3C Patch RCT dataset	1.5%	N/A	This value is used to derive the weekly probability of major amputation for patients in both arms. There was no significant difference in major amputations between the two trial arms. The amputation data were adjusted for healing when calculating the weekly probability.
Weeks 1-26 minor amputation rate, all patients	Game et al. 2018, and Supplementary analysis of 3C Patch RCT dataset	6.4%	N/A	This value is used to derive the weekly probability of minor amputation for patients in both arms. There was no significant difference in minor amputations between the two trial arms. The amputation data were adjusted for healing when calculating the weekly probability.

If any outcomes listed in table 4 are extrapolated beyond the study follow-up periods, explain the assumptions that underpin this extrapolation.

The follow-up period for the 3C Patch RCT (Game et al. 2018) was 52 weeks. The Markov model runs for 2 years, as supplementary analysis of the RCT dataset indicates that at 52 weeks, 45.8% of 3C Patch patients and 53.7% of usual care patients remain unhealed (Appendix C). As a major cost driver for these patients is ulcer duration (and it is known that some diabetic foot ulcers never heal), it was considered important to run the model for at least a second year to capture the full impact of increased healing probability and shorter ulcer duration associated with 3C Patch. It is assumed in the model that the weekly probability of healing in weeks 53-104 is the same as in weeks 21-52. The same weekly healing probability is applied to the 3C Patch and usual care arms from week 21 onwards, as the RCT dataset indicated that there was no significant difference in healing between the two cohorts in weeks 21-52. The weekly probabilities of major amputation, minor amputation, subsequent ulceration, subsequent ulcer healing and death are assumed to be the same in year 2 as in year 1. The probabilities of subsequent ulceration, subsequent ulcer healing and death (which varies depending on whether patients are ulcerated or healed, and by

whether they have undergone a major amputation) were sourced from NHS data and the literature, as shown in Table 4, below. The rate of major and minor amputation is sourced from the RCT for weeks 1-20 and adjusted for healing week by week during that period, to estimate the probability of amputation for each ulcerated week. While the incidence of major and minor amputation was recorded at week 52, there were no weekly data on the incidence of healing for that period, so it was not possible to calculate the probability of amputation for each ulcerated week beyond week 26. The weekly probability calculated for weeks 1-26 was therefore applied also to weeks 27-104. There was no significant difference in the probability of major or minor amputation between the 3C and usual care group during weeks 1-26. The same probabilities were therefore applied to both arms of the model. The probabilities were validated by comparing with National Diabetes Footcare Audit (NDFA) data and Public Health England Diabetes Footcare Profiles. During the first 26 weeks of the study, 1.5% of the combined study cohort had a major amputation rate of the index limb. In NDFA 2015-18, 1.6% of patients had a major amputation within 6 months of first expert assessment. NDFA does not provide data on minor amputations. The Diabetes Footcare Profiles indicate that the ratio of major to minor amputations in people with diabetes in England in 2016-2019 was 1:2.69. In the RCT, the ratio of index limb major to minor amputations was 1:4.25. This is higher than in the Footcare Profiles. It is considered clinically plausible as hard to heal ulcers may have a higher risk of minor amputation than average ulcers. (Expert opinion also indicates that hard to heal ulcers may have a higher probability than average ulcers of major amputation. Owing to the size of the trial cohort and the relative rarity of major amputation no firm conclusions can be reached on this.)
Owing to the very long duration of some hard to heal DFUs, the model is extended to 3 years in supplementary analysis. The probabilities applied to weeks 105-156 are the same as for weeks 53-104.

Table 4 Other parameters in the model

Describe any other parameters in the model. Examples are provided in the table. You can adapt the parameters as needed.

Parameter	Description	Justification	Source
Time horizon	2 years (In supplementary analysis the model is extended to 3 years.)	Many hard to heal ulcers remain unhealed after 1 year, as observed in the 3C Patch RCT follow-up data. A main driver of cost and QALY impacts of hard to heal DFUs is extended duration. In order to capture these impacts it is necessary to run the model for at least two years.	Game et al. 2018, and supplementary analysis of trial dataset, provided in Appendix.
Discount rate	3.5% annual	NICE recommended rate	NICE
Perspective (NHS/PSS)	NHS	It is likely that hard to heal DFUs incur PSS costs. However, no data source was identified to support robust estimation of these costs. The analysis therefore focuses	N/A

		only on NHS costs.	
Cycle length	1 week	This was considered the most appropriate cycle length for DFUs and is in line with the 3C Patch RCT which provided weekly review of progress toward healing.	N/A

Transition probabilities

Variable		Weekly probability	Source
% of 3C Patch arm who stop 3C treatment (Pdiscontinuation3C)	Week 5	0.57853	3C Patch RCT data; 75 out of 128 ulcers unhealed after 5 weeks had not reduced in area by 50% or more; probability adjusted to account for modelled healing, death and amputation in week 5 of treatment.
	Week 20	0.93655	Remainder of Index Ulcer With 3C patients who do not heal, have an amputation or die in this week of the model.
Index ulcer healing rate - usual care (Phealingno3C)	Weeks 1 - 5	0.00758	3C Patch RCT data; [redacted]
	Weeks 6 - 20	0.01375	3C Patch RCT data; of the 128 patients in the control arm that were unhealed and still in trial after 5 weeks, 24 healed by week 20.
	Weeks 21 - 104	0.01277	3C Patch RCT data; of the 169 patients in the trial (both arms) who had not healed by 20 weeks and for whom there was 52 week data, 57 healed by 52 weeks.
Index ulcer healing rate - 3C Patch (Phealing3C)	Weeks 1 - 5	0.00614	3C Patch RCT data; [redacted]
	Weeks 6 - 20	0.05693	3C Patch RCT data; of the 53 ulcers in the 3C Patch arm which were unhealed but had reduced in area by 50% or more after 5 weeks, 31 healed by week 20.

	Weeks 21 - 104	0.01277	3C Patch RCT data; of the 169 patients in the trial (both arms) who had not healed by 20 weeks and for whom there was 52 week data, 57 healed by 52 weeks.
Index ulcer healing rate - 3C Patch discontinued (Phealing3Cdiscontinued)	Weeks 6 - 20	0.00676	3C Patch RCT data from the equivalent cohort in the **control arm** (assumes no benefit from 3C Patch treatment); of the 93 ulcers in the control arm which were unhealed, still in the study and had reduced in area by less than 50% after 5 weeks, 9 healed by week 20.
	Weeks 21 - 104	0.01277	3C Patch RCT data; of the 169 patients in the trial (both arms) who had not healed by 20 weeks and for whom there was 52 week data, 57 healed by 52 weeks.
Major amputation rate (Pmajoramputation)		0.00071	3C Patch RCT data; 1.5% of patients had a major amputation within 26 weeks; probability adjusted to apply to ulcerated weeks at risk.
Minor amputation rate (Pminoramputation)		0.00301	Game et al 2018; 17 out of 266 patients in the trial (both arms) had a minor amputation on the index limb over 26 weeks; population adjusted to apply to ulcerated weeks at risk.
Death rate - ulcerated with no major amputation (Pdeathulcer)		0.00280	NDFA; 6.5% of patients died within 24 weeks of first expert assessment of ulcer.
Death rate - ulcer free with no major amputation (Pdeathhealed)		0.00196	Jupiter et al 2016, estimate of 5 year mortality post ulcer from review of studies.
Death rate - after major amputation (Pdeathpostmajoramputation)		0.00507	Average of 5 year mortality from Icks et al 2011 (68%) and Ikonen et al 2010 (78.7%).
Reulceration rate (Psubsequentulcer)		0.00586	Armstrong et al; 60% of patients reulcerate within 3 years of healing.
Subsequent ulcer healing rate (Phealingsubsequentulcer)		0.04687	NDFA 2014-17; 24 week rate: 65.5% and additional 2.9% who were ulcer free and then reulcerated.

Health state utilities

Health state	Weekly QALY value	Source
Index ulcer with 3C (Uulcer)	0.00846	Tennvall et al 2000 (utility = 0.44)
Index ulcer 3C discontinued (Uulcer)	0.00846	Tennvall et al 2000 (utility = 0.44)
Index ulcer no 3C (Uulcer)	0.00846	Tennvall et al 2000 (utility = 0.44)
Healed (Uhealed)	0.01154	Tennvall et al 2000 (utility = 0.6)
Major amputation (Umajoramputation)	0.00596	Tennvall et al 2000 (utility = 0.31)
Minor amputation (Uminoramputation)	0.01173	Tennvall et al 2000 (utility = 0.61)
Post major amputation healed (Umajoramputation)	0.00596	Tennvall et al 2000 (utility = 0.31)
Post minor amputation healed (Uminoramputation)	0.01173	Tennvall et al 2000 (utility = 0.61)
Subsequent ulcer (Uulcer)	0.00846	Tennvall et al 2000 (utility = 0.44)
Post major amputation subsequent ulcer (Umajoramputation)	0.00596	Tennvall et al 2000 (utility = 0.31)
Post minor amputation subsequent ulcer (Uulcer)	0.00846	Tennvall et al 2000 (utility = 0.61)

Sources of unit costs

Variable	Weekly cost	Source
Ulcer outpatient, community and primary care cost (Culceropcp)	£135.97	Kerr et al 2019
Ulcer inpatient cost (Culcerip)	£92.51	Kerr et al 2019, NHS Reference Costs
3C Patch cost (C3CPatch)	£125.40	Reapplix

3C Patch secondary dressings cost (C3Csecondarydress)		£0.39	List price; 3 per week
Standard care dressings cost (Cstandcaredressings)		£12.47	3C Patch RCT dataset
3C Patch medications cost (C3Cmeds)		£7.13	3C Patch RCT dataset
Standard care medications cost (Cstandcaremeds)		£9.70	3C Patch RCT dataset
3C Patch training cost (C3Ctraining)		£1.05	Expert advice; PSSRU Unit Costs for band 4 and band 6 clinical staff (nurses and podiatrists)
3C Patch extra podiatry cost (C3Cextrapodiatry)		£16.22	Expert advice; PSSRU unit costs for band 6 clinical staff
3C Patch extra nursing cost (C3Cextranursing)		£5.26	Expert advice; PSSRU Unit Costs for band 4 clinical staff (and band 6 in sensitivity analysis)
3C Patch district nursing impact (C3CDNimpact)		-£25.71	3C Patch RCT data; PSSRU unit costs for band 6 clinical staff
Index ulcer with 3C (Cindexulcer3C)		£358.22	Culceropcp + Culcerip + C3CPatch + C3Cmeds + C3Csecondarydress + C3Ctraining + C3Cextrapodiatry + C3Cextranursing + C3CDNimpact
Index ulcer no 3C (Cindexulcerstandcare)		£250.65	Culceropcp + Culcerip + Cstandcaredressings + Cstandcaremeds
Healed (Chealed)		£4.05	PSSRU; assume seen by band 6 podiatrist every 6 weeks for 15 mins
Major amputation (Cmajoramputation)		£12,139.24	Kerr et al 2019, NHS Reference Costs
Minor amputation (Cminoramputation)		£5,933.22	Kerr et al 2019, NHS Reference Costs
Post major amputation costs (Cpostmajoramputation)	Y1	£63.22	Kerr et al 2019
	Y2	£18.88	Kerr et al 2019
Post minor amputation costs (Cpostminoramputation)	Y1	£20.23	Kerr et al 2019
	Y2	£0.59	Kerr et al 2019
Subsequent ulcer (Csubsequentulcer)		£250.65	Culceropcp + Culcerip + Cstandcaremeds + Cstandcaredressings

Health state costs

Health state	**Weekly cost (variable as above)**
Index ulcer with 3C	Cindexulcer3C
Index ulcer 3C discontinued	Cindexulcerstandcare
Index ulcer no 3C	Cindexulcerstandcare
Healed	Chealed
Major amputation	Cmajoramputation
Minor amputation	Cminoramputation
Post major amputation healed	Cpostmajoramputation + Chealed
Post minor amputation healed	Cpostminoramputation + Chealed
Subsequent ulcer	Csubsequentulcer
Post major amputation subsequent ulcer	Cpostmajoramputation + Csubsequentulcer
Post minor amputation subsequent ulcer	Cpostminoramputation + Csubsequentulcer

Explain the transition matrix used in the model and the transformation of clinical outcomes, health states or other details.

All patients start with a hard to heal index ulcer. The initial health states are **Index Ulcer with 3C** and **Index Ulcer no 3C** (standard care arm).

In the standard care arm, patients continue to receive good standard care including use of advanced dressings as appropriate, for as long as they remain ulcerated. In the 3C Patch arm, patients receive 3C Patch care for up to 20 weeks. Patients receiving 3C Patch are reviewed after 5 weeks, and 3C Patch is continued only for patients whose ulcers have reduced in area by ≥50% during that period. Those who discontinue 3C Patch at this point transition to the **Index ulcer 3C discontinued** health state, and receive good standard care, as provided to the standard care arm.

In all index ulcer health states, patients have a probability in each weekly cycle of staying in the same state or transitioning to one of the following states: **Healed, Major Amputation, Minor Amputation, Dead**. Healing probabilities in each index ulcer state are derived from the 3C Patch RCT report and dataset, as described in table 3, above.

The probabilities of transition to major and minor amputation states from index ulcer states are derived from the 3C Patch RCT report and dataset, as described in table 3, above. The same probabilities are applied to all index ulcer states (both model arms), as the RCT data indicated no significant difference in the probability of amputation per ulcerated week between the study arms. (It should be noted however that over time more patients in the standard care arm of the model have amputations owing to longer ulcer duration.)

Patients remain in the **Major Amputation** and **Minor Amputation** states for only one weekly cycle. After this they move to a post amputation state (healed or subsequent ulcer) or to the **Dead** state.

Patients in the healed states can transition to **Subsequent Ulcer** or **Dead** states, or can remain in the healed state. The probability of subsequent ulceration is derived from the literature (Armstrong et al. 2017) and is the same for all healed states. The probability of healing after subsequent ulceration is the same for both arms of the model, and all subsequent ulcer states, and is derived from the National Diabetes Foot Care Audit (NDFA).

The probability of death is derived from NDFA and from the literature, as set out in Table 4, and varies depending on ulcer and major amputation status.

The transitions are presented diagrammatically in Appendix B.

Transition probabilities estimated for time periods of multiple weeks were converted into rates and then weekly transition probabilities using the following method:

Weekly rate (r) = [-ln(1-P)]/t

Weekly probability = 1 – exp {-rt}

Where:
P = probability, t = number of weeks

Resource identification, measurement and valuation

Technology costs

Provide the list price for the technology (excluding VAT).

£150

If the list price is not used in the model, provide the price used and a justification for the difference.

The list price is used in the model.

NHS and unit costs

Describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs, the national tariff and unit costs (from PSSRU and HSCIC). Please provide relevant codes and values (e.g. OPCS codes and ICD codes) for the operations, procedures and interventions included in the model.

Costs in the model are derived from Kerr et al. 2019, adjusted using resource use data from the 3C Patch RCT where available, and updated with more recent cost data from NHS Reference Costs, NHS tariffs, and PSSRU Unit Costs for staff inputs where appropriate.

All costs are inflation-adjusted where necessary using factors derived from PSSRU Unit Costs of Health and Social Care 2020 NHS cost inflation index (NHSCII), and are presented in 2020-21 prices.

Inpatient care

The following HRGs were used to estimate unit costs for inpatient care:

Major amputation: HRGs YQ21-22B (Amputation of single limb, with and without other blood vessel procedures), weighted average cost based on activity in NHS Reference Costs 2018-19.

Minor amputation: HRGs YQ24-26 (Single, Amputation Stump or Partial Foot Amputation Procedure, for Diabetes or Arterial Disease, with and without other blood vessel procedures), weighted average cost based on activity in NHS Reference Costs 2018-19.

Inpatient bed day for DFU care: HRGs KB03C-D (Diabetes with lower limb complications), weighted average

bed day cost used based on activity in NHS Reference Costs 2017-18, as bed day costs were not provided in 2018-19. This cost is used for excess bed days in admissions grouped to HRGs not considered to be primarily related to foot care, as defined in Kerr et al. 2019.

(Inpatient costs for DFU are derived from Kerr et al. 2019. In this paper, inpatient admissions that include diabetic foot care are identified using a range of ICD-10 and OPCS-4 codes. These codes are also used to identify DFU inpatient admissions for Public Health England Footcare Profiles, and are shown in Appendix C, TABLE C1. In Kerr et al., admissions identified using these codes are sub-divided into two categories, depending on the HRG to which the care is assigned for tariff purposes. For category 1, admissions grouped to HRGs that are considered to be primarily related to foot care, the full tariff for the admission is counted. A list of these HRGs can be found in Kerr et al. 2019. For category 2, admissions grouped to HRGs not primarily related to foot care, it was considered likely that much of the care received was unrelated to the foot and costs were estimated only for excess bed days relative to admissions for people with diabetes who did not have DFU. In estimating the average weekly cost of ulcer care in our model, we use data from Kerr et al. to estimate inpatient care costs, adjusting the cost of inpatient bed days for admissions in category 2 using more recent Reference Cost data, as indicated above.

Outpatient, community and primary care for DFUs

Activity and costs in these settings in the model are derived from Kerr et al. 2019, adjusted using data from the 3C Patch RCT where available, and updated using more recent cost sources where available. Routine NHS datasets do not provide sufficient granularity to identify discretely most DFU-specific care in these settings.

Costs derived from Kerr et al. are adjusted as follows:

- Dressing and medication costs are deducted from Kerr et al. 2019 cost estimates, and estimated directly from the 3C Patch RCT dataset, for both usual care and 3C Patch. Details are given in Appendix C.
- Costs of staff time for training for 3C Patch are estimated using PSSRU Unit Costs for band 4 and band 6 clinical staff (nurses and podiatrists).
- Additional weekly podiatry resource for 3C Patch is costed using PSSRU unit costs for band 6 clinical staff.
- Additional clinical input for phlebotomy and centrifuge operation for 3C Patch is costed using PSSRU Unit Costs for band 4 clinical staff (and band 6 in sensitivity analysis).
- Marginal changes in district nurse inputs between 3C Patch and usual care are costed using PSSRU unit costs for band 6 clinical staff.

Outpatient attendances in NHS Reference Costs are identified by speciality. It is likely that most DFU outpatient care is coded to Diabetic Medicine (307). However, it is not possible discretely to identify DFU outpatient care (as distinct from other diabetes outpatient care) as outpatient data do not provide this degree of granularity.

Data on community care for DFUs are not provided in NHS Reference Costs or national tariff datasets. Much of this care is funded via block contracts and activity is recorded in local datasets, which do not generally provide granular detail on diagnoses or procedures.

Some DFU care takes place in primary settings, in particular prescribing of dressings and medications. (Where care is managed in outpatient or community settings, some prescribing is undertaken by primary care.) Snomed or Read codes can be used to identify diabetic foot ulcer diagnosis in primary care databases. However, primary care databases are not considered a good source for understanding the clinical management or costs of DFU; they are likely to be incomplete in terms of diagnosis, care, resources and outcomes as most ulcer care does not take place in primary care. NICE guidance recommends that all patients with active diabetic foot problems should be referred to the multidisciplinary foot care service or foot protection service. Primary care datasets do not contain detail of the care provided by these services.

Post amputation care

Post amputation care costs are derived from Kerr et al. 2019, updated using more recent cost sources where available. Routine NHS datasets do not provide sufficient granularity to identify discretely diabetic foot care in these settings.

Costs derived from Kerr et al. are adjusted as follows:

- Wheelchair costs are taken from NHS Reference Costs 2018-19 (Weighted average costs of WC01-04, Wheelchair Services Adults, Assessment, WC05-08, Wheelchair Services Adults, Equipment, and WC90-10, Wheelchair Services Adults, Repair and Maintenance)
- Physiotherapy costs are taken from NHS Reference Costs 2018-19 (WF01B Non-Admitted Face-to-Face Attendance, First, Physiotherapy and WF01A Non-Admitted Face-to-Face Attendance, Follow up, Physiotherapy)

Resource use

Describe any relevant resource data for the NHS in England reported in published and unpublished studies. Provide sources and rationale if relevant. If a literature search was done to identify evidence for resource use then please provide details in appendix A.

Details of the literature search are provided in Appendix A. Four papers were considered relevant. These were:

1. Jeffcoate WJ, Price PE, Phillips CJ, Game FL, Mudge E, Davies S et al. Randomised controlled trial of the use of three dressing preparations in the management of chronic ulceration of the foot in diabetes. Health Technol Assess 2009; 13: 1–86, iii–iv. (Jeffcoate et al. 2009)
2. Kerr M, Rayman G, Jeffcoate WJ. Cost of diabetic foot disease to the National Health Service in England. Diabet Med 2014; 31: 1498–1504. (Kerr et al. 2014)
3. Kerr M, Barron E, Chadwick P et al. (2019). The cost of diabetic foot ulcers and amputation to the National Health Service in England. Diabetic medicine 36 (8): 995-1002 (Kerr et al. 2019)
4. Guest JF; Fuller GW; Vowden P (2018). Diabetic foot ulcer management in clinical practice in the UK: costs and outcomes. International wound journal; Feb 2018; vol. 15 (no. 1); p. 43-52. (Guest et al. 2018)

Paper 1 (Jeffcoate et al. 2009) is a report of a randomised controlled trial of three dressings. It contains details of resource use for dressings, staff inputs, and medications for the trial period. Participants in the trial all had less severe ulcers. This paper does not set out to provide comprehensive estimates of the cost of diabetic foot care. It does not contain details of inpatient resource use, and patients do not have access to the full range of dressings available in usual care. This paper is therefore not used to estimate costs for the economic model.

Paper 2 (Kerr et al. 2014) is an attributable cost of illness study, setting out comprehensive estimated costs for foot ulcers and amputations in diabetes over 12 months for the NHS in England. However, the third paper, produced by the same team, provides updated cost estimates and methodology. This paper is therefore not used to estimate costs for the economic model.

Papers 3 and 4 are both attributable cost of illness studies. A detailed comparison of these two papers was

undertaken in order to identify the best source for cost inputs to the model.

Paper 3 (Kerr et al. 2019) estimates weekly costs per patient for community, outpatient and primary care, and aggregate national costs for inpatient care, using estimates of weekly ulcer prevalence to combine these into an overall estimate of annual cost to the NHS. Paper 4 (Guest et al. 2018) estimates costs per patient over 12 months for healed and unhealed incident DFUs.

Kerr et al. 2019 estimates the cost of diabetic foot ulcers to the NHS in England in 2014-15, based on data from a variety of sources. For inpatient activity relating to ulcers and amputations, Hospital Episode Statistics at patient-level are used to identify all hospital admissions relating to the diabetic foot in England during a 12-month period, using the OPCS-4 and ICD-10 codes that are also used by Public Health England for Diabetic Foot Care Profiles. Costs are estimated for these admissions using NHS Reference Costs and inpatient tariffs. Regression analysis is undertaken to estimate the impact of ulceration on length of stay in admissions that are not primarily for foot care, relative to that for people with diabetes who do not have DFU. Bed day costs are estimated for these admissions, derived from NHS Reference Costs.

For outpatient, community and primary care, activity and weekly costs of ulcer care are estimated separately for severe and less severe ulcers. Resource use for less severe ulcers is derived from a 2009 RCT on dressing use (Jeffcoate et al. 2009). Resource use for severe ulcers is based on data provided by a London MDFT on all care provided for patients with severe DFUs (defined as SINBAD ≥3) over a 12-month period.

Guest el al. 2018 uses the THIN primary care database to estimate mean costs for 12 months for unhealed and healed diabetic foot ulcers (believed to be 2012-13 data, 2015-16 prices). These estimates are based on resource use recorded in THIN for a sample of 130 patients with incident diabetic foot ulcers. Costs are estimated for primary, community, outpatient and inpatient care.

Average weekly costs for outpatient, community and primary ulcer care are almost identical in the two papers (inflation-adjusted and excluding dressing and medication costs as values for these in the model are taken from the 3C Patch RCT); £135.97 in Kerr et al. 2019 (weighted average based on distribution of severe and less severe ulcers in NDFA), and £136.65 in Guest et al. 2018 (weighted average of healed and unhealed ulcer costs, with healed ulcer costs adjusted for mean time to healing).

In the model the estimate from Kerr et al. 2019 is used as the basis for cost estimation in these settings as it is considered a better source for care in outpatient (multidisciplinary foot care) and community settings (foot protection services and district nursing), where expert opinion suggests that most DFU care takes place. NICE guidance recommends that all patients with active diabetic foot problems should be referred to a multidisciplinary foot care service or foot protection service. Primary care databases do not contain granular detail on care in outpatient or community settings; much activity such as district nurse visits must therefore be inferred and multidisciplinary foot care and foot protection service care cannot be accurately captured. However, as there is so little difference between the estimated cost of care in these settings, the choice between these two papers as the source of a cost estimate for this element of care will not make a material impact on the model.

Kerr et al. 2019 estimates inpatient costs for ulcer care based on HES data for all inpatient activity in England over 12 months, with relevant activity identified by means of OPCS-4 and ICD-10 codes, as outlined above. These costs are estimated at £270.93 million a year in England (£299.26 million in 2021-21 prices). If it is assumed that on average 2.25% of people with diabetes have active foot ulceration in any given week (assumption in Kerr et al 2019, Scottish audit data used as a proxy as no comparable data source identified for England), the mean average weekly cost of inpatient care per ulcerated week is estimated at £92.51.

Guest et al. 2018 estimates inpatient costs at £46.57 (£51.26 inflation adjusted) per patient per year (£0.99 per week) for unhealed DFUs and £0 for healed DFUs.

These estimates were compared with NDFA data based on 33,155 ulcers in England and Wales in 2015-18, which indicate that there were on average 2.82 inpatient bed days in foot disease-related hospital admissions per ulcer within 6 months of first expert assessment. Using the weighted average bed day cost from HRGs KB03C-D (Diabetes with lower limb complications) in NHS Reference Costs 2017-18 (inflation-adjusted), £456.63, to provide an illustrative cost, and estimating mean ulcer duration at 13.58 weeks during this 6 month period, based on reported healing and death rates in NDFA (72.7% of patients have healed or died within 24 weeks – weekly probability assumed constant and applied over 26 weeks) the average cost of these admissions per ulcerated week is estimated at £94.34. This estimate is based only on admissions in the first 6 months of ulceration and is used here only for validation.

Expert opinion indicates that primary care databases such as THIN do not contain sufficiently granular detail on inpatient admissions to support estimation of activity or costs attributable to DFUs in this setting. Kerr et al. 2019 estimates for inpatient activity and costs are used in the model, as these are directly estimated from patient-level activity recorded in HES, using validated OPCS-4 and ICD-10 codes to identify DFU care.

Kerr et al. 2019 estimates of post-amputation care are used, adjusted with more recent Reference Cost data where appropriate. Guest el al. does not provide estimates of these costs.

Describe the resources needed to implement the technology in the NHS. Please provide sources and rationale.

Reapplix will provide the centrifuges used to create 3C Patches, free of charge to the NHS. They will also provide training for NHS staff in using the centrifuge to create the patch, in phlebotomy where necessary, and in applying the patch to an ulcer. Initial training and subsequent training for new staff or those who require a refresher course will be provided. These training sessions will be free of charge. (Source: Reapplix)

In addition to funding for the patch it is expected that the following NHS resources will be required to implement the technology in the NHS:

- NHS staff time for training sessions
- Additional staff inputs for phlebotomy and centrifuge operation
- Additional staff inputs for podiatry consultations

Partially offsetting these additional inputs, it is expected that there will be a reduction in the use of the following NHS resources:

- Dressings used in standard care
- District nurse inputs for dressing changes.

NHS staff time for training sessions

It is assumed that, in each foot care clinic, 2 band 3 healthcare assistants (HCAs) or band 4 nurses and 2 band 6 podiatrists are trained to use 3C Patch, and that training takes 2 hours per year on average (allowing for annual refresher courses and/or training of new staff). The cost of staff time for training is estimated at £330 (based on unit costs of £31 per hour for band 4 nurses and £50 per hour for band 6 podiatrists).

In order to apportion these costs across patients, it is necessary to estimate the likely number of patients to be

seen in a centre per year. This will depend on a number of factors, including the size of the diabetes population in the catchment area for a diabetic foot service, the incidence of ulcers, and the prevalence of other conditions included in the eligibility criteria for 3C Patch. There is uncertainty regarding all of these variables, and there will be variability across the country.

In our base case we assume that the average number of people with diabetes living in the catchment area for a diabetic foot service is 20,000. It has been estimated that 2.2% of the diabetes population experiences at least one new foot ulcer each year (Abbott er al. 2002). The number of new ulcers is likely to be higher than this, as some patients will experience more than one ulcer in a year. Taking 2.2% as a conservative estimate of ulcer incidence, we estimate that 440 patients would present with new ulcers each year from a diabetes catchment population of 20,000.

Inclusion criteria for the 3C Patch RCT included ankle brachial pressure index (ABPI) in the affected limb between 0.50 and 1.40 or the dorsalis pedis pulse and/or the tibialis posterior pulse palpable (thus excluding those with severe ischaemia). The prevalence of ABPI <0.45 has been estimated at 10% in people with diabetic foot ulcers (Reiber et al. 1999). There are a number of other exclusion criteria.

We assume here that 20% of patients with incident foot ulcers are not eligible for consideration for 3C owing to these criteria. The draft clinical pathway proposes that patients should be treated with best standard care for at least 6 weeks before 3C Patch is used. It is uncertain what proportion of patients would heal in this time or make sufficient progress that 3C Patch would not be considered. NDFA 2018 data indicate that 48.3% of patients with incident ulcers have persistent ulceration at 12 weeks. It is assumed here that those who heal or die within 12 weeks would not be screened for 3C Patch. Data from the RCT indicate that in the usual care arm, 9% of ulcers were infected in any given week. We therefore assume that 9% of ulcers would not be eligible for 3C screening owing to infection at the beginning of the screening period.

This would suggest that approximately 154 people each year may be eligible for 4-week screening for 3C Patch in a centre serving a catchment diabetes population of 20,000. In the RCT, 45% of those who undertook the screening were eligible for randomisation. (Most of the remainder were excluded owing to reduction in ulcer size during the 4 weeks.) If this pattern were repeated in routine practice, approximately 69 patients per year might be eligible for 3C in a centre of this size. If this were so, the apportioned cost of training per patient treated would be £4.78 (equivalent to £0.53 per treatment week, assuming 9 mean treatment weeks per patient.

It is acknowledged, however, that in usual practice clinicians may choose to use 3C Patch for fewer patients than the potentially eligible cohort, and/or may delay the screening period to allow a longer time frame for healing using standard care. If the numbers treated were 50% of the estimated eligible cohort, 35 per year, and mean treatment time with 3C Patch were 9 weeks the apportioned cost of training per patient per week of 3C Patch treatment would be £1.05. This value is used in the economic model, and is considered a conservative assumption. If the numbers treated were 35 per year, and mean treatment time with 3C Patch were 6 weeks the apportioned cost of training per patient per week of 3C Patch treatment would be £1.57. (Source: Draft clinical pathway, 3C Patch RCT data, literature, expert opinion)

Additional staff inputs for phlebotomy and centrifuge operation

It is considered likely that band 4 nurses will undertake phlebotomy and will operate the centrifuge in many centres. It is estimated that 10 minutes on average of a band 4 nurse's time will be required for these tasks for each patient clinic attendance involving 3C Patch application. (The centrifuge takes 20 minutes to produce a patch, but it is assumed that the nurse will undertake other tasks while the centrifuge is operating.) Some clinics may not have band 4 nursing input. If so, it may be possible to provide such input by scheduling all 3C

Patch visits in a single weekly clinic. If this is not possible, it may be necessary for other staff (e.g. band 5 or 6 nursing or podiatry staff) to undertake these tasks. If the task is to be undertaken by podiatrists, phlebotomy training may be required. As noted above, this will be provided free of charge by Reapplix where necessary and will be included in the training sessions outlined above. (Source: Reapplix, Expert opinion) In the model base case it is assumed that 10 minutes of band 4 nursing time are required for these tasks. In scenario analysis, we model the cost impact of using band 6 staff for these tasks.

Additional staff inputs for podiatry consultations

It is expected that 3C Patch patients will be seen in clinic each week for patch replacement. Expert opinion indicates that in standard care patients are generally seen in clinic (MDFT or foot protection service) once every two weeks. It is therefore estimated that standard care patients will have 0.5 clinic visits per week on average, and 3C Patch patients will have 0.5 additional dressing changes in clinic per week, relative to standard care. It is estimated that each of these visits for patch replacement will take 20 minutes of a band 6 podiatrist's time, in addition to nursing inputs outlined above. (Source: Expert opinion)

Staff inputs to screen patients for use of 3C Patch

The draft clinical pathway proposes that 3C Patch should be considered for patients with hard to heal DFUs. In the recent outcome blind randomised controlled trial of 3C Patch, hard to heal ulcers were identified as those which did not reduce in area by 50% or more after a 4 week period with best standard of care (Game et al. 2018). The draft pathway states that in most cases clinicians will wish to try best standard of care in line with NICE recommendations (NG19) for at least 6 weeks before considering use of 3C Patch (to include the 4 week run-in period described above). In the RCT reductions in ulcer area were measured using acetate tracings or digital imaging. However, it is not envisaged that centres will be required to use these methods to identify eligible ulcers. Clinical judgement will be used in most cases to identify hard to heal ulcers after a 4 week run in period. No additional staff time or equipment is considered necessary for identification of eligible patients for use of 3C Patch.

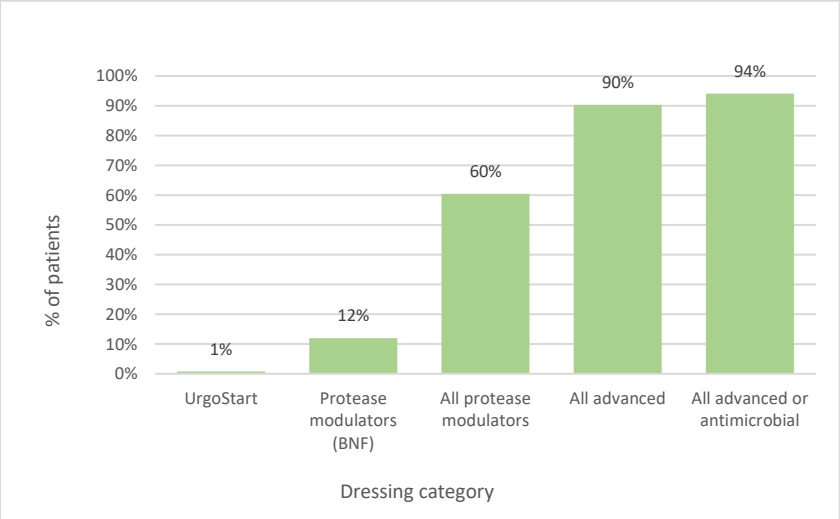
Expected reductions in resource use

Dressings used in standard care

3C Patch will replace dressings used in standard care. 3C Patch is supplied as part of a kit that contains the patch, a needle holder, a winged blood sampling set (G21) with protector, a primary cover dressing (Tricotex), an alcohol swab for disinfection of the skin before needle insertion, a post blood sample adhesive bandage, and a ruler with adhesive. Expert opinion indicates that in usual practice a simple secondary dressing such as Soft Pore is generally used in addition for protection. (Cost = £0.13, 10cm x 10cm, assumed 3 per week = £0.39 per week.) This is costed in the economic model.

After randomisation in the 3C Patch RCT, ulcers in the standard care group were treated with a wide range of dressings, according to clinical judgement. These included protease modulating dressings such as UrgoStart, and other advanced dressings. 90% of patients in the standard care arm received advanced dressings (Figure 1). One patient in the standard care arm of the trial and two patients in the run-in period had negative wound pressure therapy. The estimated cost per ulcerated week of dressings used in the standard care arm was £12.47. This cost is used in the economic model. (Source: Supplementary analysis of RCT dataset, details provided in Appendix C)

Figure 1. Percentage of patients receiving at least one week of treatment with advanced and antimicrobial dressings in control arm (3C Patch RCT)



Reductions in community nurse or equivalent inputs for dressing changes outside the clinic setting

Data from the 3C Patch RCT indicate that standard care patients had mean 1.97 dressing changes by health care professionals each week, of which 0.97 occurred outside their weekly clinic visits. 3C Patch patients had 0.92 such dressing changes outside their weekly clinic visits. (In the case of 3C Patch some experts have questioned this HCP input, as the patch is not changed between clinic visits. These inputs are assumed to be for changes to the outer secondary dressing). In base case analysis we assume that the differential between 3C Patch and standard care is as observed in the trial. Adjusting for fortnightly clinic visits in standard care patients in usual practice, we estimate in the base case that standard care patients have 0.56 more district nurse or equivalent HCP inputs than 3C Patch patients per ulcerated week. (Standard care patients attend clinic in 50% of ulcerated weeks, district nurse or equivalent inputs are needed for (1.97-0.5 = 1.47) dressing changes per week.) Costs are estimated for 30 minutes of a band 6 nurse's time for 0.56 dressing changes per week. In scenario analysis we reduce HCP inputs for dressing changes outside weekly clinic visits for 3C Patch patients.

Describe the resources needed to manage the change in patient outcomes after implementing the technology. Please provide sources and rationale.

The expected changes in patient outcomes after implementing the technology are reductions in duration of hard to heal DFUs, and increased numbers of patients achieving healing of these ulcers, relative to standard care. It is also likely that over time there will be a reduction in major and minor amputations, owing to reduced ulcer duration and increased healing. All these changes will reduce the need for NHS resources for DFU care, in outpatient, community, primary and inpatient settings. (Source: 3C Patch RCT)

Patients who have healed will require follow up care in line with NICE guidance for patients at high risk of diabetic foot problems (frequent assessment by the foot protection service, for example every 1-2 months if there is no immediate concern and every 1-2 weeks if there is immediate concern). Foot protection services generally have well established services for regular assessment of high risk patients. As 3C Patch is only recommended for hard to heal ulcers, and is likely to be used on a minority of DFU patients, it is not anticipated that increased numbers of patients healing will create a significant burden for assessment services. The increased need for assessment will be substantially outweighed by the reduction in resource use for ongoing DFU care for hard to heal ulcers. (Source: 3C Patch RCT, NICE)

Describe the resources needed to manage the change in system outcomes after implementing the technology. Please provide sources and rationale.

No additional resource requirements to manage the change in system outcomes have been identified, beyond those outlined under implementation and patient outcomes above.

Table 5 Resource use costs

In this table, summarise how the model calculates the results of these changes in resource use. Please adapt the table as necessary.

Weekly cost of DFU care	3C Patch ulcer care costs	Standard care ulcer care costs	Difference in resource use costs (3C Patch versus standard care for hard to heal ulcers)	Source/Notes
Routine DFU care in outpatient, community and primary care settings, to include clinic attendances, podiatry, imaging, hospital outreach, NHS transport and orthotics	£135.97	£135.97	£0	Kerr et al. 2019, minus dressings and prescribing
Routine DFU care in inpatient settings	£92.51	£92.51	£0	Kerr et al. 2019, bed day costs updated using NHS Reference Costs, activity apportioned across estimated annual ulcer weeks

3C Patch	£125.40	£0	£125.40	0.836 patches used on average per week, as in 3C Patch RCT
Secondary dressing	£0.39	£0.00	£0.39	Assumed Soft Pore 10cm x 10cm, 3 per week
Alternative dressings	£0.00	£12.47	-£12.47	Costs of dressings estimated from 3C Patch RCT trial dataset, BNF unit costs
Antibiotic medications	£7.13	£9.70	-£2.57	Cost of medications estimated from 3C Patch trial dataset, BNF unit costs
Training	£1.05	£0.00	£1.05	Annual staff training, apportioned across estimated patient weeks of 3C Care per 3C centre
Additional podiatry inputs	£16.22		£16.22	3C Patch patients attend MDFT or foot protection clinic weekly for dressing change, standard care patients attend 0.5 times per week (fortnightly unless infected), PSSRU unit costs, 20 mins Band 6 podiatrist per clinic dressing change
Additional nurse inputs	£5.26	£0.00	£5.26	3C Patch patients require additional staff time for phlebotomy and centrifuge operation, PSSRU unit costs, 10 minutes band 4 nurse time,

Reduced district nurse visits	-£25.71	£0.00	-£25.71	0.56 fewer district nurse visits for dressing changes for 3C Patch than standard care. 3C Patch RCT data analysis, adjusted for fewer dressing change clinic visits in usual practice (standard care) than in trial. PSSRU Unit costs, 30 mins band 6 nurse time
Total costs	£358.22	£250.65	£107.57	

Adverse event costs

If costs of adverse events were included in the analysis, explain how and why the risk of each adverse event was calculated.

No adverse events are included in the analysis.

Table 6 Adverse events and costs in the model

In this table, summarise the costs associated with each adverse event included in the model. Include all adverse events and complication costs, both during and after long-term use of the technology. Please explain whether costs are provided per patient or per event.

Not applicable.

Miscellaneous costs

Describe any additional costs or resource considerations that have not been included elsewhere (for example, PSS costs, and patient and carer costs). If none, please state.

None

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

It has not been possible to quantify social care resource use impacts. It is considered likely that reduced ulcer duration and an increase in patients experiencing healing will lead to reductions in social care resource use. However, no datasets or studies were identified to support estimation of these impacts.

Total costs

In the following tables, summarise the total costs:

- Summarise total costs for the technology in table 7.
- Summarise total costs for the comparator in table 8. This can only be completed if the comparator is another technology.

Table 7 Total costs for the technology in the model

This approach to costing is not appropriate as the device (centrifuge), maintenance and training delivery are all provided free of charge by Reapplix. All relevant NHS cost impacts are set out in table 5 above.

Table 8 Total costs for the comparator in the model

See note under table 7.

Results

Table 9 Base-case results

In this table, report the results of the base-case analysis. Specify whether costs are provided per treatment or per year. Adapt the table as necessary to suit the cost model. If appropriate, describe costs by health state.

Total QALYs and costs per patient (2 years, discounted)

	3C Patch Base Case	Standard Care	Impact of 3C Patch
QALYs	0.8958	0.8803	0.0155
Total cost over 2 years	£13,674	£13,865	-£191

Cost breakdown (2 years, discounted)

	3C Patch Base Case	Standard Care	Impact of 3C Patch
Index ulcer (includes 3C Patch cost)	£11,144	£11,331	-£187
Regular assessment for patients whose ulcers have healed	£148	£128	£20
Subsequent ulcers	£971	£867	£103
Major amputation	£376	£411	-£34
Minor amputation	£779	£851	-£71
Post amputation costs	£255	£278	-£22

3C Patch usage and costs (included in index ulcer cost above, 2 years, discounted)

	3C Patch Base Case
3C Patch device	£1,092
Mean number of patches per treated patient	7.28
Training	£9

Cost profile over time

	Annual			Cumulative		
	3C Patch Base Case	Standard Care	Impact of 3C Patch	3C Patch Base Case	Standard Care	Impact of 3C Patch
Total cost in year 1	£9,838	£9,657	£182	£9,838	£9,657	£182
Total cost in year 2	£3,835	£4,208	-£373	£13,674	£13,865	-£191
Total cost in year 3	£2,073	£2,202	-£129	£15,747	£16,067	-£321

Model clinical outcomes (2 years)

	3C Base Case	Standard Care	Impact of 3C Patch
Average weeks of ulceration (index ulcer)	41.08	45.62	-4.54
Proportion of people who remain unhealed after 2 years	11.8%	13.6%	-1.8%
Incidence of major amputation over 2 years	3.13%	3.42%	-0.29%
Incidence of minor amputation over 2 years	13.27%	14.48%	-1.22%
Incidence of death over 2 years	22.10%	22.45%	-0.35%

Scenario analysis

If relevant, explain how scenario analyses were identified and done. Cross-reference your response to the decision problem in part 1, section 1 of the submission.

Scenario 1: Weekly quantity of 3C Patches varied by 10%. This scenario was undertaken as the scope indicates that scenarios should be explored in which different numbers and combinations of devices are needed. As the centrifuge and associated maintenance are provided free of charge by Reapplix, scenario analysis was conducted only on variation in the number of patches.

Scenario 2: Band 6 staff instead of band 4 undertake phlebotomy and centrifuge operation. The scope indicates that NHS resource use should be considered as an outcome. Expert opinion indicates that in most cases it is likely that band 4 nursing staff would undertake these tasks. However, in some centres it may not be possible to provide band 4 inputs, and band 5 or 6 staff may need to undertake these tasks.

Scenario 3: 3C Patch patients have mean 0.5 district nurse or equivalent HCP dressing changes outside clinic per week. This scenario was identified as some experts stated that in their experience 3C Patch patients generally have no HCP dressing changes between clinic visits, owing to the fact that unlike conventional dressings the patch lasts for a week and is not to be changed or adjusted between weekly clinic visits.

Scenario 4: The weekly probability of healing in weeks 6-20 for those who stop 3C Patch after 5 weeks of treatment is increased from the base case value of 0.00676 to 0.00812

Describe the differences between the base case and each scenario analysis.

In scenario 1, the mean quantity of patches used per patient per week was varied from the base case level of 0.836 by 10% to

a) 0.752

b) 0.920

In scenario 2, the additional staff input for phlebotomy and centrifuge operation is varied from the base case assumption (10 minutes of band 4 nurse time) to 10 minutes of band 6 nurse/podiatrist time. As in the base case it is assumed that the nurse/podiatrist will undertake other tasks while the centrifuge is operating.

In scenario 3, the mean number of weekly dressing changes performed by district nurses or equivalent HCPs for 3C Patch patients is varied from the base case level of 0.92 to 0.5.

In scenario 4, the weekly probability of healing in weeks 6-20 for those who stop 3C Patch after 5 weeks of treatment is increased from the base case value of 0.00676 to 0.00812

Describe how the scenario analyses were included in the cost analysis.

In scenario 1, the weekly cost input for the patch was varied from the base case level of £125.40 by 10% to

a) £112.86

b) £137.94.

In scenario 2, the weekly cost of additional nursing input for 3C Patch administration was increased from the base case level of £5.26 to £15.72. Unit costs are sourced from PSSRU Unit Cost of Health and Social Care.

In scenario 3, the mean weekly cost reduction for 3C Patch relative to standard care for averted district nurse or equivalent visits for dressing changes is increased from £25.71 to £45.03.

In scenario 4, the cost impacts were generated in the Markov model by the change in probabilities.

Describe the evidence that justifies including any scenario analyses.

Scenario 1: Expert opinion indicates that in usual practice the mean weekly number of patches per patient may be lower than the base case estimate of 0.836, which was taken from the 3C Patch RCT. In the RCT, the protocol specified that 3C Patch should be used until healing or for 20 weeks. The draft clinical pathway indicates that clinical judgement should be exercised and patch use should be discontinued or suspended in certain situations, for example if it is believed that healing will be completed without further patch application. For completeness, scenario analysis 1b explores an increase in the mean weekly number of patches, although expert opinion indicates that mean patch use in excess of the RCT level is unlikely.

Scenario 2: Expert opinion indicates that in most cases it is likely that band 4 nursing staff would undertake these tasks. However, in some centres it may not be possible to provide band 4 inputs, and band 5 or 6 staff may need to undertake these tasks.

Scenario 3: The 3C Patch RCT indicated that 3C patients had mean 0.92 district nurse or other HCP inputs for dressing changes between weekly clinic visits (while standard care patients had 0.97 such inputs). These values were used in the base case. Expert opinion is divided, however, on whether this level of input is likely for 3C Patch in routine care. Several experts have stated that in their experience 3C Patch patients generally have no (or very few) HCP dressing changes between clinic visits, owing to the fact that unlike conventional dressings the patch lasts for a week and is not to be changed or adjusted between weekly clinic visits.

Scenario 4: The value used in the base case for 3C Patch patients who stop receiving the patch after 5 weeks is calculated from the healing observed in standard care patients whose ulcers did not reduce in area by 50% or more in the first five weeks. This is considered a conservative assumption. The value used in scenario 4 is the mid-point between the base case value and the rate actually observed in the RCT for 3C Patch patients whose ulcers did not reduce in area by 50% or more in the first five weeks of the intervention period. It should be noted that in the RCT these patients continue to receive 3C Patch, while in the model they stop 3C Patch. This is the reason for assuming reduced healing in this group, relative to that observed in the trial. In this scenario it is assumed that these patients have derived some benefit from 3C Patch.

Table 10 Scenario analyses results

In this table, describe the results of any scenario analyse that were done. Adapt the table as necessary.

	Mean discounted total cost per patient using the technology (£)	Mean discounted total cost per patient using the comparator (£)	Difference in total cost per patient (£)*
Base case (for reference)	£13,674	£13,865	-£191
Scenario 1a: 10% fewer mean 3C Patches per week of treatment	£13,564	£13,865	-£301
Scenario 1b: 10% more mean 3C Patches per week of treatment	£13,783	£13,865	-£82

Scenario 2: Band 6 staff undertake phlebotomy and centrifuge operation	£13,765	£13,865	-£100
Scenario 3: 0.5 mean DN dressing change visits per week for 3C Patch	£13,505	£13,865	-£360
Scenario 4: Adjusted 6-20 week healing rate for those who stop 3C Patch after 5 weeks	£13,561	£13,865	-£304
* Negative values indicate a cost saving. .			

Sensitivity analysis

Describe what kinds of sensitivity analyses were done. If no sensitivity analyses have been done, please explain why.

Probabilistic sensitivity analysis (PSA) was conducted to explore the impact of uncertainty in cost and probability inputs. All cost and probabilities in the model were included.

Summarise the variables used in the sensitivity analyses and provide a justification for them. This may be easier to present in a table (adapt as necessary).

Variables used in the PSA are summarised in the tables below. A gamma distribution was assumed for cost inputs, and a beta distribution for probabilities and utilities. For costs, where the standard deviation and sample size were known, these were used to generate parameters for the analysis. Where they were not known, it was assumed that 95% of values would fall within a range of 20% (10% above and below the mean), and standard deviations were estimated accordingly. For probabilities and utilities, it was assumed that 95% of values would fall within a range of 20% (10% above and below the mean), and standard deviations were estimated accordingly.

Costs

	Mean	Standard deviation
Ulcer outpatient, community and primary care cost (Culceropcp)	£135.97	£0.82

Ulcer inpatient cost (Culcerip)		£92.51	£4.72
3C Patch cost (C3CPatch)		£125.40	£6.40
3C Patch secondary dressings cost (C3Csecondarydress)		£0.39	£0.02
Standard care dressings cost (Cstandcaredressings)		£12.47	£0.72
3C Patch medications cost (C3Cmeds)		£7.13	£1.99
Standard care medications cost (Cstandcaremeds)		£9.70	£6.87
3C Patch training cost (C3Ctraining)		£1.05	£0.05
3C Patch extra podiatry cost (C3Cextrapodiatry)		£16.22	£0.83
3C Patch extra nursing cost (C3Cextranursing)		£5.26	£0.27
3C Patch district nursing impact (C3CDNimpact)		-£25.71	£1.31
Healed (Chealed)		£4.05	£0.21
Post major amputation costs (Cpostmajoramputation)	Y1	£63.22	£3.23
	Y2	£18.88	£0.96
Post minor amputation costs (Cpostminoramputation)	Y1	£20.23	£1.03
	Y2	£0.59	£0.03
Major amputation (Cmajoramputation)		£12,139.24	£619.35
Minor amputation (Cminoramputation)		£5,933.22	£302.72

Probabilities

		Mean	Standard deviation
% of 3C Patch arm who stop 3C treatment (Pdiscontinuation3C)	Week 5	0.57853	0.02952
Index ulcer healing rate - standard care (Phealingno3C)	Weeks 1 - 5	0.00758	0.00039
	Weeks 6 - 20	0.01375	0.00070
	Weeks 21 - 104	0.01277	0.00065
Index ulcer healing rate - 3C Patch (Phealing3C)	Weeks 1 - 5	0.00614	0.00031
	Weeks 6 - 20	0.05693	0.00290
	Weeks 21 - 104	0.01277	0.00065
Index ulcer healing rate - 3C Patch discontinued (Phealing3Cdiscontinued)	Weeks 6 - 20	0.00676	0.00035
	Weeks 21 - 104	0.01277	0.00065
Major amputation rate (Pmajoramputation)		0.00071	0.00004
Minor amputation rate (Pminoramputation)		0.00301	0.00015
Death rate - ulcerated with no major amputation (Pdeathulcer)		0.00280	0.00014

Death rate - ulcer free with no major amputation (Pdeathhealed)	0.00196	0.00010
Death rate - after major amputation (Pdeathpostmajoramputation)	0.00507	0.00026
Reulceration rate (Psubsequentulcer)	0.00586	0.00030
Subsequent ulcer healing rate (Phealingsubsequentulcer)	0.04687	0.00239

Weekly QALY Values

State	Mean	Standard deviation
Index ulcer with 3C (Uulcer)	0.00846	0.00043
Index ulcer 3C discontinued (Uulcer)	0.00846	0.00043
Index ulcer no 3C (Uulcer)	0.00846	0.00043
Healed (Uhealed)	0.01154	0.00059
Major amputation (Umajoramputation)	0.00596	0.00030
Minor amputation (Uminoramputation)	0.01173	0.00060
Post major amputation healed (Umajoramputation)	0.00596	0.00030
Post minor amputation healed (Uminoramputation)	0.01173	0.00060
Subsequent ulcer (Uulcer)	0.00846	0.00043
Post major amputation subsequent ulcer (Umajoramputation)	0.00596	0.00030
Post minor amputation subsequent ulcer (Uulcer)	0.00846	0.00043

If any parameters or variables listed in table 3 were omitted from the sensitivity analysis, please explain why.

All values in table 3 were included in the sensitivity analysis.

Sensitivity analyses results

Present the results of any sensitivity analyses using tornado plots when appropriate.

The 2-year results over 10,000 runs, are presented in Figure 2 and Table 11, below.

Figure 2: Incremental cost, 3C Patch (strategy 1) v. standard care (strategy 2), PSA, 2 years

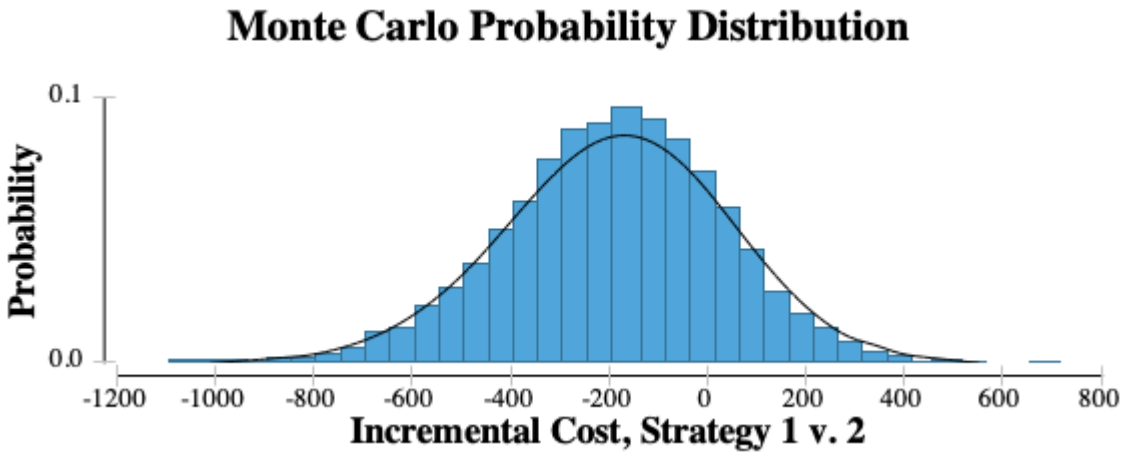


Table 11 Summary output from Probabilistic Sensitivity Analysis, 2 years, 3C Patch versus standard care

Mean	-£191.56
Std Deviation	£214.57
Minimum	-£1,082.61
2.5%	-£637.89
10%	-£470.43
Median	-£184.10
90%	£72.67
97.5%	£216.87
Maximum	£677.45

The PSA was also run over a 3 year time period. The results are presented in Figure 3 and Table 12, below.

Figure 3: Incremental cost, 3C Patch (strategy 1) v. standard care (strategy 2), PSA, 3 years

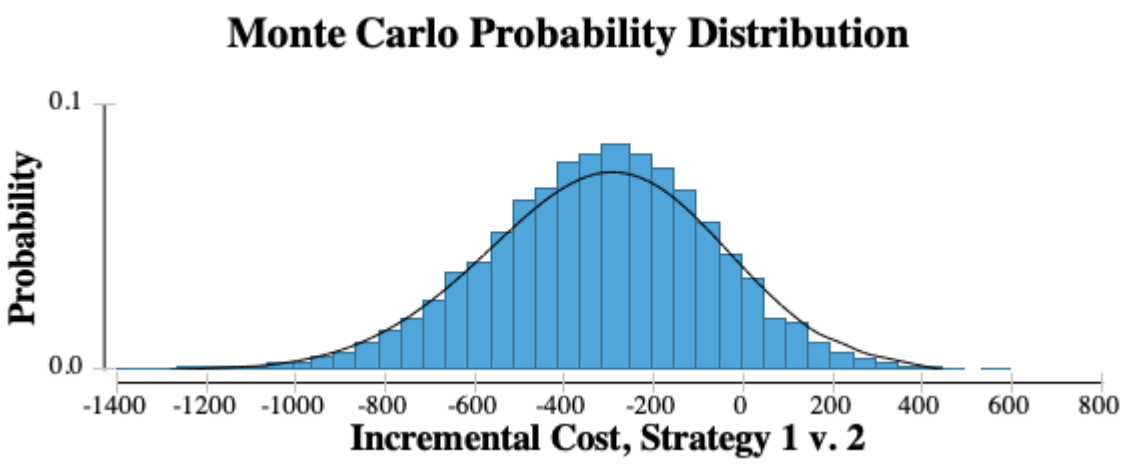


Table 12 Summary output from Probabilistic Sensitivity Analysis, 3 years, 3C Patch versus standard care

Mean	-£321.66
Std Deviation	£242.53
Minimum	-£1,408.78
2.5%	-£818.67
10%	-£638.27
Median	-£310.80
90%	-£21.01
97.5%	£132.30
Maximum	£562.65

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

The PSAs indicate that in a majority of cases 3C Patch is likely to be cost saving to the NHS (almost 90% of cases over a 3 year perspective).

What are the main sources of uncertainty about the model's conclusions?

Supplementary analysis was conducted to explore the sources of uncertainty. The main uncertainty driving the PSA results are probabilities rather than costs. PSA conducted on costs alone indicated that in more than 90% of runs, 3C Patch was cost saving to the NHS over 2 years.

Miscellaneous results

Include any other relevant results here.

N/A

Validation

Describe the methods used to validate, cross-validate (for example with external evidence sources) and quality assure the model. Provide sources and cross-reference to evidence when appropriate.

Tests of descriptive, technical, face and predictive validity were conducted. The key questions addressed in each were:

- Descriptive validity – does the model provide a simplified but adequate picture of reality? Does it consider all relevant aspects?
- Technical validity – does the model function correctly?
- Face validity – does the model produce outputs that are consistent with the theoretical basis of the disease and the medical intervention?

Descriptive validity

Key model inputs are derived from a peer reviewed RCT, and supplementary analysis of the RCT dataset. The supplementary analysis was conducted with advice from the original trial team, and key assumptions in the model were tested with them and with other experts. Expert advice was provided iteratively, covering the relationship of the model to reality and whether it covered all relevant aspects. The model was refined several times in the light of expert feedback. Other model inputs were validated by reference to peer reviewed literature, NHS data and expert opinion. For example, the estimated weekly cost of routine DFU care was validated by detailed comparison of cost estimates in two peer reviewed studies (Kerr et al. 2019 and Guest et al. 2018), as outlined in the Resource Use section above. Where the studies indicated substantially different values (for inpatient care), further validation was undertaken, using published NHS data (NDFA data on inpatient activity associated with DFU and Public Health England Diabetes Foot Care Profiles. Methods used for cost estimation in these studies were also critically appraised, examining the suitability of the datasets used and the appropriateness of assumptions. For example, the OPCS-4 and ICD-10 codes used in Kerr et al. 2019 to identify inpatient care related to DFUs was validated by reference to the codes used by PHE for Foot Care Profiles.

Where there were uncertainties over resource use inputs (for example, frequency of clinic visits in standard care, staff grade and time for phlebotomy and centrifuge operation, frequency of dressing changes with HCP input) expert opinion was sought. These uncertainties are also examined in scenario analyses.

Probabilities in the model were sourced from the 3C Patch RCT (Game et al. 2018), from supplementary analysis of the RCT dataset, from NHS data and from peer reviewed literature. Where suitable data were available, probabilities were cross-validated. For example, the major amputation rate in the 3C Patch RCT was compared with that reported in NDFA (1.5% in the RCT over 26 weeks, 1.6% in NDFA over 6 months from first expert assessment). The minor amputation rate was validated by comparing the ratio of major to minor amputations in the RCT to the ratio in PHE Foot Care Profiles, as NDFA does not provide data on minor

amputations. The ratio in the RCT was higher, but expert opinion indicates that an increased probability of minor amputation is plausible, given that the ulcers in this population are hard to heal.

Where the model deviates from the RCT (stopping 3C Patch after 5 weeks for patients whose ulcers have not reduced in area by at least 50%), this was validated with reference to the clinical pathway proposed in the clinical submission, and by expert opinion. Expert opinion was sought particularly on whether it was feasible to implement this element of the pathway in usual practice.

Technical validity

The technical functioning of the model was tested by means of an extensive sensitivity analysis. Extreme values of input variables were used, to test the impact on model outcomes. Model inputs and outputs were checked and verified independently by two researchers. Outputs by stage were exported to Excel and for each health state the progression of probabilities and costs were checked against expected behaviour. Discrepancies were investigated and resolved. Calibration was performed by comparing model outputs with observable data from the RCT Patch RCT, NHS datasets and peer reviewed literature.

Face validity

Face validity was assessed by comparison of model outputs with evidence from NHS datasets, peer reviewed literature and expert opinion. For example, the proportion of patients predicted to experience major amputation over two years was compared with major amputation rates reported in NDFA. In the model, 3.42% of patients in the standard care arm and 3.13% of 3C Patch patients experience major amputation over 2 years. In NDFA, 1.6% of patients experience major amputation within 6 months of first expert assessment. The major amputation rates in the model appear reasonable, allowing for healing and death over the two years. In the model 22.10% of 3C Patch patients and 22.45% of standard care patients die during the two years. This was compared with mortality rates in NDFA (10.2% over 1 year).

It was not possible to perform convergent validity tests as no suitable models were identified for corroboration.

Give details of any clinical experts who were involved in validating the model, including names and contact details. Highlight any personal information as confidential.

The advice of the following experts was taken in order to validate inputs and assumptions in the economic model:

Prof. Fran Game, Consultant Diabetologist and Director of R&D, Royal Derby Hospital

Prof. William Jeffcoate, Clinical Lead in the National Diabetes Foot Care Audit of England and Wales

Prof Gerry Rayman, Consultant Diabetologist, Ipswich Hospital, East Suffolk and North East Essex NHS Foundation Trust

Rachel Berrington, Senior Diabetes Specialist Nurse, University Hospitals of Leicester NHS Trust

Hannah Bond, Advanced Diabetes Podiatrist, Nottingham University Hospitals NHS Trust

Nikki Drake, Lead Podiatrist Diabetes Bristol, Sirona Care and Health CIC

4 Summary and interpretation of economic evidence

Describe the main findings from the economic evidence and cost model. Explain any potential cost savings and the reasons for them.

The economic evidence and cost model indicate that 3C Patch is likely to be cost saving to the NHS over a two year time perspective. The cost savings arise from increased numbers of patients with hard to heal DFUs healing, 34% of patients with 3C Patch versus 22% of standard care patients over 20 weeks in the 3C Patch RCT. (The intervention period in the trial was 20 weeks. Healing rates in the published RCT report (Game et al. 2018) are given for 26 weeks, but the rates for 20 weeks are the same, as no additional healing occurred between weeks 20 and 26). In addition to the estimated cost savings, the model predicts QALY gains (0.0155 per treated patient over 2 years).

The economic model uses 52-week follow-up data from the trial and parameters derived from large NHS datasets and peer reviewed literature to extrapolate the impact of 3C Patch beyond the intervention period. The 52-week data indicate that the proportion of patients who have achieved healing remains substantially higher in the 3C Patch cohort than in the standard care trial arm, even though all patients have received standard care from week 20. At 52 weeks, 54.55% of 3C Patch patients and 44.03% of standard care patients have achieved healing over the course of the year (intention to treat basis, data on healing status available for 95.45% of 3C Patch patients and 87.31% of standard care patients).

In the base case, it is estimated that use of 3C Patch results in savings of £191 per treated patient over 2 years, relative to standard care including advanced dressings where appropriate, and a QALY gain of 0.0155 per treated patient over the same time period. These savings arise owing to increased healing in patients who have been treated with 3C Patch, and averted weeks of ulcer care for these patients. There are further savings from averted major and minor amputations. The model predicts that over 2 years there are 8% fewer major and minor amputations in 3C Patch than in standard care patients. The economic model applied the same weekly probability of amputation to both arms while ulcerated; the higher rate of amputations arises because in the standard care arm patients spend longer in the ulcerated state. These further savings are offset by the cost of regular assessment once healing has been achieved, and by re-ulceration. QALY gains in the model arise from increased healing, reduced ulcer duration, and averted amputations.

The NHS savings and increased healing generated in the model are relative to a comparator that has received best standard care including a wide range of dressings. In the 3C Patch RCT, 90% of patients in the standard care arm received advanced dressings including protease modulating dressings. One patient in the standard care group also received negative pressure wound therapy during the trial period (as did two patients in the run-in period).

In supplementary analysis the model duration is extended from 2 years to 3 years, to take account of the very long duration of some hard to heal ulcers. (In the base case model, 11.8% of 3C patients and 13.6% of standard care patients are predicted to have index ulcers that have never healed at the end of year 2.) Over a three year time horizon, the net saving from 3C Patch increases by 67%, from £191 to £321. One year cost impacts are also provided; at the end of year 1 3C Patch is estimated to have a net cost of £182 per treated patient, reflecting the fact that the entire cost of the intervention is incurred in year 1, and the savings accumulate over time owing to averted weeks of DFU care and averted amputations.

Probabilistic sensitivity analysis indicates that in a majority of cases 3C Patch is likely to be cost saving to the NHS (almost 90% of cases over a 3 year perspective).

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Briefly discuss the relevance of the evidence base to the scope.

The population identified in the scope is the one used for the economic model, people with diabetic foot ulcers that are not healing despite standard wound care. The comparator is as identified in the scope, patients receiving standard conventional and advanced wound dressings for diabetic foot ulcers, including UrgoStart.

Model cost and probability inputs for the index ulcer are derived from the 3C Patch RCT published results (Game et al. 2018) and supplementary analysis of the RCT dataset. This RCT provides an evidence base that is specific to the population identified in the scope. Patients in the 3C Patch RCT all had hard to heal ulcers (meaning that the cross-sectional area decreased by less than 50%, and the cross-sectional area of the index ulcer was 50–1000 mm., at the end of a 4-week run-in period with good standard care). The evidence base suggests that reduction in ulcer area over 4 weeks of best standard of care is a good indicator of the probability of healing; several studies have indicated that an area reduction of less than 50% during 4 weeks of treatment is associated with a lower long-term probability of healing (Coerper 2009, Sheehan 2003, Snyder 2010). Patients received a full range of dressings, including substantial use of advanced dressings including protease modulating dressings such as UrgoStart (and negative pressure wound therapy in two cases) during the run-in period. Patients in the standard care trial arm received a full range of dressings, including substantial use of advanced dressings including protease modulating dressings such as UrgoStart (and negative pressure wound therapy in one case) during the trial intervention period.

Parameters derived from the RCT include healing probabilities for 3C Patch and standard care patients, major amputation and minor probability, and resource use for dressings (standard care) and antibiotic prescribing (3C Patch and standard care). The model deviates from the RCT in two respects in terms of index ulcer care. First, it is assumed that after 5 weeks of 3C Patch treatments, 3C Patch treatment is stopped for patients whose ulcers have not reduced in area by at least 50%. Weekly healing probability for this sub-group is assumed conservatively to equal that observed in the RCT for standard care patients whose ulcers have not reduced in area by at least 50% during the first 5 weeks of treatment. Second, it is assumed that clinic visits (MDFT or foot protection service) for standard care are fortnightly rather than weekly, although both arms had weekly visits in the trial. This adjustment was made as expert opinion indicates that fortnightly visits for standard care are more in keeping with usual practice in the NHS. Relative costs between the model arms are adjusted to reflect this, but no adjustment is made to outcomes.

A summary of the relevance of the evidence base and economic model to scope outcomes is set out in Table 13.

Table 13 Scope outcomes and relevance of evidence base

Scope outcomes	Relevance of evidence base
Measures of treatment effectiveness and wound healing, for example: - proportion of people with complete epithelialisation or healing - time to complete epithelialisation or healing - change in ulcer area	The 3C Patch RCT trial report (Game et al. 2018) provides results in all of these areas. Key drivers of cost and QALY impacts in the economic model are the proportion of people with complete epithelialisation or healing, and time to complete epithelialisation. The model also uses data on change in ulcer area to identify patients for whom 3C Patch treatment should be continued after 5 weeks of treatment.

Complications related to non-healing wounds, for example: - incidence of wound-related complications (including new infection) - number of new amputations - pain at ulcer location - frequency and amounts of antibiotic or pain medication requirements	The 3C Patch RCT trial report (Game et al. 2018) reports on all of these. Infection was reported at 10.1% of standard care visits, and 8.6% of 3C Patch visits. The total number of days of antibiotic therapy in the trial was 2822 in standard care patients and 2662 in 3C Patch patients. The cost impact of wound related infections is incorporated in the economic model by means of weekly antibiotic prescribing costs estimated from the RCT dataset. The mean cost of antibiotic prescribing per ulcerated week in the model is £9.70 in standard care patients and £7.13 in 3C Patch patients. The number of new amputations is explicitly modelled. The model predicts that over 2 years there are 8% fewer major and minor amputations in 3C Patch than in standard care patients. Pain at ulcer location is not explicitly included in the economic model. The VAS score reported in Game et al. 2018 did not show a significant difference in pain between the trial arms. It is considered likely that the most important factors impacting pain and broader quality of life are ulcer duration and amputation incidence. Quality of life impacts are captured in the economic model via EQ-5D.
Device-related adverse events	The 3C Patch RCT trial report (Game et al. 2018) reports no significant difference between the trial arms in the incidence of adverse events. In particular, there was no increased incidence of anaemia in the intervention group despite the need for weekly venesection. Adverse events are therefore not included in the economic model
Patient-reported outcomes, for example: - patient tolerance and acceptability - health related quality of life	The 3C Patch RCT trial report (Game et al. 2018) states that although acceptability was not directly tested in this study, the low number of dropouts from the study protocol suggests that patients find this an acceptable treatment strategy. Acceptability was not included in the economic model. Health related quality of life and QALY impacts were modelled using EQ-5D.
Measures of resource use: -total number of 3C Patch treatments needed -frequency and total number of secondary dressing changes -demand for NHS diabetic foot ulcer care – outpatient, community, primary care and inpatient care	The economic model uses the 3C Patch RCT dataset to estimate the total number of 3C Patch treatments needed, the frequency and total number of secondary dressing changes, and demand for NHS diabetic foot care in outpatient, community, primary care and inpatient settings.

The scope states that costs should be considered from an NHS and PSS perspective. Costs in the model are considered only from an NHS perspective, as no datasets or studies were identified to support estimation of PSS impacts. It is considered likely that reduced ulcer duration and an increase in patients experiencing healing will lead to reductions in social care resource use. If so, the model may have underestimated overall NHS/PSS savings associated with 3C Patch.

The scope specifies that the time horizon for the model should be long enough to reflect differences in costs and

consequences between the technologies being compared. Owing to the high proportion of hard to heal ulcer patients in the 3C Patch RCT who remain unhealed at 52 weeks, and the wide gap between 3C Patch and standard care patients at this point, a 2 year perspective was adopted. The model predicts that at the end of the second year, for 11.8% of 3C Patch patients and 13.6% of usual care patients, the index ulcer remains unhealed. This indicates that there are likely to be further cost and QALY benefits associated with 3C Patch in year 3. However, it was considered that decision makers would be more interested in a shorter time frame for benefits. In supplementary analysis the model duration is extended to 3 years. At the end of this period the cost saving with 3C Patch relative to standard care has increased by 67% (£321 cost saving after 3 years, £191 after two years).

The scope states that sensitivity analysis should be undertaken to address uncertainties in the model parameters, which will include scenarios in which different numbers and combinations of devices are needed. A range of sensitivity analyses and scenario analyses have been undertaken to address uncertainties in model parameters, including different mean numbers of patches were treatment week.

Briefly discuss if the results are consistent with the published literature. If they are not, explain why and justify why the results in the submission be favoured over those in the published literature.

The results are consistent with the published literature. The key literature source is Game et al. 2018. Supplementary analysis of the 3C Patch trial dataset was also conducted to provide model inputs in areas where the published report did not provide sufficient detail. These include 52 week follow up data, healing data for sub-groups in the model, and prescribing data for dressings and medications (Appendix C).

Healing probabilities for index ulcers for 3C Patch and standard care are calculated from healing rates observed in the 3C Patch RCT. The probability of healing over 20 weeks for the standard care arm of the model is calculated directly from the results reported in Game et al. 2018. (The 26 week healing rate reported in Game et al. 2018 is the same as the 20 week rate. The intervention period ended at 20 weeks and no further patients in either trial arm healed in weeks 21-26.)

To reflect the proposed clinical pathway and expert opinion about likely use of 3C Patch in usual care, the model divides 3C Patch patients after 5 weeks of treatment, depending on whether their ulcers have reduced in area by ≥50%. Only those whose ulcers have reduced by this amount continue with 3C Patch in the model. Others transfer at this point to standard care. The published paper did not provide data on area reduction at this point, nor on healing for sub-groups identified by this criterion. Supplementary analysis of the trial dataset was used to estimate weekly healing probabilities for these two sub-groups in weeks 6-20. Of those whose ulcers had reduced in area by ≥50% after 5 weeks of treatment, the RCT dataset indicates that 31/53 (58.49%) healed by week 20. This rate is used to estimate the weekly healing probability for those who continue with 3C Patch. The rate for patients in the standard care arm whose ulcers had not reduced in area by ≥50% during the first 5 weeks is used to estimate the weekly probability of healing in weeks 6-20 for those who stop 3C Patch after 5 weeks. This is considered a conservative assumption and is varied in scenario analysis.

The RCT dataset was also used to estimate the weekly probability of healing for all index ulcers (both model arms) in weeks 21-52. 52 week healing data from the trial were used to derive these probabilities. These follow up data were not published in Game et al. 2018. As noted above, the RCT dataset was also used to examine dressing and antibiotic prescribing data. These were combined with BNF and other cost sources to estimate weekly costs in these areas for the model.

Where the model departs from the results published in Game et al. 2018 this is considered justified as the RCT

dataset provides additional information of the same quality as the summary data published in Game et al. 2018 which increases the detail and precision of the model. It also supports more accurate modelling of the proposed clinical pathway than could be supported by the published data alone.

Other model inputs – costs, probabilities and utilities which could not be derived from Game et al. 2018 or the RCT dataset, are consistent with the broader published literature and with published NHS audit data.

Describe if the cost analysis is relevant to all patient groups and NHS settings in England that could potentially use the technology as identified in the scope.

The cost analysis is considered relevant to all patient groups in England with hard to heal DFUs, as defined in the draft clinical pathway, and to all NHS settings in England that could potentially use the technology as identified in the scope.

Briefly summarise the strengths and limitations of the cost analysis, and how these might affect the results.

Strengths: Unit costs used in the model are supported by data from the 3C Patch RCT where available, from published NHS sources (NHS Reference Costs and tariffs), from validated sources such as PSSRU Unit Costs (for staff inputs) and from peer reviewed papers. Where alternative sources were available, detailed analysis was undertaken to determine which source was likely to be more accurate and fit for purpose. Details have been set out above of some of the analysis undertaken to inform these decisions (in particular analysis of Kerr et al. 2019 and Guest et al. for estimation of routine weekly costs for DFU care in the NHS).

Probabilities in the model for index ulcer healing for both 3C Patch and standard care (during the intervention period and at 52 week follow up), and for major and minor amputation, are derived from the 3C Patch RCT dataset. Other probabilities are derived from NDFA, which is large-scale NHS audit of DFU care and outcomes (covering 33,150 DFUs in 2015-18), or from peer reviewed papers. Papers synthesising or reviewing results from multiple studies were selected where available.

The model also reflects expert opinion on practical considerations of 3C implementation in usual care. A range of opinions were sought on a number of practical questions which could not be fully addressed using the RCT data or published sources. These include likely staff inputs for tasks such as phlebotomy and centrifuge operation, likely clinic visit frequency in standard care, and the likely impact of 3C Patch on HCP inputs for dressing changes outside clinic. The model is therefore designed to reflect real life implementation of 3C Patch in the NHS.

Limitations: As with all health economic models, there is a degree of uncertainty surrounding inputs and results. As far as possible this has been addressed in sensitivity analyses, but can never be entirely eliminated.

Detail any further analyses that could be done to improve the reliability of the results.

It is not considered necessary to conduct further analysis at this point. However, it is recommended that, as with all new interventions, clinicians using 3C Patch should monitor its effectiveness in their patient cohort and should review its use regularly in line with the clinical pathway.

In particular, the proposed clinical pathway recommends the following:

1. If there has not been adequate progress toward healing (for example a reduction in ulcer area of 50% or more) during 4-6 weeks of 3C Patch treatment, use of the patch should be discontinued and other treatment options considered.
2. Where there has been adequate progress during 4-6 weeks of 3C Patch treatment, clinicians should consider continued use if they believe this is necessary to achieve complete healing. Clinicians should continue to monitor progress towards healing and regularly review use of the patch. Use of the patch should be discontinued if clinical judgement indicates that progress towards healing has stalled.
3. Use may also be discontinued in cases where clinical judgement indicates that sufficient progress has been made and healing is likely to be achieved without further use of the patch. In cases where good progress has been made and the patch is discontinued, 3C Patch treatment may be resumed if progress toward healing stalls.

Local audits to record the impact of implementation of these pathway recommendations on healing and costs would inform future use and ensure that the patch is used most cost effectively.

Further research on social care costs associated with hard to heal DFUs and diabetes-related amputations would support analysis on the PSS cost impacts of increased healing, reduced weeks of ulceration, and reduced amputations. It is considered likely that the improved clinical outcomes observed with 3C Patch in the RCT and modelled here would lead to net PSS cost savings, in addition to the NHS cost impacts explored here, but it has not been possible to estimate those savings.

5 References

Please include all references below using NICE's standard referencing style.

Abbott CA, Carrington AL, Ashe H, Bath S, Every LC, Griffiths J et al. (2002)The North-West Diabetes Foot Care Study: incidence of, and risk factors for, new diabetic foot ulceration in a community-based patient cohort. Diabet Med; 19: 377–384.

Coerper S, Beckert S, Kuper MA, Jekov M, Konigsrainer A. (2009) Fifty percent area reduction after 4 weeks of treatment is a reliable indicator for healing—analysis of a single centre cohort of 704 diabetic patients. J Diabetes Complications 23: 49–53.

Curtis, L. & Burns, A. (2020) Unit Costs of Health and Social Care 2020, Personal Social Services Research Unit, University of Kent, Canterbury.

Edmonds M, Lázaro-Martínez JL, Alfayate-García JM, Martini J, 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. Lancet Diabetes Endocrinol. 6(3):186-196. doi: 10.1016/S2213-8587(17)30438-2.
Epub 2017 Dec 20. Erratum in: Lancet Diabetes Endocrinol. 2018 Mar 6; PMID: 29275068.

Game F, Jeffcoate W et al, LeucoPatch II trial team. (2017) The LeucoPatch® system in the management of hard-to-heal diabetic foot ulcers: study protocol for a randomised controlled trial. Trials 18 (1); 469-476

Game F, Jeffcoate W et al, LeucoPatch II trial team. (2018b) LeucoPatch system for the management of hard-to-heal diabetic foot ulcers in the UK, Denmark, and Sweden: an observer-masked, randomised controlled trial. The Lancet. Diabetes & endocrinology 6 (11): 870-878

Guest, J.F., Fuller, G.W. and Vowden, P. (2018), Diabetic foot ulcer management in clinical practice in the UK: costs and outcomes. Int Wound J, 15: 43-52.

Hicks CW, Canner JK, Mathioudakis N, Lippincott C, Sherman RL, Abularrage CJ. (2020) Incidence and Risk Factors Associated With Ulcer Recurrence Among Patients With Diabetic Foot Ulcers Treated in a Multidisciplinary Setting, Journal of Surgical Research, Volume 246, Pages 243-250

Jeffcoate WJ, Price PE, Phillips CJ, Game FL, Mudge E, Davies S et al. (2009) Randomised controlled trial of the use of three dressing preparations in the management of chronic ulceration of the foot in diabetes. Health Technol Assess; 13: 1–86, iii–iv.

Kerr M, Barron E, Chadwick P et al. (2019). The cost of diabetic foot ulcers and amputation to the National Health Service in England. Diabetic medicine 36 (8): 995-1002

Margolis DJ, Gelfand JM, Hoffstad O, Berlin JA. (2003) Surrogate end points for the treatment of diabetic neuropathic foot ulcers. Diabetes Care 26(6):1696-700. doi: 10.2337/diacare.26.6.1696. PMID: 12766096.

National Diabetes Foot Audit. https://digital.nhs.uk/data-and-information/publications/statistical/national-diabetes-footcare-audit/2014-2018) [online; accessed 15th March 2021]

NICE Guideline. NG19. Diabetic foot problems: prevention and management

https://www.nice.org.uk/guidance/ng19 [online: accessed 15th March 2021]

Rayman G, Vas P, International Working Group on the Diabetic Foot (IWGDF). (2020) Guidelines on use of interventions to enhance healing of chronic foot ulcers in diabetes (IWGDF 2019 update). Diabetes Metab Res Rev. 36 (Suppl1):e3283.

Reiber GE, Vileikyte L, Boyko EJ, del Aguila M, Smith DG, Lavery LA*, et al.* Causal pathways for incident lower-extremity ulcers in patients with diabetes from two settings. *Diabetes care* 1999; **22**:157-162.

Sheehan P, Jones P, Caselli A, Giurini JM, Veves A. (2003) Percent change in wound area of diabetic foot ulcers over a 4-week period is a robust predictor of complete healing in a 12-week prospective trial. Diabetes Care 26(6):1879-82. doi: 10.2337/diacare.26.6.1879. PMID: 12766127.

Snyder RJ, Cardinal M, Dauphinee DM and Stavosky J. (2010) A post-hoc analysis of reduction in diabetic foot ulcer size at 4 weeks as a predictor of healing at 21 weeks. Ostomy Wound Manage 55: 44–50.

Tennvall GR and J Apelqvist. (2000) Health-related quality of life in patients with diabetes mellitus and foot ulcers, Journal of Diabetes and Its Complications 14(5):235-41. doi: 10.1016/s1056-8727(00)00133-1.

Vas P, Rayman G, Dhatariya K et al. (2020) Effectiveness of interventions to enhance healing of chronic foot ulcers in diabetes: a systematic review. Diabetes/metabolism research and reviews; 2020: e3284

Jupiter DC, Thorud JC, Buckley CJ, Shibuya N. (2016) The impact of foot ulceration and amputation on mortality in diabetic patients. I: from ulceration to death, a systematic review. Int Wound J 2016; 13: 892–903.

Icks A, Scheer M, Morbach S, Genz J, Haastert B, Giani G et al. (2011) Time-dependent impact of diabetes on mortality in patients after major lower extremity amputation: survival in a population-based 5-year cohort in Germany. Diabetes Care 2011; 34: 1350–1354.

Ikonen TS, Sund R, Venermo M, Winell K. (2010) Fewer major amputations among individuals with diabetes in Finland in 1997–2007: a population-based study. Diabetes Care 2010; 33: 2598–2603.

Armstrong DG, Boulton AJM, Bus SA. (2017) Diabetic foot ulcers and their recurrence. N Engl J Med 2017; 376:2367–2375

6 Appendices

Appendix A: Search strategy for economic evidence

Describe the process and methods used to identify and select the studies relevant to the technology being evaluated. See section 2 of the user guide for full details of how to complete this section.

Date search conducted:	8 and 15th March 2021
Date span of search:	2000 to present

List the complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean). List the databases that were searched.

<table>
<tr><td>Date search conducted:</td><td>8 and 15th March 2021</td></tr>
<tr><td>Date span of search:</td><td>2000 to present</td></tr>
<tr><td colspan="2">List the complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean). List the databases that were searched.</td></tr>
<tr><td colspan="2">Search strings were drawn from the following phrases or words
Population – “Diabetic foot” and “Foot ulcer, diabetic” from the HDAS Thesauraus as exploded as major Terms
Intervention
• Reapplix OR leucopatch OR leukopatch OR 3C patch
• Patch
• Leucocytes OR leukocytes
• Fibrin
• Platelets
Comparator – Standard wound care, standard care, advanced wound care, urgo
Outcomes
• Cost savings, cost benefit, cost effectiveness, health economics, resource use</td></tr>
</table>

Published studies

DATE	DATABASE	TERMS	RESULTS
08/03/2021	Medline	((3C patch OR leucopatch OR leukopatch).ti,ab AND ((health econom*).ti,ab OR (Cost savings OR cost benefit OR cost analysis).ti,ab)	1
		((exp *"DIABETIC FOOT"/ OR exp *"FOOT ULCER"/) AND ((leucocytes OR leukocytes).ti,ab OR (fibrin).ti,ab OR (platelets).ti,ab)) AND ((health econom*).ti,ab OR (Cost savings OR cost benefit OR cost analysis).ti,ab)	3
		((exp *"DIABETIC FOOT"/ OR exp *"FOOT ULCER"/) AND ((leucocytes OR leukocytes).ti,ab OR (fibrin).ti,ab OR (platelets).ti,ab)) AND (cost effectiveness OR cost effective OR cost).ti,ab"	1
		(3C patch OR leucopatch OR leukopatch).ti,ab AND (cost effectiveness OR cost effective OR cost).ti,ab	0
		(exp *"DIABETIC FOOT"/ OR exp *"FOOT ULCER"/) AND ((health econom*).ti,ab AND (Cost savings OR cost benefit OR cost analysis).ti,ab)	32
DATE	**DATABASE**	**TERMS**	**RESULTS**
08/03/2021	PubMed including The Cochrane database of systematic reviews	(3C patch OR leucopatch OR leukopatch).ti,ab AND ((health econom*).ti,ab OR (cost saving OR cost benefit OR cost analysis).ti,ab)	2
		((leucocytes OR leukocytes).ti,ab OR (fibrin OR platelets).ti,ab) AND ((diabetic foot OR foot ulcer).ti,ab AND ((health econom*).ti,ab OR (cost saving OR cost benefit OR cost analysis).ti,ab))	7
		((diabetic foot OR foot ulcer).ti,ab AND ((leucocytes OR leukocytes).ti,ab OR (fibrin OR platelets).ti,ab)) AND (cost effectiveness OR cost effective OR cost).ti,ab	18
		(((diabetic foot OR foot ulcer).ti,ab AND ((leucocytes OR leukocytes).ti,ab OR (fibrin OR platelets).ti,ab)) AND (clinical trial OR RCT OR clinical OR evaluation OR randomised controlled trial OR randomised clinical trial OR observation trial).ti,ab) AND (cost effectiveness OR cost effective OR cost).ti,ab	15
		(3C patch OR leucopatch OR leukopatch).ti,ab AND (cost effectiveness OR cost effective OR cost).ti,ab	2

DATE	DATABASE	TERMS	RESULTS
08/03/2021	Cinahl	(3C patch OR leucopatch OR leukopatch).ti,ab AND ((health econom*).ti,ab OR (cost saving OR cost benefit OR cost analysis).ti,ab)	1
		((exp *"DIABETIC FOOT"/ OR exp *"FOOT ULCER"/) AND ((leucocytes OR leukocytes).ti,ab OR (fibrin OR platelets).ti,ab)) AND ((health econom*).ti,ab OR (cost saving OR cost benefit OR cost analysis).ti,ab)	9
		(3C patch OR leucopatch OR leukopatch).ti,ab AND (cost effectiveness OR cost effect OR cost).ti,ab	1
		((exp *"DIABETIC FOOT"/ OR exp *"FOOT ULCER"/) AND ((leucocytes OR leukocytes).ti,ab OR (fibrin OR platelets).ti,ab)) AND (cost effectiveness OR cost effect OR cost).ti,ab	15

DATE	DATABASE	TERMS	RESULTS
08/03/2021	Embase	(3C patch OR leucopatch OR leukopatch).ti,ab AND ((health econom*).ti,ab OR (cost savings OR cost benefit OR cost analysis).ti,ab)	0
		((exp *"DIABETIC FOOT"/ OR (exp *"FOOT ULCER"/ OR	1

		exp *"FOOT ULCER, DIABETIC"/)) AND ((leucocytes OR leukocytes).ti,ab OR (fibrin OR platelets).ti,ab)) AND ((health econom*).ti,ab OR (cost savings OR cost benefit OR cost analysis).ti,ab)	
		(3C patch OR leucopatch OR leukopatch).ti,ab AND (cost effectiveness OR cost effective OR cost).ti,ab	0
		"((exp *"DIABETIC FOOT"/ OR (exp *"FOOT ULCER"/ OR exp *"FOOT ULCER, DIABETIC"/)) AND ((leucocytes OR leukocytes).ti,ab OR (fibrin OR platelets).ti,ab)) AND (cost effectiveness OR cost effective OR cost).ti,ab	5

Published studies – Diabetic Foot Resource Use

DATE	DATABASE	TERMS	RESULTS
15/04/2021	Medline	(exp *"DIABETIC FOOT"/ OR exp *"FOOT ULCER"/) AND (cost OR economic* OR resource).ti,ab	609
		(exp *"DIABETIC FOOT"/ OR exp *"FOOT ULCER"/) AND (cost effectiveness OR cost effective OR cost).ti,ab	428
		(exp *"DIABETIC FOOT"/ OR exp *"FOOT ULCER"/) AND ((health econom*).ti,ab AND (Cost savings OR cost benefit OR cost analysis).ti,ab)	32

DATE	DATABASE	TERMS	RESULTS
15/04/2021	Pubmed	(cost OR economic* OR resource).ti,ab AND ((diabetic foot).ti,ab OR (foot ulcer).ti,ab)	1500
		(diabetic foot OR foot ulcer).ti,ab AND (cost effectiveness OR cost effective OR cost).ti,ab	1109
		(diabetic foot OR foot ulcer).ti,ab AND ((health econom*).ti,ab OR (cost saving OR cost benefit OR cost analysis).ti,ab)	686

DATE	DATABASE	TERMS	RESULTS
15/04/2021	Cinahl	(exp *"DIABETIC FOOT"/ OR exp *"FOOT ULCER"/) AND ((health econom*).ti,ab OR (cost saving OR cost benefit OR cost analysis).ti,ab	190
		(exp *"DIABETIC FOOT"/ OR exp *"FOOT ULCER"/) AND (cost effectiveness OR cost effect OR cost).ti,ab	383
		((cost OR economic* OR resource) AND (exp *"DIABETIC FOOT"/ OR exp *"FOOT ULCER"/))	724

DATE	DATABASE	TERMS	RESULTS
15/04/2021	Embase	(exp *"DIABETIC FOOT"/ OR (exp *"FOOT ULCER"/ OR exp *"FOOT ULCER, DIABETIC"/)) AND ((health econom*).ti,ab OR (cost savings OR cost benefit OR cost analysis).ti,ab)	85
		(exp *"DIABETIC FOOT"/ OR (exp *"FOOT ULCER"/ OR exp *"FOOT ULCER, DIABETIC"/)) AND (cost effectiveness OR cost effective OR cost).ti,ab	608
		((cost OR economic* OR resource) AND exp *"DIABETIC FOOT"/)	953

Brief details of any additional searches, such as searches of company or professional organisation databases (include a description of each database):

None

Inclusion and exclusion criteria:

Inclusion – Leucopatch, 3C patch, DFU, recalcitrant or heard-to-heal wounds, costs or resources associated with treating DFU, DFU management

Exclusion – use of platelet-rich plasma products, non-3C Patch products

Data abstraction strategy:

The literature search was conducted as above by a researcher and reviewed by two health economists. The papers from the studies identified in the search were examined by each of the health economists to assess relevance for the economic modelling. Discrepancies were resolved through discussion and re-review.

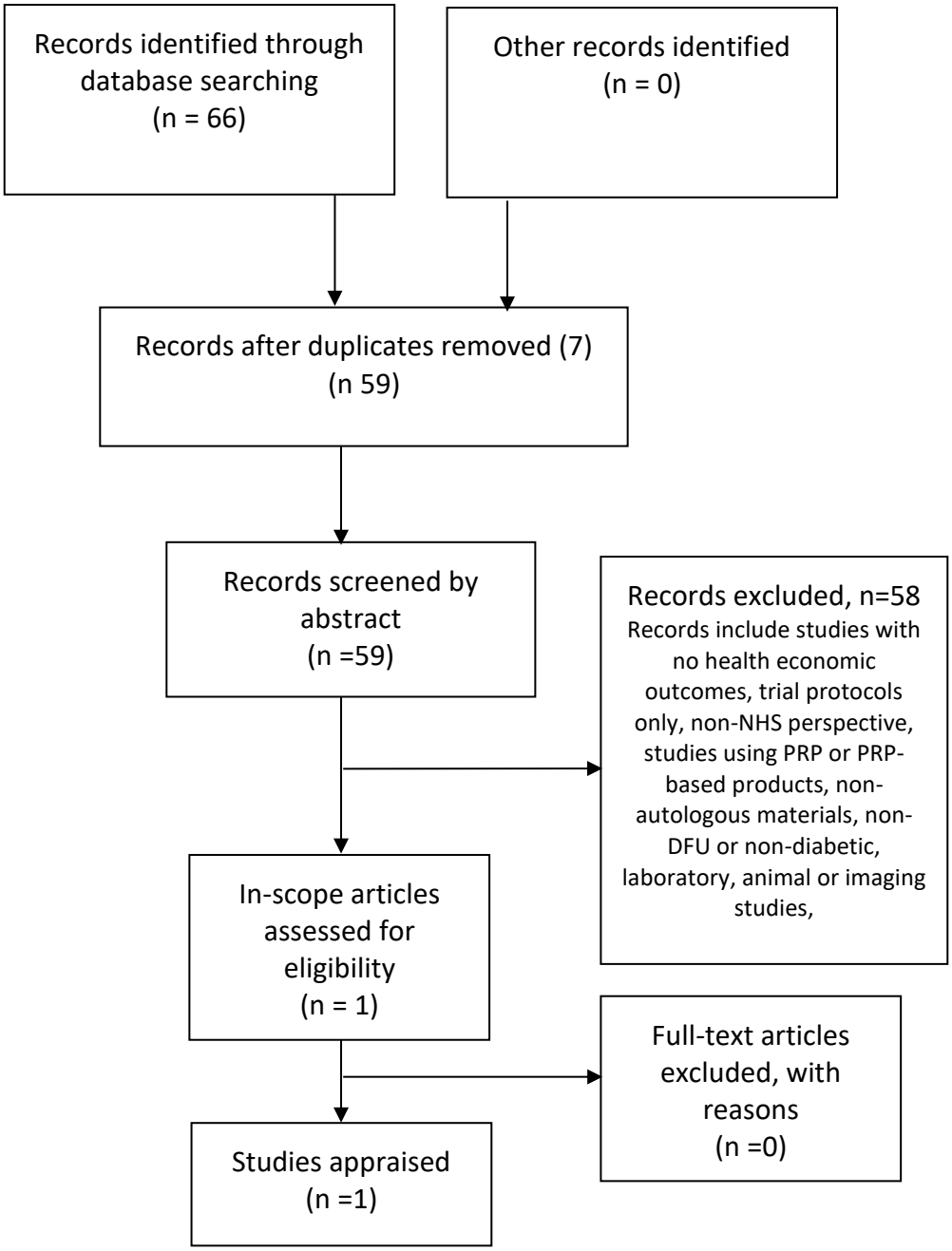
Excluded studies

List any excluded studies below. These are studies that were initially considered for inclusion at the level of full text review, but were later excluded for specific reasons.

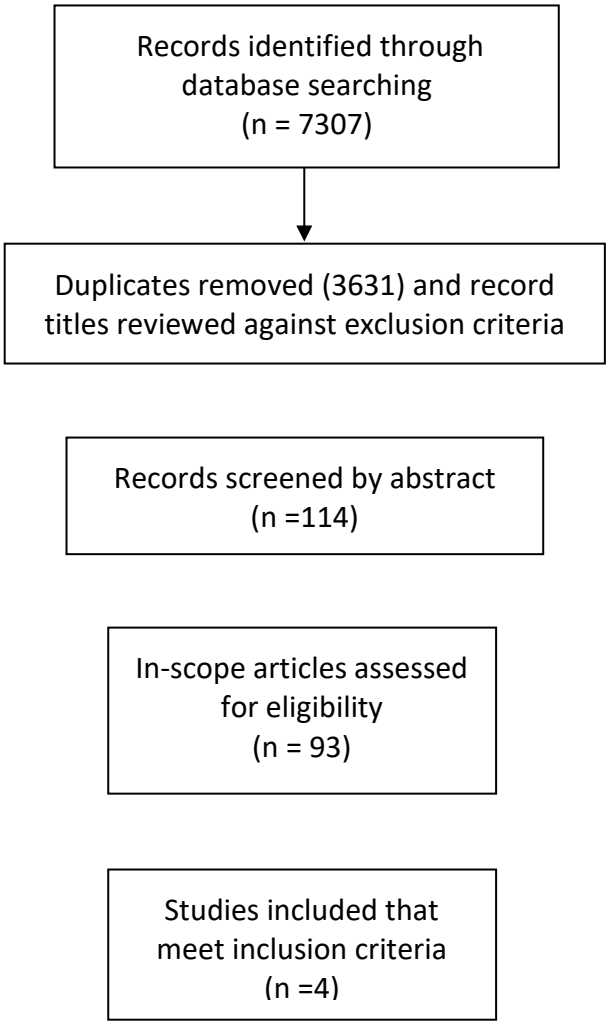
Excluded study	Design and intervention(s)	Rationale for exclusion	Company comments
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text
Text	Text	Text	Text

Report the numbers of published studies included and excluded at each stage in an appropriate format (e.g. PRISMA flow diagram).

PRISMA for 3C Patch Economic Literature



PRISMA Diagram for DFU Resource Literature

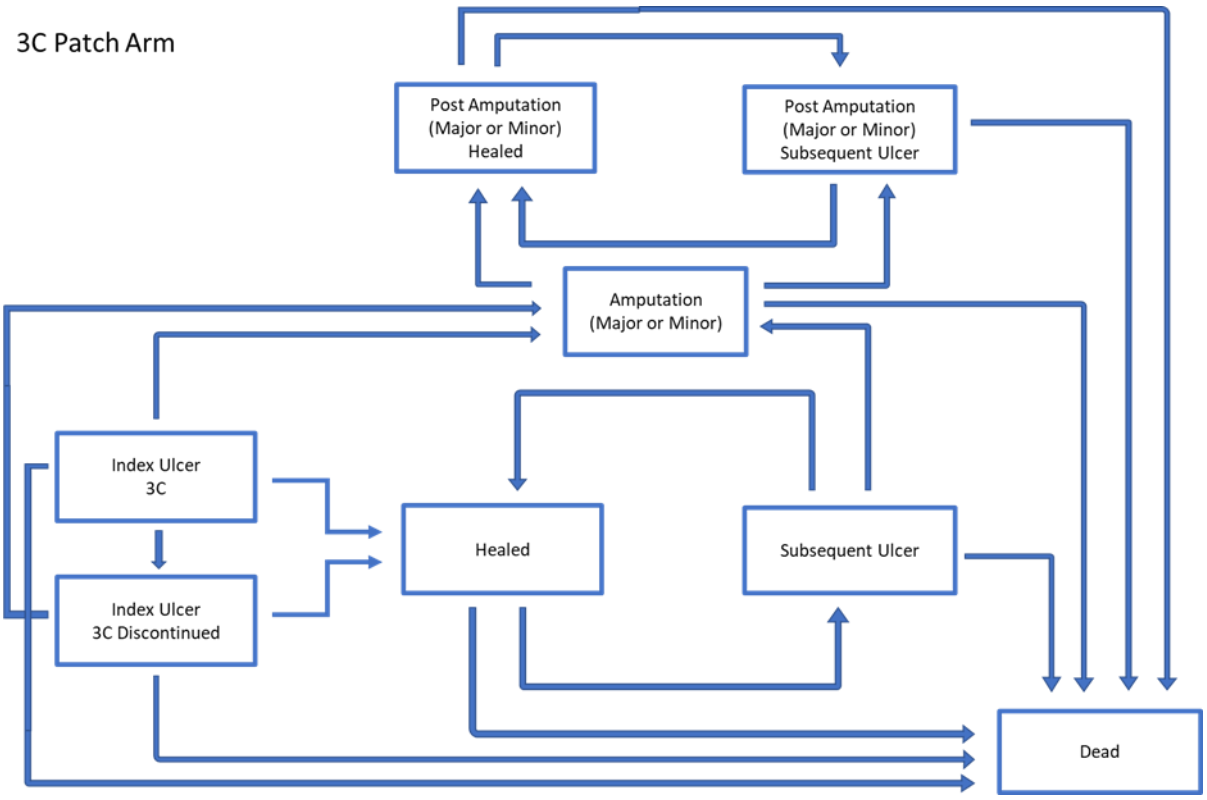


Structured abstracts for unpublished studies

Study title and authors
Introduction
Objectives
Methods
Results
Conclusion
Article status and expected publication: Provide details of journal and anticipated publication date

Appendix B: Model structure

Please provide a diagram of the structure of your economic model.



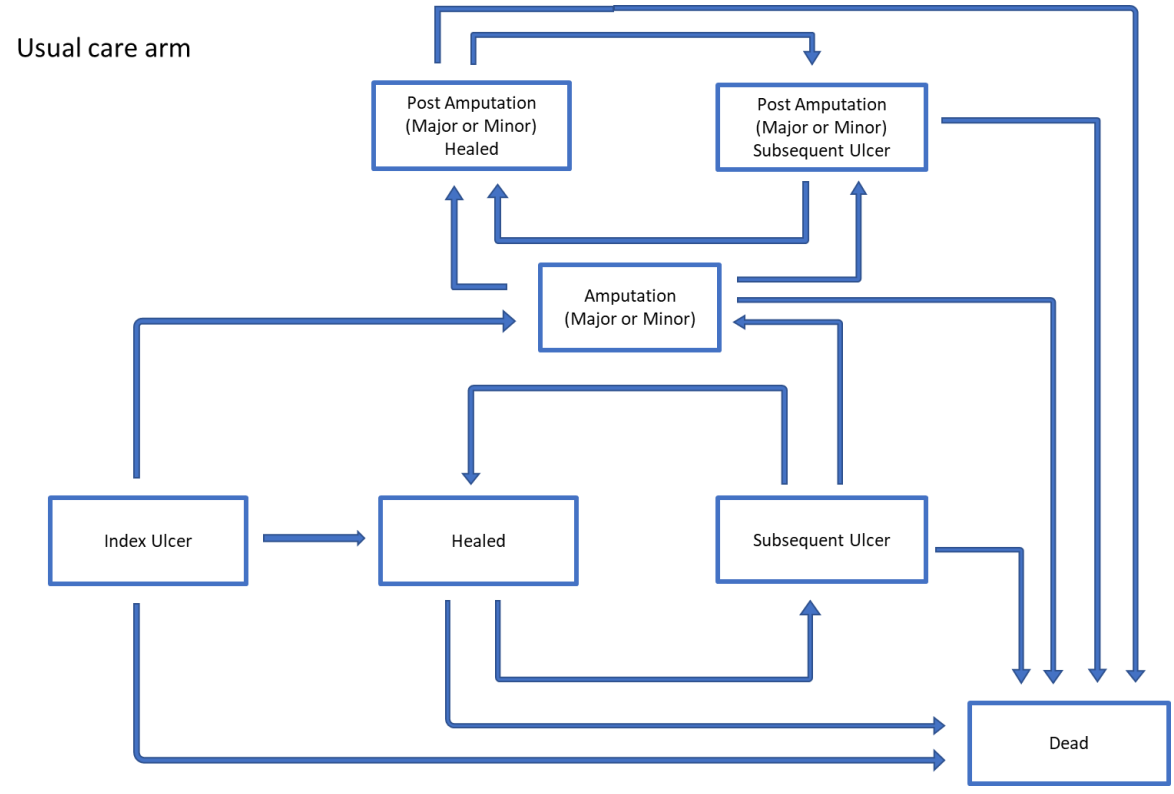


Table C1 ICD-10 and OPCS-4 codes used to identify inpatient admissions that include diabetic foot care in Kerr et al. 2019

	Diagnosis code (ICD-10)	Procedure code (OPCS- 4)	Other ICD-10 code required	Other OPCS- 4 code required
Amputation				
Major amputation	At least one of E10, E11, E12, E13, E14	At least one of X09, X10		
Minor amputation	At least one of E10, E11, E12, E13, E14	X11		
Procedures on amputation stumps	At least one of E10, E11, E12, E13, E14	X12		
Ulceration				
Ulcer of the lower limb	At least one of E10, E11, E12, E13, E14		L97	
Decubitus ulcer	At least one of E10, E11, E12, E13, E14		L89	
Cellulitis	At least one of E10, E11, E12, E13, E14		At least one of L03.0, L03.1	
Gangrene	At least one of E10, E11, E12, E13, E14		R02	
Atherosclerosis	At least one of E10, E11, E12, E13, E14		I70.2 AND at least one of L97, L89, L03.0, L03.1, R02	
Bacteraemia/ Septicaemia/ Septic shock/ Sepsis syndrome	At least one of E10, E11, E12, E13, E14		At least one of A40, A41, A49.9 AND at least one of L97, L89, L03.0, L03.1, R02	
Debridement of a foot/Leg wound	At least one of E10, E11, E12, E13, E14	S57.1		At least one of Z50.4, Z50.5, Z50.6
Diabetes mellitus with peripheral circulatory complications	At least one of E10.5, E11.5, E12.5, E13.5. E14.5			

Summary of supplementary analysis of 3C Patch RCT dataset

Table C2 Healing and ulcer area reduction in first 5 weeks

Table C3 Healing in weeks 6 - 20

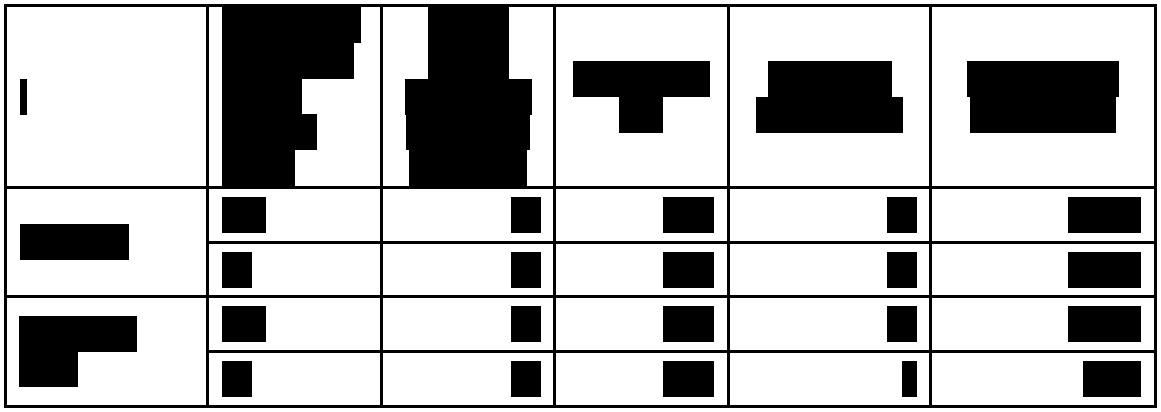


Table C4 Healing in weeks 21 - 52

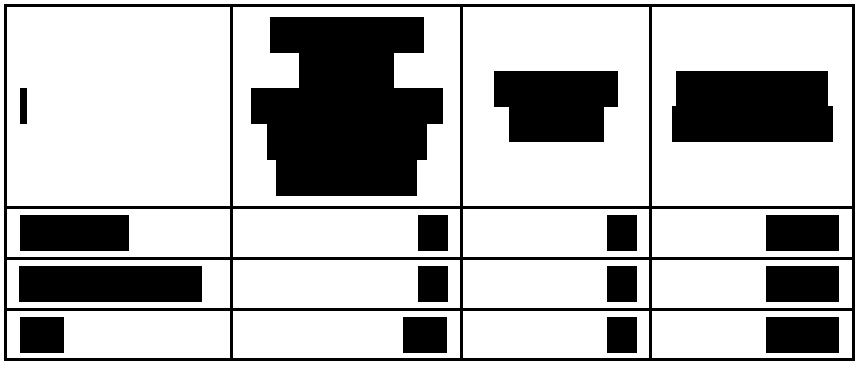
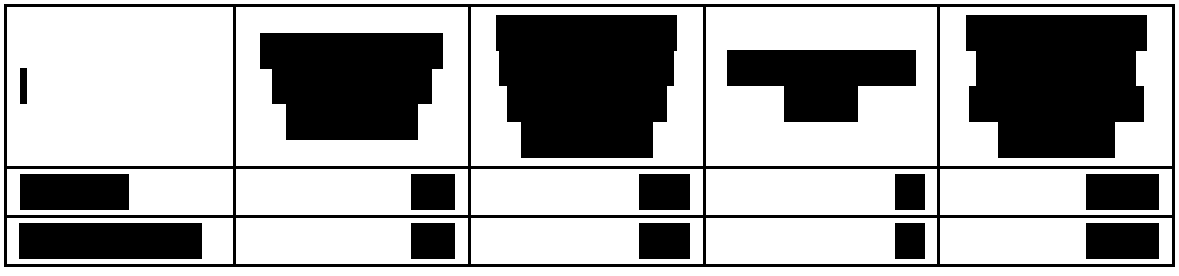


Table C5 Patients unhealed at week 52



Dressings for standard care patients

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Appendix D: Checklist of confidential information

Please see section 1 of the user guide for instructions on how to complete this section.

Does your submission of evidence contain any confidential information? (please check appropriate box):

No ☐ If no, please proceed to declaration (below)

Yes ☒ If yes, please complete the table below (insert or delete rows as necessary). Ensure that all relevant sections of your submission of evidence are clearly highlighted and underlined in your submission document, and match the information provided in the table. Please add the referenced confidential content (text, graphs, figures, illustrations, etc.) to which this applies.

Page	Nature of confidential information	Rationale for confidential status	Timeframe of confidentiality restriction
62-67	☐ Commercial in confidence ☒ Academic in confidence	Unpublished data from the RCT (Game 2018) and includes small numbers of patients therefore could be considered patient identifiable data	TBD
Details	Enter text.		
15	☐ Commercial in confidence ☒ Academic in confidence	Unpublished data from the RCT (Game 2018) and includes small numbers of patients therefore could be considered patient identifiable data	TBD
Details	Enter text.		

Confidential information declaration

I confirm that:

- all relevant data pertinent to the development of medical technology guidance (MTG) has been disclosed to NICE
- all confidential sections in the submission have been marked correctly
- if I have attached any publication or other information in support of this notification, I have obtained the appropriate permission or paid the appropriate copyright fee to enable my organisation to share this publication or information with NICE.

Please note that NICE does not accept any responsibility for the disclosure of confidential information through publication of documentation on our website that has not been correctly marked. If a completed checklist is not included then NICE will consider all information contained in your submission of evidence as not confidential.

Signed*: ** Must be Medical Director or equivalent*	[redacted]	**Date:**	April 27th 2021
Print:	Rasmus Lundquist	**Role / organisation:**	Chief Scientific Officer Reapplix A/S Blokken 45 3460 Birkerød, Denmark
Contact email:	[redacted]		

National Institute for Health and Care Excellence

Collated comments table

MTG Medtech Guidance:

Expert contact details and declarations of interest:

Expert #1	Ms Alison Musgrove, Advanced Podiatrist – Diabetes, Nottinghamshire Healthcare Foundation Trust
	Nominated by: Company
	Provision of a practical training session on a diabetic foot module based on my experience of using 3CP in the trial. Reapplix offered accommodation payment at a conference which was subsequently cancelled due to COVID
Expert #2	Professor Andrew JM Boulton, Professor of Medicine, Consultant Physician, University of Manchester, Manchester Royal Infirmary
	Nominated by: NICE
	DOI: None
Expert #3	David Russell, Associate Professor and Honorary Consultant Vascular Surgeon, University of Leeds
	Nominated by: NICE
	DOI: Local principal investigator for Leucopatch trial and named collaborator on trial publication Chief investigator for the MIDFUT study investigating the role of hydrosurgical debridement, negative pressure wound therapy and decellularized cadaveric dermis graft in wound healing
Expert #4	Elaine Ricci, clinical lead Podiatrist, South Tyneside and Sunderland NHS Trust
	Nominated by: Company
	DOI: None
Expert #5	Professor Frances Game, Consultant Diabetologist and Director of R&D, Royal Derby Hospital, University Hospitals of Derby and Burton NHS FT.
	Nominated by: Company
	DOI: Chief Investigator on the largest RCT of this technology
Expert #6	Ms Joanne Thorpe, Diabetes & Endocrinology. Lead Research Nurse, Bradford Teaching Hospitals NHS Trust
	Nominated by: Company
	DOI: None
Expert #7	Paul Chadwick, Clinical Director, College of Podiatry

	Nominated by: NICE
	DOI: None
Expert #8	Rachel Berrington, Senior Diabetes Nurse Specialist, University Hospitals of Leicester NHS Trust
	Nominated by: NICE
	DOI: None
Expert #9	Professor Edward Jude, Consultant in Diabetes & Endocrinology, Tameside Hospital NHS Foundation Trust
	Nominated by: NICE
	DOI: NONE

			Response
1	Please describe your level of experience with the procedure/technology, for example: Are you familiar with the procedure/technology? Have you used it or are you currently using it?	Expert #1:	I was involved in the UK Leucopatch study as an investigator and have been trained in the use of the 3CP. I have used it during and since the trial. The technology is very new and currently is not widely used within the NHS as procurement complexities mean that uptake may have been slower particularly due to COVID.
	Do you know how widely this procedure/technology is used in the NHS or what is the likely speed of uptake?	Expert #2	Yes No No No

	Is this procedure/technology performed/used by clinicians in specialities other than your own? − If your specialty is involved in patient selection or referral to another specialty for this procedure/technology, please indicate your experience with it.		No
		Expert #3	I am familiar with the technology and have used it as part of the Leucopatch RCT for which I was a local principal investigator. I have not been directly involved in the development of the technology. We are not currently using the product locally and I am not aware of the uptake of this technology across the NHS.
		Expert #4	I was involved in the original multicentre trial in approximately 2014 as the lead for the site. I then did a product evaluation following this and subsequently we now use it in the clinic on a regular basis in the treatment of hard to heal wounds in patients with diabetes I don't think this is a widely used technology in the NHS as it is aimed at a very niche market in hard to heal diabetes foot ulcers and principally in well supported MDT units.
		Expert #5	Yes I am familiar with the technology and have used itRCT (Game et al 2018) as part of the large . I am not currently using it, as the cost effectiveness has not yet been accepted by the Trust I work in. I was the UK Chief Investigator for the large RCT; I developed the protocol, oversaw the running of the trial, was involved in the analysis of the data and wrote the paper.

			I know a few specialist centres are using it in clinical practice, but am not aware of how this is being included in the patient pathway, or exactly how many centres took up the offer of the free centrifuge.
		Expert #6	I am familiar with the 3C Patch as Bradford Teaching Hospitals was one of the research sites to participate in the research Study. Post research study we worked with the manufacturer of the 3C Patch with the podiatry clinic mimicking delivery of the patch as a standard of care treatment within the unit-23 case studies were evaluated at the Bradford Site-not necessarily adhering to the original inclusion/exclusion criteria of the study enabling the podiatrist to utilise their professional judgements in the care and treatment of patients with hard to heel DFU's. Bradford Teaching Hospitals were the joint highest recruiting site in the UK in the research study randomising 29 participants in the study, we have a good working knowledge of the 3C Patch and have worked with the manufacturer troubleshooting and enhancing the devise. The Hospital Trust is not using the 3C Patch at this present time, as we are awaiting a health economics report from the manufacturer and without the report, we are unable to present a valid business plan to the trust. At this present time point, I unsure how widely used the 3C Patch technology is used in the NHS.

		Expert #7	I am aware of the technology but have not used it in practice. I have not been involved in the research my understanding is this is not being widely used in the NHS currently
		Expert #8	I am familiar with the technology as we were involved in as a research site. We used it on those patients and have used it since in foot clinic patients We are not currently using it but that is due to COVID and limiting the number of visits as most of our patients have multiple co-morbidies so we have only been offering routine care. Yes we were part of the research and rollout. Currently this is not widely used within the NHS
		Expert #9	Yes No No No Not at the moment
2	− Please indicate your research experience relating to this procedure (please choose one or more if relevant):	Expert #1:	N/A
		Expert #2	N/A

		Expert #3	N/A
		Expert #4	N/A
		Expert #5	N/A
		Expert #6	N/A
		Expert #7	N/A
		Expert #8	N/A
		Expert #9	N/A

Current management

3	How innovative is this procedure/technology, compared to the current standard of care? Is it a minor variation or a novel approach/concept/design? Which of the following best describes the procedure (please choose one):	Expert #1:	There is currently no other technology available that is using this form of wound treatment It is a major innovation. The technology to use a person's own white blood cells (autologous) in chronic wounds is a breakthrough. There are other blood product wound care technologies but these require the addition of chemicals or to apply as an injection rather than a wound contact layer.
		Expert #2	No, this technology has not been superseded. In my view this is a novel concept and design and is on one of the few therapies that has been shown in well designed, randomised controlled trials to be efficacious in the management of hard to heal diabetic foot ulcers. It is entirely innovative with respect to current standard of care.
		Expert #3	No, this technology has not been superseded. The technology is a variation on other technologies that have aimed to use the biological properties of blood or blood products to influence the wound biology and promote healing. Most have concentrated on platelets rather than leucocytes/whole blood. Up to now none have been adopted into routine standard of care.

		Expert #4	The only changes have been upgrades to the centrifuge system and the company have replaced this or upgraded the software as required. It's a novel technology in its use there is no other like for like comparator.
		Expert #5	Not as far as I am aware, this technology has not been superseded It is a novel design
		Expert #6	The centrifuge has been superseded: Initially the coagulation process was performed manually by the research nurse, 18 months ago post study-the manufacturer developed a centrifuge that produced the patch without any manual input. This has been ground-breaking for the manufacturer in the roll out of the patch from research to standard of care treatment in an NHS care setting removing the requirement for additional personnel, thus reducing costs in delivery of the patch. The 3C Patch is a novel innovative treatment that has been well received from both practitioners as well as patients within the trust.
		Expert #7	No, this technology has not been superseded. It is a novel concept and an adjunctive therapy to standard of care
		Expert #8	No but there is another trail currently being carried out that is looking to recruit within Leicester

		Expert #9	No, this technology has not been superseded Innovative
4	Does this procedure/technology have the potential to replace current standard care or would it be used as an addition to existing standard care?	Expert #1:	Addition but replace the more expensive dressings.
		Expert #2	This would be in addition to current standard of care. Many neuropathic ulcers heal with simple offloading and debridement and would not require more expensive technology such as this one.
		Expert #3	It would be an addition to current standard of care
		Expert #4	addition
		Expert #5	It would be used in addition to standard care (offloading, treatment of infection, revascularisation if appropriate, wound debridement)
		Expert #6	The treatment will be an addition to current standard of care.
		Expert #7	Addition too
		Expert #8	additional
		Expert #9	-

Potential patient benefits

5	Please describe the current standard of care that is used in the NHS.	Expert #1:	N/A
		Expert #2	N/A
		Expert #3	N/A
		Expert #4	N/A
		Expert #5	N/A
		Expert #6	N/A
		Expert #7	N/A
		Expert #8	N/A
		Expert #9	N/A
6	Are you aware of any other competing or alternative procedure/technology available	Expert #1:	Please see above (Q3)

	to the NHS which have a similar function/mode of action to this? If so, how do these differ from the procedure/technology described in the briefing?	Expert #2	There are a number of new therapies which have been showing promise in recent randomised controlled trials. Not sure if these are available on the NHS or not but these would certainly include the sucrose octasulfate dressing which is proven in RCTs to be helpful in neuroischaemic ulcers (this is available on the NHS). Their function is similar but mode of action likely to be different. Others include topical oxygen delivery and these are likely not currently available in the NHS but are available in the USA and again have promising RCT data. These differ entirely from the technology described in this briefing which is for Glucopatch which involves bedside centrifugation to generate a disc which is then applied to the wound surface.
		Expert #3	There are a number of other cellular and cell based biological products available within the NHS which aim to influence cell biology in a similar fashion. However, none of these has evidence of efficacy in an NHS setting and are therefore currently in various stages of research and evidence development rather than being used routinely. These include platelet gels or platelet rich fibrin fractions from autologous blood; placental based products with Mimedx amniotic membrane available and evidence from the US of efficacy but no NHS trial data.
		Expert #4	No

		Expert #5	Not aware of any
		Expert #6	Not aware of any competing or alternative technologies available to the NHS at this present time. That is not to say that there are products of similar function/mode of delivery in research.
		Expert #7	No
		Expert #8	There is the current trial that is looking to recruit but no product available currently. The main difference the new trail takes 50mls of blood which is a significant amount.
		Expert #9	No
7	What do you consider to be the potential benefits to patients from using this procedure/technology?	Expert #1:	The patients I have spoken to say that the use of their own blood makes sense and allows them to feel “invested” in their wound healing. These are people who cannot feel and often (because of its position) cannot see there foot ulcer. The danger is that because of their neuropathy they become disengaged with the care of ulcers. The time and effort invested by themselves and the clinician appears (anecdotally) to increase their motivation in other aspects of the wound healing process such as off-loading the pressure from the area.

		Expert #2	The aim of treating diabetic foot ulcers is to enhance wound healing. Any new agent with proven efficacy in this regard must be of potential benefit. An open wound is always susceptible to infection and it is infection which, if it progresses, may lead to poor outcomes including amputation.
		Expert #3	Evidence of efficacy in improving the healing of hard-to-heal ulcers has been shown, but the healing rate at 20 weeks was low in both arms of the trial (22vs 34%). There are potential benefits to those with chronic wounds of early healing reducing pain, risk of infection and therefore potential hospitalisation, although it should be noted that infection rates were similar in both arms of the Leucopatch study. Earlier healing of diabetic foot ulcers is associated with improvements in health related QoL.
		Expert #4	Healing in chronic proven 'hard to heal' wounds
		Expert #5	In a blinded outcome RCT it significantly improved healing in patients with hard to heal diabetic foot ulcers and reduced the time to healing in those that healed. This has the potential to save limbs as well as costs to society and the patient. There are few high quality adequately powered blinded RCTs of wound care products in the literature, and the cost of wound care is staggeringly high for the NHS. The majority of wound care products are not evidence based.

		Expert #6	From experience of using the 3C Patch the benefits are not immediate, the 3C Patch can take 2-3 applications before a noticeable change in the wound colour, texture and size. The 3C Patch has to be very carefully observed as the wound heals the exudate levels increase and the wound can become 'boggy' therefore the patients may be required to attend podiatry clinic twice weekly to reduce risk of infection and deterioration of the wound can be quite profound if the wound becomes boggy sometimes having a negative effect-training and education of podiatrists is an important factor if the 3C Patch is to be implemented as part of a trusts standard of care.
		Expert #7	Reduction in healing times for DFU on going reduction in complications including hospitalisation/ amputation
		Expert #8	Fasting healing times and patient satisfaction
		Expert #9	Better wound healing

Potential system impact

8		Expert #1:	I think this technology has wider applications than just chronic diabetes foot ulcers in which it was trialled. The use of a 3CP early on in

	Are there any groups of patients who would particularly benefit from using this procedure/technology?		ulcer development or on wounds that do not have a diabetic aetiology I believe would enhance wound healing at an earlier stage. People on dialysis particularly have a high lower limb amputation rate for a multitude of reasons. The application of the 3CP to foot ulcers in these patients who were excluded from the trials would be a great cost saving.
		Expert #2	Patients with predominantly neuropathic foot ulcers that fail to heal appropriately in the first few weeks of standard of care therapy.
		Expert #3	Patients with chronic non-healing wounds.
		Expert #4	Patients who have proven hard to heal wounds.
		Expert #5	Those with hard to heal ulcers. That is those who are not responding to 4 weeks good standard care including offloading.
		Expert #6	Hard to heel diabetic foot ulcer patients whom have had a wound >28 days. In an off-loading boot or cast. The position of the wound is critical, from the data and evidence found at site any weight bearing sites on the foot i.e. heel do not respond to the 3C Patch and also if the patients ABPI is poor, and if the patients HBA1C is >10mmol/l.
		Expert #7	Patients with diabetes and hard to heal ulcers

		Expert #8	Hard to heal wounds, allergies to dressings.
		Expert #9	Diabetic foot and other wounds
9	Does this procedure/technology have the potential to change the current pathway or clinical outcomes to benefit the healthcare system? Could it lead, for example, to improved outcomes, fewer hospital visits or less invasive treatment?	Expert #1:	The study results indicate improved outcomes compared to usual care alone, the potential to avoid lower limb amputations is not something that studies such as this can do. However the early healing of ulcers means the chances of amputations, hospital stays and other interventions could be greatly reduced. Another aspect of the care neglected by the study was QoL – it has been shown that diabetes foot ulcers dramatically reduce quality of life for those suffering from them along with their ability to socialise and work. Again the sooner ulcers heal the more likely someone is able to resume such activities thus increasing QoL.
		Expert #2	I believe that the potential adoption of this therapy may well lead to improved outcomes, more rapid wound healing and thus fewer hospital visits. Benefit would be more rapid healing of foot ulcers than is achieved by standard of care which will reduce morbidity from diabetic foot ulceration.
		Expert #3	The technology may lead to reduced time to healing of chronic ulcers. To my knowledge the technology is delivered weekly in secondary care settings which may increase the frequency of hospital visits, but over a

			shorter period of time overall for some patients who achieve earlier ulcer healing. There is no reason why the technology could not be delivered in community clinic settings. Increased healing of hard-to-heal chronic wound will reduce costs associated with non-healing wounds, reduce burden on MDT clinics (diabetic foot), and may have a potential to reduce hospitalisations if used earlier in the patient pathway.
		Expert #4	It has the potential to change all of the things mentioned here Healing in chronic proven 'hard to heal' wounds
		Expert #5	Yes – if ulcers heal then there is no requirement for patients to attend wound care clinics or have their wounds dressed by other HCPs. Once a wound heals there is no risk of infection, and the risk of amputation major or minor is greatly reduced. However in the trial the 3C patch was applied weekly which is probably a more frequent clinic visit scedule than usual. Patients who missed visits were not included in the per protocol analysis and there was no difference between the outcomes in this analysis vs the ITT, which suggests that missed applications had little effect on the outcome. Never the less this is not actually known, and if applied as in the trial could lead to more visits to a specialist centre.

			More wounds healed, fewer wound infections, lower costs of wound care, fewer amputations, better patient quality of life.
		Expert #6	The technology has the potential to revolutionise the current pathway for certain patients whom have a diabetic foot ulcer which is hard to heel. The data from the research study and case studies indicated improved outcomes and fewer podiatry visit appointments for the patients receiving the 3C Patch. Further research is required with more participants to determine if the 3C Patch reduces amputation risk in this high-risk population The benefits of utilising the 3C Patch into the NHS Standard of care can be revolutionary. The reduced clinic visits, improved patient outcomes and quality of life.
		Expert #7	Yes it adds in an extra option for those that have not responded to gold standard care not currently available. Anything that reduced healing time will impact on resource utilisation (less nursing visits less hospitalisation less infection less amputation)
		Expert #8	Yes, it could lead to more personalised care. If we heal wound quick people can get back to normal living and working, improved quality of life, reduces depression and anxiety. Less visits and the risk of amputation

			Quicker healing
		Expert #9	Improved outcomes, fewer amputations
10	Considering the care pathway as a whole, including initial capital and possible future costs avoided, is the procedure/technology likely to cost more or less than current standard care, or about the same? (in terms of staff, equipment, care setting etc)	Expert #1:	The technology itself is more expensive however I believe it has the potential to reduce costs overall compared to standard care alone if the wider issues such as hospitalisation, social considerations and patient satisfaction were to be considered
		Expert #2	If wound healing is shortened and hospital visits reduced then although technology may be expensive initially, long-term savings should be seen.
		Expert #3	This would need a formal health economic evaluation to see if the increased cost of the technology were offset by reduced costs of earlier healing and potential for reduced complications.
		Expert #4	Same
		Expert #5	Difficult to say, as I've not seen the full health economic model, but my guess is that it would cost more than usual care even with the above.
		Expert #6	The implementation of the 3C Patch within the care pathway for patients with diabetic foot ulcers (hard to heel) requires careful management and administration from a competent practitioner. If the 3C Patch is

			administered to the right patient, right wound morphology, and correct anatomical and physiological requirements, the outcome can be positive and future cost savings to the NHS can be proven. For the 3C Patch to be a cost saving pathway the practitioners and patients must be motivated, open and engaged to the treatment pathway.
		Expert #7	Less if you account for the potential savings within the system
		Expert #8	It would cost more short term but if healed quicker long term it could be less.
		Expert #9	Will cost more
11	What do you consider to be the resource impact from adopting this procedure/technology (is it likely to cost more or less than standard care, or about same-in terms of staff, equipment, and care setting)?	Expert #1:	The potential for care outside of an MDT for dressing changes once an initial assessment by the team has been made could feasibly shift care to community settings. The number and type of staff would not be affected however as it would still require specialist input at points of the care pathway. The only extra equipment would be the 3CP equipment itself.
		Expert #2	This is difficult to assess as of course this technology does involve the need for bedside centrifugation of blood samples from the patient. In this regard there is a potential that it might require more specialist staff to initiate this therapy.

		Expert #3	This could be delivered in community or secondary care. There is a time requirement for the technology and it would therefore increase weekly time in clinic and potentially increased frequency of clinic visits during treatment. There is no additional equipment above the centrifuge which is loaned for use of the technology. It may need additional staff in clinic as less wounds could be treated by an individual in a clinic session if this was being used routinely.
		Expert #4	Need for a staff member to be able to competently take blood.
		Expert #5	There would be a need for trained phlebotomists to take blood, and there would need to be an area where the blood could be processed safely away from the usual wound care area. This can clearly not be carried out in the patients own home, and given the training required for staff would likely only be suitable for larger clinics.
		Expert #6	The resource impact at the hospital trust is quite minimal due to the development of the centrifuge from the manufacturer. We work in an outpatient setting-which is beneficial for the 3C Patch due to having phlebotomists within the unit supporting the podiatry clinic. In a primary care setting the impact will be huge as additional staff will be required to obtain the blood from the patients prior to treatment, the 3C Patch takes around 20 minutes to produce once loaded into the centrifuge-The only other input required after

			the devises are removed is the treatment of administering the 3C Patch treatment, all other treatment follows the patients routine standard of care i.e. debridement/cleaning/dressing of wound.
		Expert #7	More equipment/ training but I would imagine this would sit in local MDTs rather than in the wider community
		Expert #8	Long appointment times, staff able to bleed patients. More frequent appointments as needs changing weekly.
		Expert #9	Will cost-effectiveness study
12	What clinical facilities (or changes to existing facilities) are needed to do this procedure/technology safely?	Expert #1:	Training is required in the use of the centrifuge but this is a brief session. Those staff trained in blood taking could be utilised for this purpose. However if the staff were not trained this would be an added training requirement.
		Expert #2	As I am fully aware of this technology being an expert in diabetic foot ulceration, for many years, I have not had personal experience of seeing its use, therefore this is difficult to accurately respond to. There may be need for specific training to staff who are going to be applying this new therapy.
		Expert #3	There would be training required for the technology, but it is relatively straight forward to learn to use.
		Expert #4	Training provided by the company in the use of the 3cp device and the centrifuge.

		Expert #5	Yes. it not be usual for wound care nurses or podiatrists to have phlebotomy skills. In the trial this was a problem for some sites, although we trained podiatrists to do the venesection. However in usual care this would not be the case.
		Expert #6	Additional staff will be required to perform the phlebotomy process for the devise. Training will be required for the podiatrists, so they are treating the correct types of wounds for the 3C Patch and continuation of care pathway so they are aware when to stop treatment with the 3C Patch and changing the patient to another treatment pathway or discharging from the service if the wound has healed.
		Expert #7	Training but this could be minimised if focussed on MDT use only
		Expert #8	Training on the centrifuge, bleeding of patients and application of patch.
		Expert #9	-

General advice

13	Is any specific training needed in order to use the procedure/technology with respect to efficacy or safety?	Expert #1:	N/A
		Expert #2	N/A
		Expert #3	N/A
		Expert #4	N/A
		Expert #5	N/A
		Expert #6	N/A
		Expert #7	N/A
		Expert #8	N/A
		Expert #9	N/A

Other considerations

14		Expert #1:	N/A

	What are the potential harms of the procedure/technology? Please list any adverse events and potential risks (even if uncommon) and, if possible, estimate their incidence: Adverse events reported in the literature (if possible, please cite literature) Anecdotal adverse events (known from experience) Theoretical adverse events		
		Expert #2	N/A
		Expert #3	N/A
		Expert #4	N/A
		Expert #5	N/A
		Expert #6	N/A
		Expert #7	N/A
		Expert #8	N/A
		Expert #9	N/A
15	Please list the key efficacy outcomes for this procedure/technology?	Expert #1:	N/A
		Expert #2	N/A
		Expert #3	N/A

		Expert #4	N/A
		Expert #5	N/A
		Expert #6	N/A
		Expert #7	N/A
		Expert #8	N/A
		Expert #9	N/A
16	Please list any uncertainties or concerns about the efficacy and safety of this procedure/?	Expert #1:	Nothing in excess of usual blood taking procedures common in care settings.
		Expert #2	No.
		Expert #3	No.
		Expert #4	No.

		Expert #5	No.
		Expert #6	No.
		Expert #7	No
		Expert #8	no
		Expert #9	-
17	Is there controversy, or important uncertainty, about any aspect of the procedure/technology?	Expert #1:	N/A
		Expert #2	N/A
		Expert #3	N/A
		Expert #4	N/A
		Expert #5	N/A
		Expert #6	N/A

		Expert #7	N/A
		Expert #8	N/A
		Expert #9	N/A
18	If it is safe and efficacious, in your opinion, will this procedure be carried out in (please choose one):	Expert #1:	N/A
		Expert #2	N/A
		Expert #3	N/A
		Expert #4	N/A
		Expert #5	N/A
		Expert #6	N/A
		Expert #7	N/A
		Expert #8	N/A

		Expert #9	N/A
19	Please list any abstracts or conference proceedings that you are aware of that have been recently presented / published on this procedure/technology (this can include your own work). Please note that NICE will do a comprehensive literature search; we are only asking you for any very recent abstracts or conference proceedings which might not be found using standard literature searches. You do not need to supply a comprehensive reference list but it will help us if you list any that you think are particularly important.	Expert #1:	No The company may be collecting case studies as may other centres using the technology
		Expert #2	No. No.
		Expert #3	No. No.
		Expert #4	No No
		Expert #5	No No
		Expert #6	No Not aware of any further research. We have the data we collected from the case studies and with the patients consent and manufacturers consent-we would be happy to share anonymised data
		Expert #7	No No
		Expert #8	No

			No
		Expert #9	No No
20	Are there any major trials or registries of this procedure/technology currently in progress? If so, please list.	Expert #1	N/A
		Expert #2	N/A
		Expert #3	N/A
		Expert #4	N/A
		Expert #5	N/A
		Expert #6	N/A
		Expert #7	N/A
		Expert #8	N/A
		Expert #9	N/A
21	Approximately how many people each year would be eligible for an intervention with this	Expert #1:	If the target population is diabetes foot ulcers there is the potential to use the technology on

	procedure/technology, (give either as an estimated number, or a proportion of the target population)?		all of them I suppose. If it were to go by trial results the number of ulcerations which become chronic with no ischemia or other exclusions would be around 500,000 a year (a very rough estimate based on 2.2% incidence of DFU annually in population of 43 million people with diabetes)
		Expert #2	Diabetic foot ulcers are common and there is a 25% lifetime risk of any person with diabetes developing one. From our large North West Diabetes Foot Care study, approximately 2% of community-based diabetic patients develop new foot ulcers each year. Although difficult to give an estimated number for the target population, ie., those with predominantly hard-to-heal neuropathic foot ulcers, possibly 10% or so might benefit from this.
		Expert #3	Up to 50% of diabetic foot ulcers are “hard-to-heal” and would therefore benefit from adjuvant therapies.
		Expert #4	Probably 2 patients per month in my foot clinic with proven hard to heal wounds that we can also get blood from easily
		Expert #5	We estimated that about 60% of our patient population would have been suitable (as 40% healed well with usual care).
		Expert #6	Within our trust we treated 23 patients in six months with the 3C Patch as part of the case studies project. We anticipate 4-5 patients from a clinic size of 130 patients per week being treated with the 3C Patch. From our

			experience only a small percentage of patients will be eligible for treatment with the patch.
		Expert #7	An estimate from my practice 275,000 population , 15,000 diabetes 500 ulcers per year which are hard to heal around 60% heal with conventional therapy at 12 weeks take away eople who are not suitable e.g renal etc so for that population around 100
		Expert #8	20-40 within my clinical setting
		Expert #9	-

22	Are there any issues with the usability or practical aspects of the procedure/technology?	Expert#1	The taking of blood from a person carries its own issues as is well recognised but these can be largely avoided by following usual protocols the patch making carries no more risk than these
		Expert#2	Not as I understand it.
		Expert#3	It requires a centrifuge which means that it is not portable and therefore couldn't be used outside a hospital/community clinic setting.
		Expert #4	Time taken to become competent and efficient at using it. It starts off being time consuming but is less so as you become used to using it.
		Expert #5	Just the requirement for trained phlebotomists and the associated risks of blood handling
		Expert #6	The main issue with the 3C Patch devise is the requirement that the devise must be full of blood prior to manufacture of the patch within the centrifuge. Diabetic patients are notoriously difficult to bleed and obtain 24ml of blood in one devise can be challenging. We have found that if a vein blows-the devise cannot be re-used (even if the devise is ¾ full) and a new devise must be used-this can be distressing for the patient and has a cost implication for the trust.
		Expert #7	Access to intact vein in multimorbid complex patients

			Patch size reduced would help
		Expert #8	Servicing of centrifuge and training
		Expert #9	-
23	Are you aware of any issues which would prevent (or have prevented) this procedure/technology being adopted in your organisation or across the wider NHS?	Expert#1	I think the use of unknown technology in any environment carries adoption issues. In our trust it was simply a matter of coming up with cleaning and decontamination procedures that are required for any equipment used in patient care and in the use of centrifuges generally these are not ratified.
		Expert#2	No.
		Expert#3	There is a time requirement for technology, and overall with blood taking, preparation and wound dressing application this takes at least 45 minutes per patient. This is a significant increase on standard of care or simple adjuvant therapy dressings, and needs to be performed weekly compared to one off interventions.
		Expert #4	It can be perceived as time consuming and the issue around have someone on hand to competently take blood can be a barrier. The actual number of patients you would use it on is not high.
		Expert #5	Just the lack of cost effectiveness data

		Expert #6	The cost of the 3C Patch must be transparent and as the health economic data of the study has not been published this can be detrimental in the implementation in certain trusts whom are managing costs and treatment pathways. Overall, in the correct patient the patch can be an effective cost saving treatment
		Expert #7	I believe this would be an intervention focussed at the MDT
		Expert #8	cost
		Expert #9	-
24	Is there any research that you feel would be needed to address uncertainties in the evidence base?	Expert#1	No – I think that the patient population used were robust enough in terms of being the hardest to heal ulcers / patients and that the safety has been assured
		Expert#2	No.
		Expert#3	The evidence in DFU patients is based on a particularly hard to heal group. The uncertainty is whether there would be greater benefit in patients who have a less severe impairment of wound healing biology.
		Expert #4	No
		Expert #5	Weekly vs 2 weekly application would have been important rather than relying on PP vs

			ITT analyses. And including a population of patients with end stage renal disease would have been helpful.
		Expert #6	12 month follow-up visit was performed during the research study, I feel that further data could be collected at longer time points i.e. 2 and 3 years post use of the devise to assess wound recurrence/amputation risk and admission/further treatment costing to determine the long term outcomes of patients treated with the patch. Also, a post-operative amputation study to determine the use of the patch in this environment. We used the patch on hard to heel amputation site with excellent outcomes, this also could be a cost saving utilisation of the patch in all forms of wounds not necessarily feet.
		Expert #7	-
		Expert #8	It would be nice to use in those patients with inadequate circulation to aid with pain relief.
		Expert #9	Cost effectiveness
25	Please suggest potential audit criteria for this procedure/technology. If known, please describe:	Expert#1	N/A

	− Beneficial outcome measures. These should include short- and long-term clinical outcomes, quality-of-life measures and patient-related outcomes. Please suggest the most appropriate method of measurement for each and the timescales over which these should be measured. − Adverse outcome measures. These should include early and late complications. Please state the post procedure timescales over which these should be measured	Expert#2	N/A
		Expert#3	N/A
		Expert #4	N/A
		Expert #5	N/A
		Expert #6	N/A
		Expert #7	N/A

		Expert #8	N/A
		Expert #9	N/A
26	Please add any further comments on your particular experiences or knowledge of the procedure/technology	Expert#1	As said before the technology has been used in the MDT within which I work and I have used the system on over twenty people with no issues or side effects
		Expert# 2	The foot has been plagued by poor research evidence in the treatments used for the last 3 or 4 decades. Recent guidelines on clinical trials for new therapies for the diabetic foot by experts in the US and UK including myself, are now being adhered to and its clinical trial design is much improved so we are seeing good evidence now of efficacious therapies including the one discussed in this application for Leucopatch therapy.
		Expert#3	We had no issues with training in the technology, or delivery of the technology, during our involvement in the clinical trial. Concerns over impact on clinic capacity due to time to deliver the treatment and the need for weekly visits has limited our uptake of this outside a clinical trial setting.

		Expert #4	N/A
		Expert #5	With a little bit of thought about the organisation of the clinic and the staff training required it was in the end relatively straightforward to run a research clinic with multiple patients being treated as part of the trial. We were the largest recruiter in the UK, and that certainly helped in terms of staff training, and ease of use. With some thought this could be transferred to NHS usual care, but would require people with the relevant skills to be working in a multi-disciplinary environment. Whilst this is national guidance, it isn't always the case I the UK.
		Expert #6	I have previously discussed the positives and negative of the devise. Overall, the devise is an innovative novel treatment that has the potential to change how we treat wounds by empowering and engaging patients in their treatment.
		Expert #7	-
		Expert #8	It was nice to be able to offer another treatment to those who we were struggling to heal with conventional dressing and offloading.
		Expert #9	-

NICE National Institute for Health and Care Excellence

Patient expert statement

MT539 3C Patch System for treating diabetic foot ulcers

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]
2. Are you (please tick all that apply):	☒ a patient with the condition? ☐ a carer of a patient with the condition?

	☐ a patient organisation employee or volunteer? ☐ other (please specify):
3. Name of your nominating organisation	Reapplix A/S
4. Did your nominating organisation submit a submission?	☐ yes, they did ☐ no, they didn't ☒ I don't know
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ other (they didn't submit one, I don't know if they submitted one etc.)

6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes
7. How did you gather the information included in your statement? (please tick all that apply)	☒ I have personal experience of the condition ☐ I have personal experience of the technology being appraised ☐ I have other relevant personal experience. Please specify what other experience: ☐ I am drawing on others' experiences. Please specify how this information was gathered:
Living with the condition	
8. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	As someone living with the condition it is; **frustrating –** never being sure if the condition is getting better or worse, **time consuming –** constantly striving to keep the ulcer dry, clean and free from infection, **worrying** – it is like waiting on a ticking time-bomb as it is probably only a matter of time till infection gets in, **painful** – it is a well known fact that diabetic neuropathy is a common complication of both type one and type two diabetes, and many patients with diabetic neuropathy may find that this condition has already affected their peripheral nervous system to the extent that sensation in the feet is much reduced. I am fortunate or unfortunate (depending how you look at this) to be from a cohort of patients that suffer from hypersensitivity in the feet, so pain for me is a major concern.

Current treatment of the condition in the NHS	
9. What do patients or carers think of current treatments and care available on the NHS?	I am fortunate enough to have my diabetes care provided by a centre of excellence - Leicester General Hospital Specialist Diabetes Centre. So, the current treatment available to me and fellow patients in the Leicestershire area on the NHS is first rate, but I am conscious that this level of care may not be available to all patients around the country. The Centre as far as I am aware took part in the clinical trials for the 3C Patch System, which I believe is in keeping with their aspirations to trial and test new technologies to complement existing toolbox of treatments.
10. Is there an unmet need for patients with this condition?	I don't know the statistical numbers, but if my condition is anything to go by, I would say yes there is an unm need for patients with this condition. I myself have undergone a series of angioplasty procedures, which gre increased circulation to the lower limbs but was un-successful in increasing the circulation to the toe tips, wl is where the 3C Patch System was used, after exhausting traditional more conventional treatments.
Advantages of the technology	
11. What do patients or carers think are the advantages of the technology?	• My person observation number one advantage would be the reduction of pain that the system propagated, which for me was obvious after the second application. • Once applied the system is very convenient in that, the outer coverings can be left in place for a long period of time. • knowing that the ulcer is completely covered, meaning less chance of infections being introduced.
Disadvantages of the technology	
12. What do patients or carers think are the disadvantages of the technology?	• Main one for me that comes to mind is the taking of blood to make the patch, especially if you hate needles like I do. • Having to have the 3C Patch applied in hospital by a specialist.

Patient population	
13. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Not too sure about the answer to this question, but I would suggest patients with advanced diabetic neuropathy, and especially patients who have difficulty independent living, so things like general walking and moving around is problematic. Also, younger patient groups would benefit greatly as the 3C Patch has the potential of providing quicker healing.
Equality	
14. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Not sure?
Other issues	
15. Are there any other issues that you would like the committee to consider?	• If the 3C Patch was to be provided by the NHS - What would be the patient pathways for referral to the system • The length of time that a patient could be on the system

Key messages
17. In up to 5 bullet points, please summarise the key messages of your statement: • The System has great potential for increasing the quality of life for the patient • Cost effectiveness due to quicker healing hence less burden on the NHS, and better quality of life for the patient • • •

Thank you for your time.

Please log in to your NICE Docs account to upload your completed statement, declaration of interest form and consent form.

……..

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☒ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

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NICE National Institute for Health and Care Excellence

External Assessment Centre correspondence log

MT539 - 3c Patch Systems for Treating Diabetic Foot Ulcers

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

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

These events are recorded in the table to ensure that all information relevant to the assessment of the topic is captured. The table is shared with the NICE medical technologies advisory committee (MTAC) as part of the committee documentation, and is published on the NICE website at public consultation.

#	Date	Who / Purpose	Question/request	Response received
1.	07/04/2021	**Company** Initial questions	Are all components single use except the 3CP centrifuge?	• Yes
2.	07/04/2021	**Company** Initial questions	Any evidence on the 7 year life span of the 3CP centrifuge?	• Data based on components of the centrifuge. Testing included c.12,600 runs over some months which equals ~ c.35 runs per week for 7 years. • The company noted that the centrifuge is on loan to the NHS, and if there are any problems with this then it will be replaced.

3.	07/04/2021	**Company** Initial questions	We know from the submission that the product was first launched in 2011. When was it first used in research?	● First developed as a manual process in 2009 and the initial device was developed in 2010.
4.	07/04/2021	**Company** Initial questions	Previous names for the device (just Leucopatch/Leucopatch /Leukopatch system)?	● The company said that this should be with a 'c' not a 'k. ● From the submission, the previous names include Leucopatch, LeucoPatch and LeucoPatch system before 3C Patch
5.	07/04/2021	**Company** Initial questions	It is noted that the 3CP centrifuge has been developed to automate the patch, but that in the clinical studies this was done manually. A. Is there any evidence to suggest the two systems provide identical outcomes? B. In cases in the NHS in what percentage would each of the methods be used?	A. ● The manual process involves spinning for 8 minutes, leaving for 10 minutes, checking coagulation manually, then spinning for 2 minutes to compress into the patch. ● The automated process is the same but with no manual checking ● The company have compared the manual and automated procedure and reported no differences in the outcomes(e.g. the strength of the patch or the fibrin content) ● The company will provide a report with these results ● Post meeting note - File has been sent, named "TR277, Physico-Chemical Testing Epp vs 3C Patch Centrifuge - Confidential" B. ● All are using the automated process and will do in the future ● The RCT, all patches were prepared with a standard centrifuge but all of today's cases would be with the 3C patch centrifuge running the automated program.
6.	07/04/2021	**Company** Initial questions	It is noted that the IFU states the patch can be used for up to 20 weeks, but that expert opinion indicates treatment times will be considerably shorter. Can this be quantified?	● In the RCT, patients were treated for up to 20 weeks or until healing occurred. ● Experts stated that they wouldn't use the 3C Patch for this long duration - In the RCT, the mean treatment duration was ~ 17 weeks and the mean number of patches per patient was 14 - The company could provide the range/median if needed ● 78% of ulcers which healed by week 20 had a 50% reduction in ulcer area by week 5 - If only those patients whose ulcers had reduced by 50% at 5 weeks had continued treatment, mean treatment duration would have been 9 weeks with 7.6 patches per patient.

				● The 3C Patch is also used in Germany, with an average of [redacted] treatments per patient (not weeks) in a normal clinical setting.
7.	07/04/2021	**Company** Initial questions	Are there any particular diseases/conditions that are important to the healing of diabetic foot ulcers? For example, those reported in Hess CT. Clinical Guide to Skin and Wound Care. 6th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008.	● Classification systems have been developed ● The SINBAD system is commonly used ● From this, ischaemia and neuropathy could be important comorbidities ● Age, ulcer duration at first expert review, and renal failure could impact healing times ● The company don't think there is enough evidence for subgroup analysis for these specific patient characteristics

8.	07/04 /2021	**Company** Initial questions	Deviation from the scope - population "standard wound care including the use of advanced dressings where appropriate". Please can you explain further about the types of advanced dressings used and how reflective these are of standard care in the NHS today?	• In the RCT, all patients had a 4 week run-in period with best standard of care • Hard-to-heal ulcers were defined as those which did not reduce in area by 50% over 4 weeks with best standard of care • Best standard of care included a wide range of dressings based on clinical judgement • Protease modulating dressings were classified using BNF categories and the Journal of Wound Care classification system (these classifications differ so both were used) • In the RCT, 3/4 of patients received advanced dressings and 40% received protease modulating dressings (JWC classification) • Clinicians would try best standard of care (with full range of dressings available) for 6 weeks before using the 3C Patch • The company referred to the NICE report on wound care (including use of advanced wound dressings and antimicrobial dressings) which stated that these dressings are widely used in the NHS with a substantial expenditure (note this report was not specific to diabetic foot ulcers)
9.	07/04 /2021	**Company** Initial questions	What format will the economic model be submitted in (e.g. MS Excel)?	• Model will be in TreeAge format with accompanying elements provided in Excel
10.	07/04 /2021	**Company** Initial questions	Can you provide more information on the Wagner system used for classifying ulcers?	This system is not recommended by NICE but is commonly used in the US • In the UK, the SINBAD system is frequently used • There is a question about whether any of the classification scales adequately capture the complexity of long-term hard-to-heal ulcers • Earlier studies tended to use the Wagner scale to describe the depth of the ulcer and if there was evidence of infection, but this scale does not capture all the important factors. This is more focussed on how the ulcer looks and how deep the wound is.
11.	07/04 /2021	**Company** Initial questions	Can you provide more information on the economic modelling side of the submission,	• The model will be a Markov model created in TreeAge. Almost completed the base case. Using healing probability from the trial data. The Markov model runs on a 2- year time frame. The model proposes that after the first 5 weeks of healing the groups will be divided into 2 cohorts. 1 group will continue with the 3C Patch System and 1 group will stop. 52-week healing rate was gathered from the trial but not reported in the paper.

			including outcomes from the “Game trial”?	Probabilities relating to amputation and death are taken from literature as these cases are rare.
12.	13/04 /2021	**Experts** Q&A via zoom	Do the experts agree with the company’s portrayal of the care pathway?	● The experts agreed that the overall structure of the clinical pathway presented by the company and the positioning of 3C Patch as an end of line treatment option for those in which other advanced dressings had failed seemed reasonable according to NICE and other international guidelines. ● The experts raised concerns about whether the ‘50% reduction in ulcer area’ used by the company to define adequate progress and continuation with the 3C Patch was appropriate. They suggested: ● The 50% threshold may be too high and that any improvement/progression (e.g. a 30% reduction in ulcer area) with the 3C Patch could be beneficial in this population and could warrant continuation with the patch provided a greater improvement was seen with the patch compared with previous treatments. ● The 50% threshold could be ‘too hard and fast’ and that a patient orientated approach could be used as some patients respond better to treatment than others. ● That (from a patient perspective) it might be difficult to stop using the 3C Patch if there was some improvement in ulcer healing (but not reaching the 50% threshold). ● The measures employed to determine ulcer area in many clinics are not very accurate so determining the 50% reduction could be difficult or would require specialist equipment. ● One of the experts also suggested that this 50% threshold may have been led by the evidence. The Game1 trial excluded patients from randomisation if a change in ulcer area of more than 50% was observed during the 4-week run-in period. ● Other comments related to the use of ‘6 weeks’ stated in the first level of the pathway and ‘4 weeks’ stated in the second level of the pathway in relation to the run-in period. The experts suggested that this was unclear in the pathway and that the reasons for this difference in duration should be clarified i.e. it suggests there is a 2-week run in period prior to the 4-week period where the ulcer is assessed for reduction in ulcer area. The experts agreed that a formal run-in (as in a trial setting) was not needed in practice if they could tell from the patient’s history that their wound had not progressed with previous treatment.

13.	13/04/2021	**Experts** Q&A via zoom	Do the experts agree with the company's suggestion that hard to heal wounds should be defined (for the purposes of this assessment) as "foot ulcers that are not healing despite standard wound care including the use of advanced dressings where appropriate"?	• The experts raised questions about how 'advanced dressings' are defined and suggested that there is limited evidence around the effectiveness of most advanced dressings. One expert noted that the only advanced dressing with proven efficacy in people with diabetic foot ulcers is UrgoStart. • The experts suggested that there is a need to define advanced dressings clearly and to explicitly state what is covered within 'standard wound care' in the scope (e.g. offloading, wound debridement). • The experts agreed that the things noted in the NICE clinical guideline (i.e. offloading, control of foot infection, control of ischaemia, debridement and dressings) are the core components of standard care, with or without advanced dressings such as UrgoStart.
14.	13/04/2021	**Experts** Q&A via zoom	The pathway notes that "adequate progress" related to wound surface area is determined. Is this simple and quick to measure in practice, or would it incur additional resource use?	• The experts confirmed that standard practice generally involves the use of a measuring tape or clinical photos to determine wound area and that with these methods the accuracy may be poor if trying to determine an accurate measure for the purposes of a cut-off measure of 50% reduction in ulcer area. • The experts suggested that most clinics do not have access to more advanced methods to reach the required accuracy and that additional resource would be required for more accurate measurements of wound area reduction. • The experts also suggested that area is not always the best measure and that reduction in volume/depth could be a better measure.
15.	13/04/2021	**Experts** Q&A via zoom	The scope states that the comparator is "standard conventional/advanced wound dressings". Do the experts think that this could include interventions such as (i) platelet-rich plasma made from blood donor blood, (ii) autologous	• The experts confirmed that these interventions are rarely used in standard care and that there is limited evidence supporting their use.

			platelet-rich plasma gel with thrombin, (iii) platelet-rich fibrin matrix, or are these interventions used too infrequently to consider them as 'standard care'?	
16.	13/04/2021	**Experts** Q&A via zoom	How would UrgoStart fit into the care pathway?	• The experts confirmed that UrgoStart would be used before 3C Patch in practice (as this is easier to use) and that they would not use 3C Patch unless UrgoStart had not worked.
17.	13/04/2021	**Experts** Q&A via zoom	Are the experts happy that the population in the trial led by Game is representative of the population that would receive the 3C Patch device if it were to be used within the NHS?	• Yes, the experts agreed.
18.	13/04/2021	**Experts** Q&A via zoom	85% of participants in the Game1 trial had received advanced dressings in the run up to the trial. Is this likely to have influenced the outcome in terms of the benefits of the 3C Patch?	• This question should state 'run-in period' not 'run up'. • One expert stated that there are no data on what happened to patients before they consented to go into the trial. • The experts agreed that the dressings used in the 4-week run-in period were not particularly advanced (most were iodine or foam, and none were UrgoStart). • The experts suggested that the use of these dressings is not likely to have influenced the outcome.

19.	13/04/2021	**Experts** Q&A via zoom	The trial led by Game1 includes a relatively high proportion of male participants (82%). Do the experts think that outcomes would be similar for male and female participants?	• Yes, the experts agreed. • The experts suggested that whilst diabetic foot ulcers are more common in males (which is standard across the UK), the treatment response rates are equal for each gender. • The experts agreed that the high proportion of male participants is reflective of what would usually be seen in clinical practice. Most experts agreed that they see 60-70% males in their clinics.
20.	13/04/2021	**Experts** Q&A via zoom	Had the patients in the Game1 trial used UrgoStart?	• The experts stated that none of the patients in the Game trial had used UrgoStart due to the trials running at similar times. • The experts said that because the two trials were conducted at the similar times, UrgoStart was not used as part of standard care when recruitment for the Game trial was undertaken. Therefore, it was not possible to assess the efficacy of 3C Patch in an UrgoStart experienced population, even though this is the group that is likely to receive it in practice. • The experts agreed that there were differences in the populations between the two trials due to the selection process for each trial. The experts noted that the inclusion criteria were more permissive for 3C Patch trial compared with the UrgoStart trial. Specifically, the experts said that people in the UrgoStart trial had to have had a 30% reduction in ulcer area over a 2-week run in period, prior to starting treatment with UrgoStart. Also, that people with specific comorbidities were excluded from the UrgoStart trial, who would have been included in the 3C Patch trial. Therefore, it is possible that some patients in the 3C Patch trial would have had ulcers that could be considered 'harder to heal' ulcers than those in the UrgoStart trial. • Therefore, the experts doubt this would have made any difference to the outcomes of the Game trial because the patient groups would likely be different in clinical practice.
21.	13/04/2021	**Experts** Q&A via zoom	Of the outcomes included within the scope (shown for convenience in Appendix B below), which do the experts	• The experts agreed that speed of healing is the most important outcome. • The experts suggested that other important outcomes are the incidence of wound-related complications/infections, number of new amputations, total number of 3C Patch treatments needed, and frequency and total number of secondary dressing changes (which would all be influenced by speed of healing).

			think are the most important for decision making (this could be from a clinical and/or economic perspective)?	● The experts suggested that change in ulcer area and pain at ulcer location are less important. The experts also suggested that change in ulcer area is not as important an outcome as time to healing. One expert stated that a smaller ulcer could still be a source of infection and cause of amputation.
22.	13/04/2021	**Experts** Q&A via zoom	The Wagner grading scale is used to measure some outcomes. Is this scale appropriate, or do the experts think that more recent scales should be used?	● The experts noted that although the Wagner scale is a validated tool, it is not the best and other similar tools for assessing ulcer severity are available (e.g. SINBAD, WIfI). They also noted that the Wagner scale is not recommended by NICE. ● The experts suggested that the Wagner scale is too blunt and not granular enough for use in clinical trials. Trials with inclusion/exclusion criteria based on this scale would not necessarily be comparable because there could be differences between patients that would not be captured in the Wagner scale. ● Also, this scale would not be granular enough when measuring change in ulcer area over the duration of a study. ● Overall, the experts agreed that these types of scales are mainly used as input scores for benchmarking between different centres. ● One of the experts said that the Wagner scale measures depth, grade, infection and gangrene and that most ulcers would be in the region of Wagner grade 2/3. They also said that the Wagner scale does not measure neuropathy.
23.	13/04/2021	**Experts** Q&A via zoom	Wound recurrence and wound deterioration is likely to be an important consideration when estimating the long-term benefits of treatment. Please could the experts comment on whether the population being considered here (i.e. those with hard to heal diabetic foot ulcers) would be likely to have different recurrence rates	● The experts agreed that this question is very difficult to answer. ● The experts noted that recurrence rates are high with diabetic foot ulcers. Even in the best centres they expect recurrence rates of 30-50%. ● The experts suggested that healing derived from the 3C Patch would be the same as healing achieved via any other agent/intervention. Therefore, risk of recurrence would likely be similar regardless of how the wound came to be healed. ● The experts said that hard to heal ulcers are hard to heal due to a range of factors that vary from each individual. ● The experts agreed that it is difficult to answer whether characteristics of this patient group would influence recurrence rates. They were able to define what factors contribute to wounds recurring (poor diet, loss of feeling or sensation, disease progression etc.), but as there are so many factors, it would be hard to make general statements which would apply across the whole population.

			compared with a wider patient demographic?	
24.	13/04/2021	**Experts** Q&A via zoom	The company submission makes use of an unpublished German consensus document, which provides guidance on the use of 3C Patch. This is based on clinical experience with the patch in outpatient and inpatient settings, presumably in Germany. Are the experts happy that this would be relevant to the decision problem in the UK?	● The experts agreed that this question is difficult to answer without seeing the consensus document. ● The experts speculated that there are differences in the healthcare system (i.e. more private medicine, insurance claims, and no podiatry) but could not say exactly what the differences are without seeing the document.
25.	13/04/2021	**Experts** Q&A via zoom	Much of the evidence is based on data from single arm studies. Are the experts confident that healing rate data and safety data can be used from non-controlled studies?	● The experts agreed that safety data can be used from non-controlled studies. ● The experts agreed that the use of healing rate data from non-controlled studies is harder to justify (linked with the heterogeneity in wounds).

26.	13/04/2021	**Experts** Q&A via zoom	In the Game trial, the patch was changed every week, is this standard practice?	• The experts agreed that in the trial, it was quite a burden for patients to attend weekly. • The experts stated that there were also no significant differences between the intention-to-treat and per-protocol analyses, and the vast majority of drop out in the study was due to missed visits. From this, it can be assumed that it might not be necessary to change the patch each week as missed visits in the trial did not appear to make any significant differences to the outcome.
27.	13/04/2021	**Experts** Q&A via zoom	The experts were asked to comment on the practicalities of using the 3C Patch in practice	• The experts explained that it is difficult to take blood from some patients on such a regular basis (especially given the multi-morbidity in this population) and that you need an experienced phlebotomist to do this. • The experts agreed that it is sometimes difficult to get a complete blood sample (i.e. 18ml of blood) to fill the device and that as the device is single-use and cannot be refilled, when this happens it must be discarded. If the device is only part full this can lead to wastage and increased resource in some cases, and the need to obtain an adequate blood sample may be a barrier to treatment for some patients. However, this process was easier with smaller gauge needles. • The experts suggested that a smaller patch for smaller wounds would be useful (and therefore less blood would be required) and should be considered in the future, as at the moment only one standard size 3C Patch is commercially available
28.	13/04/2021	**Experts** Q&A via zoom	For this specific population, do the appointments for dressing changes happen in hospital anyway or would some patients need to be brought into hospital rather than being seen in community or primary care settings?	• The experts agreed that it is difficult to see how this could be delivered in the community due to the training and resource needs (e.g. phlebotomy, podiatrist to apply the patch). Additionally, the need for equipment such as the centrifuge could present a barrier. • The experts commented on the fact that this could result in an inequitable service for housebound patients. • The experts noted here that in the Game trial, the first few applications of the 3C Patch system were less likely to heal, as staff became accustomed to using the device their efficiency increased. If the first 3 to 4 procedures were excluded from the analysis this led to an improvement in outcomes. The experts noted that this was unpublished data.

29.	13/04 /2021	**Experts** Q&A via zoom	The experts were asked to provide some detail about what happens in practice once they have tried UrgoStart and the 3C Patch and there is no improvement in the hard to heal ulcer	● The experts agreed that they would not try 3C Patch or UrgoStart more than once and would go back to the other aspects of standard care (i.e. offloading, infection control or vascular interventions). Advice from the experts was that standard care can be effective if used correctly and consistently, and that offloading can be very effective. However, many patients struggle with adherence to offloading interventions, often for practical reasons or because loss of sensation means that pain is not a trigger for using supports. ● The experts agreed that they would always use a simple dressing and would not leave an ulcer uncovered as the dressing keeps it clean.
30.	13/04 /2021	**Experts** Q&A via zoom	How widely used is UrgoStart and is it considered standard care?	● The experts agreed that UrgoStart is pretty widely used.
31.	21/04 /2021	Frances Game (expert) was contacted via email	We have come across an ongoing study involving patients with malleoli ulcers and just wondered if these are generally considered in the same category as foot ulcers, or if they tend to have a different natural history/treatment as they are not weight-bearing areas? i.e. should this be included as a relevant ongoing study in our assessment or not? Also, are we correct to say that all the patients involved in the studies	● When doing the trial we spent a lot of time debating whether we should include malleolar ulcers or not, in the end deciding that they shouldn't be included. There were 2 main reasons. Firstly, being pedantic, the malleoli were not actually part of the foot and secondly they were much more likely to be related to a more vascular pathology either being pure arterial, venous or arterio-venous ulcers. It was difficult to decide though, as these ulcers are seen frequently in a diabetic foot ulcer clinic. Which is why I suspect there is an ongoing study. I wasn't aware of this study though, where is it being done? So my gut feeling would be not to include this study in a diabetic foot ulcer appraisal, but others may argue the more pragmatic view. ● And yes, all the patients in the study were out-patients. We didn't specifically exclude in-patients but in-patients are generally there for reasons of infection of the ulcer, for revascularisation, both of which were exclusions and/or were sick with other co-morbidities.

			of 3C patches were outpatients?	
32.	21/04/2021	**Company** Via email	Please can the Company supply 15 references cited on the Reapplix references page (https://3cpatch.com/proven/references/) that our reviewers would like to assess further?. In addition, we wanted to check if the Company is able to supply the full text for 5 papers we are unable to access without purchasing. We can do this if necessary, but thought we would check if the Company is able to supply before we go ahead and do so.	• All 15 references supplied • Unable to provide the 5 additional papers
33.	27/04/2021	**Company** Via email	Could the Company please advise where these quality of life data regarding the RCT come from, and supply the relevant paper/data, ideally by close of play on 28th April?	[redacted]

			Also please could the Company supply ITT data for quality of life from the trial (as these data mentioned are only in patients who became ulcer-free).	[redacted] 
34.	28/04/2021 / - 29/04/2021	**Company** Via email	Please could the company clarify some queries regarding which abstracts related to which study? Also, do you have any information on the "matched control group" please? Percentages of the controls healing are reported, but not the	*"Reply received 29/04/2021"* ● The assessment made by EAC was correct regarding which abstracts link to which study. ● Jørgensen et al. 2011 - 13. patients of different etiologies (Paper attached) (Sponsor: Reapplix) Appendix 1 ● Löndahl et al 2015 - 44 patients in included (60 pts screened for inclusion) (Paper attached)(Sponsor: Reapplix) Appendix 1 ● Löndahl et al - probe to bone DFUs - 22 patients (26 wounds) (Only presentation/Poster) (independet) Appendix 1 ● Löndahl et al - Malleoli wounds - 6 patients (Only poster, Fagher et al)(independent) Appendix 1 ● RCT - Game et al. 2018 (Sponsor: NHS Trust, Funder: Reapplix) Appendix 1 ● Regarding the matched control group, we have very limited knowledge - according to Dr-Löndahl and his colleague Dr. Fagher it was matched by Wagner grade, ulcer duration,

			number of people this applies to.	ulcer location and ulcer size (see attached presentation). Dr. Faghers speak notes included "When we matched our patients in the study with a control group from our diabetic foot unit, whit the same ulcerlocation, duration, size and Wagnergrade the Leukopatch treated patients seemed to havebetter healing rates compared to the reference group. However, we cannot draw any conclusions from this result since this wasn´t a randomized controlled study." ● This aligns well with the fact that Dr. Löndahl were a key PI in the Game et al 2018 RCT Study, as such the matched control data were only used to support (among other data) moving to a larger RCT. ● As many of the clinical data are investigator driven, we regrettably do not have access to the full data sets.
35.	06/05 /2021	**Company** Q&A via zoom . Written responses to the questions were also provided after the meeting and have been included in the responses here.	Please can the position of the company on where 3C patch falls in the patient pathway be clarified? There is some inconsistency between the submission and the model as to whether 3C patch is used concurrently or following advanced dressings such as Urgostart.	● The draft clinical pathway proposes that 3C Patch should be considered for use in cases where insufficient progress toward healing has been made in spite of best standard of care as currently recommended by NICE (including offloading, debridement, control of modifiable factors and use of dressings such as UrgoStart and other protease modulating and advanced dressings where appropriate) over a number of weeks. It is likely that best standard of care would be tried for at least 6 weeks before 3C Patch is considered. During this time progress towards healing should be reviewed regularly and the patch should only be considered in cases where ulcer area has not reduced by 50% or more during the 4-week period prior to proposed use, as in the 3C Patch RCT. Clinical judgement and patient preference will determine at this point whether 3C Patch should be used for eligible patients. ● Where 3C Patch is not chosen, experts indicate that best standard of care as recommended by NICE (and outlined above) would be continued. If 3C Patch is tried, and does not result in ulcer healing, best standard of care as recommended by NICE including advanced dressings where appropriate would continue after 3C Patch until healing is achieved (or the patient has an amputation or dies). ● 3C Patch is not used in combination with other advanced dressings. However, other elements of NICE-recommended ulcer care (such as offloading, debridement, and control of modifiable factors) will be provided along with 3C Patch where appropriate. (These are not alternative treatments but parallel interventions.) These other elements of NICE-recommended ulcer care will also be provided along with advanced and other

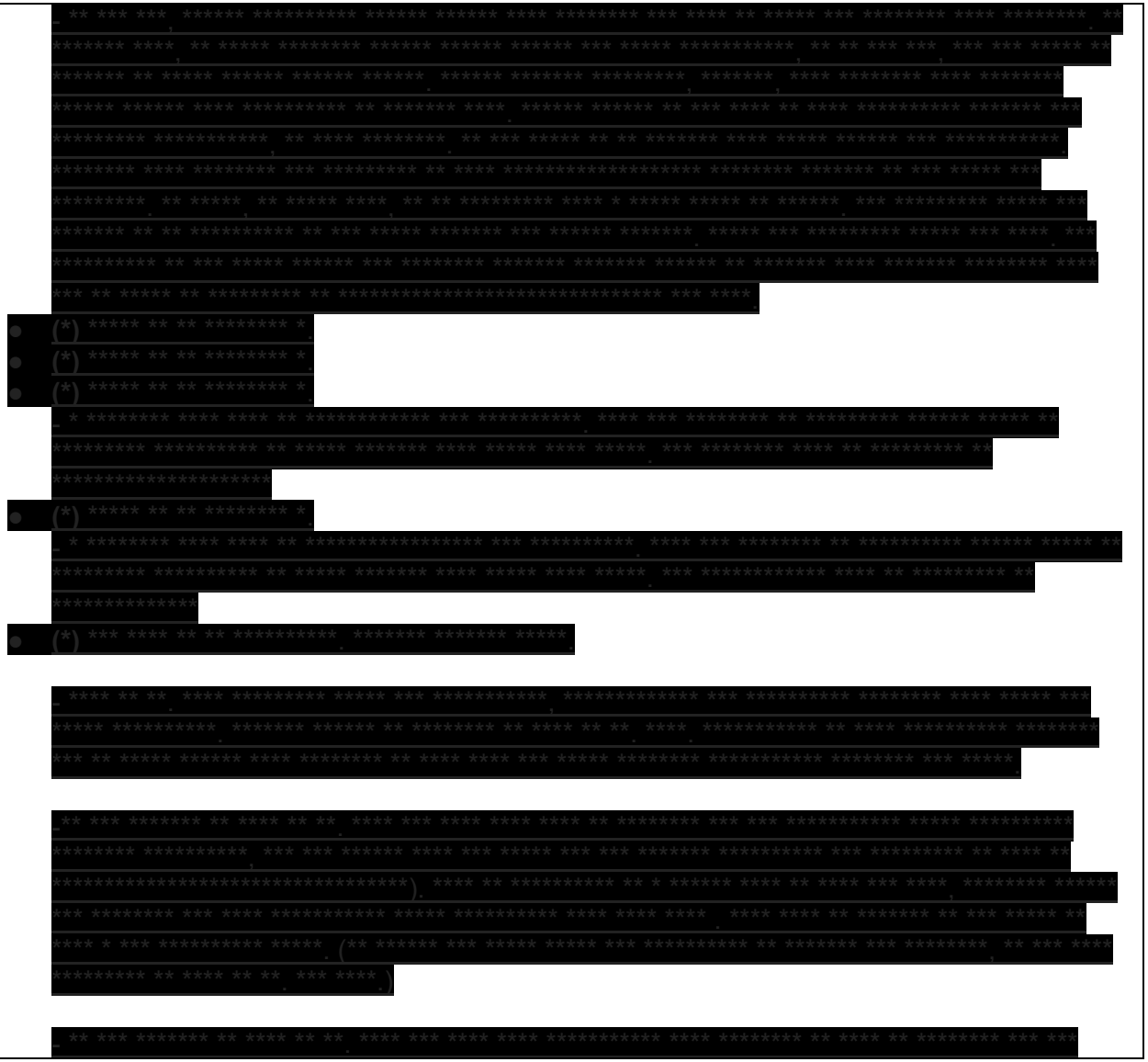
				dressings for patients who are not receiving 3C Patch. It is expected that best standard of care as recommended by NICE will continue as long as the patient remains ulcerated, whether or not 3C Patch has been tried. ● In the economic model, it is assumed (as described in the pathway) that all patients have hard to heal ulcers, identified by insufficient progress toward healing during a 4-week run-in period in which best standard of care is provided, including advanced and protease-modulating dressings where clinical judgement indicates these are appropriate. The model is based on the RCT, in which a 4-week run-in period preceded randomisation, and hard to heal ulcers were identified by a reduction in ulcer area of less than 50% during this run-in period. In the RCT, 73% of patients received advanced dressings, and 40% received protease modulating dressings such as UrgoStart in the 4-week run in period. ● Parameters for the economic model are derived from the RCT dataset. We consider that the patient population in the proposed clinical pathway, the RCT population and the model population are aligned in respect of prior care and previous progress toward healing. ● The standard care arm in the RCT received best standard of care, including advanced and protease-modulating dressings where clinical judgement indicated these were appropriate. During the trial intervention period, 90% of patients in the standard care arm received advanced dressings and 60% received protease modulating dressings such as UrgoStart. The economic model assumes that the comparator arm receives best standard of care, including advanced and protease-modulating dressings, as in the standard care arm of the RCT. The data on dressing use and clinical outcomes from the RCT are used to derive parameters for the comparator group in the economic model. We consider that the RCT and the economic model are aligned in respect of care for the comparator group. The proposed clinical pathway does not set out expectations for care in cases where 3C Patch is not adopted. However, expert opinion indicates that in routine care, patients who are eligible for 3C Patch but do not receive it (because of clinical or patient preference or other factors) would continue to receive best standard of care as recommended by NICE, including advanced and protease-modulating dressings where clinical judgement indicates these are appropriate. ● The economic model assumes that, for ulcers that remain unhealed after 20 weeks, both arms receive best standard of care as recommended by NICE, including advanced

				dressings where appropriate, until healing is achieved (or the patient has an amputation or dies). The proposed clinical pathway for 3C Patch does not specify which treatments should be used after the patch in cases where healing has not been achieved, as this is outside the scope. However, experts indicate that best standard of care as recommended by NICE would be used.
36:	06/05 /2021	**Company** Q&A via zoom . Written responses to the questions were also provided after the meeting and have been included in the responses here.	We note that 0.836 3C patches are applied per patient per week: A) Is this calculated based on those patients with unhealed and uninfected wounds only? B) If so, why is this lower than 1 per week? C) Does this value take into consideration any patient who required more than 1 patch per treatment (due to wound size) D) Does this value take into consideration any wastage where blood could not be obtained from patients?	[redacted] • [redacted]

37.	06/05 /2021	**Company** Q&A via zoom . Written responses to the questions were also provided after the meeting and have been included in the responses here.	Please can further information on how the following transition probabilities were calculated be provided (i.e., how the data from Appendix C were transformed for use in the model): A) % discontinuing at week 5 with 3C patch – specifically how this was adjusted for death and amputation B) % discontinuing at week 20 with 3C patch – specifically how this was adjusted for death and amputation C) % undergoing major and minor amputation – specifically how this was adjusted for death	[redacted]

38.	06/05/2021	**Company** Q&A via zoom . Written responses to the questions were also provided after the meeting and have been included in the responses here.	Please can further information on how the following costs were derived be provided (e.g., all components of the cost, source for these and how the components were combined): A) Ulcer inpatient care cost - please provide further detail on what was used from Kerr et al. and how this was updated using NHS reference costs B) Ulcer outpatient, community and primary care cost - please provide further detail on what was used from Kerr et al. C) 3C patch medication cost – please provide proportion on each medication in additional to the additional data provided in Appendix C. D) 3C Patch district nursing impact - please provide further	

			information on how the difference in district nursing visits of 0.56 was derived. E) Standard care medication cost – please provide proportion on each medication in additional to the additional data provided in Appendix C. F) Standard care district nursing impact - please provide the relevant data from the Game RCT G) Major amputation – please provide a list of the NHS reference costs code used and how these were combined H) Minor amputation – please provide a list of the NHS reference costs code used and how these were combined	

			I) Post major/minor amputation – please provide detail on how these costs were determined from Kerr et al. for both year 1 and year 2.	

39.	06/05/2021	**Company** Q&A via zoom . Written responses to the questions were also provided after the meeting and have been included in the responses here.	Where additional analyses were conducted for the model using data from the Game RCT have any of these analyses been conducted previously (e.g., as part of the clinical study report) or are they new analysis for the MTEP submission?	• Most of the additional analyses are new and were conducted for the MTEP submission. However, some analysis was conducted earlier but not published. Specifically, analysis of healthcare professional resource use for dressing changes between weekly clinic visits, and estimates of dosage for antibiotic medications, were conducted previously by the trial team.
40.	06/05/2021	**Company** Q&A via zoom . Written responses to the questions were also provided after the meeting and have been included in the responses here.	We assume that no half cycle correction was applied in the model based upon the setting selected within Treeage. Is this correct?	• This is correct. We did not consider half cycle correction appropriate as the cycle length is one week, and determination of healed status and decisions regarding patch application, dressing choice and medications in the trial were taken at weekly clinic visits.
41.	06/05/2021	**Company** Q&A via zoom . Written responses to the questions were also provided after the meeting and have been included in the responses here.	We understand that the only impact of infection on the model is in the antibiotic costs applied in the unhealed ulcer health state. Is this correct or is this also considered within the discontinuation rate applied to patients in	• This is correct. Discontinuation at 5 weeks is based on trial data on ulcer area reduction. Discontinuation at 20 weeks is applied to all unhealed patients as the treatment is only given for up to 20 weeks. In the model, patients do not discontinue 3C Patch owing to infection. This approach to infection reflects the approach used in the RCT. However, expert opinion indicates that in routine practice, it is likely that 3C Patch use might be suspended in the event of infection and resumed after the infection had healed. In this case patch use and associated costs would be lower than in our model.

			the 3C arm to capture them stopping use of 3C patch when infected?	
42.	06/05/021	**Company** Q&A via zoom . Written responses to the questions were also provided after the meeting and have been included in the responses here.	We note a cost of training is applied. Please can you describe what this training entails and whether trained staff can be considered "expert" users achieving the level of effectiveness seen in the Game RCT after the training? Has any evidence been collected on this?	● The training was and is provided by the Company, it is practical in nature and is centred around making a patch in the centrifuge and applying a patch. Those practical steps are: • Attaching the device to the needle holder for blood collection • Power the centrifuge • Operate the centrifuge's function buttons • Understand and process the messages on the centrifuge display • Know how to load the device in the centrifuge and when a counterbalance is needed • Recognise the 3 step process (the 3 C's) for making a patch – centrifugation, coagulation and compaction • Handling and practical application of the patch treatment • Routine cleaning of the centrifuge ● Ideally, initial training takes place alongside the first patient's treatment in each clinic. ● The training in the clinical trial was also provided by the company and the hands-on, practical focus is the same as in the trial. In addition, clinicians are now using a fully integrated automated 3C Patch system incl. the specific 3C Patch centrifuge. Due to this there is significantly less hands-on work compared to the RCT. The company provides support and training free of charge at any time and whenever needed. ● In the trial, everyone made their first patch and, through experience, became experts, just as clinics that are new to the system will do now. Therefore, we do believe the staff can be considered "expert users" achieving at least the level of effectiveness seen in the RCT. ● Today's training follows the exact same protocol as in the RCT. In fact, training now usually occurs a lot closer to the first utilization while in the RCT training was typically done months prior to first enrolment and the Company was not allowed access to the sites after that. ● The only thing that could be seen as evidence in some way is a small customer satisfaction survey conducted in 2019 where the ease of use of the integrated system was clearly rated with the max. available points by each participating user.

43.	06/05/2021	**Company** Q&A via zoom . Written responses to the questions were also provided after the meeting and have been included in the responses here.	The trial protocol for the Game RCT mentions that a cost-effectiveness and cost-utility analysis will be conducted. Do you know if this has taken place?	• Initial analysis was done, not finalised and not published. The Company was not involved in the design of the study and the HE analysis.
44.	07/05/2021	**Experts** Q&A via email	If a patient's diabetic foot ulcer becomes infected whilst using the 3C Patch, would you continue to use the 3C Patch or would you discontinue use until the ulcer was no longer infected?	• A Musgrove: Would continue to use unless the person was going for surgery on this area for example for a biopsy / tissue sample or debridement of the area under a surgical team. • E Ricci: I would discontinue use as it is unlikely to be beneficial within this environment. I would wait until the clinical signs of infection had subsided before restarting. • J Thorpe: At the trust I work at we would discontinue the 3C Patch treatment until the infection has cleared. • F Game: In the trial it wasn't discontinued and no additional infections were noted. So I would continue especially as there are no other topical agents or dressings with any evidence of benefit for the treatment of a clinically infected ulcer. • P ChadwickI think this might depend on the extent of infection if it was moderate or severe(IDSA 12) then I would probably stop as the destruction from the infection would negate any positive impact of the patch . Mild infection might be ok • R Berrington This would depend, if it was a wound swab which indicated clinical infection then an assessment of the wound would be required to see if this fitted the clinical picture, if the wound itself looked clinically infected then antibiotics would be required and I would stop the use of 3c patch until the infection had subsided and then recommenced. • D Russell I would discontinue dressings that were required to stay in situ for 1 week during acute infections and recommence when the infection has settled. •
45.	07/05/2021	**Experts** Q&A via email	The company's clinical pathway and economic model proposes discontinuation of 3C	• A Musgrove: I think the definition of "respond" I would use in this case would be if I saw no improvement rather than a quantification of this. Each wound and person are different and circumstances of individuals have to be taken into consideration. For example if someone had shown no improvement or deterioration of wound size prior to using a patch and their

			patch at 5 weeks for those people with a less than 50% reduction in ulcer size. a. When using 3C patch, would you discontinue use at around 5 weeks for patients not responding sufficiently? b. If so, is a less than 50% reduction in ulcer size a reasonable cut-off or would you use a different measure?	wound then showed even a small reduction in size over the 5 week period I would not discontinue. • E Ricci: (a) I would discontinue at 4 weeks if there was not a 50% reduction however in my clinical experience I have not ever had to use it for that long. I would probably have discontinued it a lot earlier at around 3 weeks 4 weeks max as my clinical experience is that you see a reaction very quickly to this therapy. (b) Yes! We use a 50% reduction at 4 weeks as a clinical outcome in our clinics as a standard measure of the efficacy of all our interventions. It is a good indicator of the need to escalate or re-evaluate care based in evidence (Snyder 2010) • J Thorpe: (a)Yes-Treatment would be evaluated on an ongoing basis-so if the 3c patch was having no therapeutic effect by week 4-the treatment plan for the DFU would be reviewed.(b) Treatment of the ulcer would continue with the 3 c patch treatment until the wound reaches a point where the 3c patch is having no therapeutic effect. The wound evaluation would take place over a two week period-to determine that the 3c patch is having no effect on the wound • F Game(a):Possibly but 5 weeks seems an odd choice – absolute wound healing is predicted on 4 week wound area reduction.(b) I would discontinue only if the healing trajectory was no better than the pre treatment ie. the period of time when usual care was applied. If the healing trajectory was better than this then I would continue, but that need not be 50% reduction. For example had there only been a 20% reduction over 4-6 weeks with best standard care alone then a 30-40% reduction over the following 4 weeks would be a good outcome. • P Chadwick (a) Yes I would (b)Reasonable but it should not be an absolute if its 48% then I would continue so there needs to be some clinical judgement used • R Berrington (a)Yes (b) Pain reduction, patient perception, compliance, if the wound had been present for a very long time and static and had shown signs of reduction then there could be justification for continuation with close observation. • D Russell (a) I would be guided by the manufacturer as to the expected response to treatment. I note that the manufacturers guidance on the website FAQs is to stop or pause the treatment at 6 weeks “if there is no effect” which is different to <50% reduction in wound area at 5 week. (b) 50% wound healing at 4 weeks is a good predictor of wounds that would go on to heal

				in a timely fashion with low incidence of complications and is therefore recognised as a wound healing trajectory. Allowing time for a change in wound biology with the dressing to occur, a 50% healing at 5 weeks is an ambitious target.
46.	07/05/2021	**Experts** Q&A via email	Questions relating to appointments for the application of 3C patch: a. Our understanding of current practice is that patients with DFUs are seen once a fortnight for an outpatient appointment. Please can you confirm whether this is correct? b. If yes, what are the practicalities of moving from fortnightly visits to weekly visits for patients using 3C Patch for dressing changes in terms of capacity within multidisciplinary	• A Musgrove:(a) I suspect this is an average but again each centre and individual is different. Sometimes the length of time between out-patient appointments is greater than two weeks due to transportation and access issues. Some centres see people more regularly. The length of time at our centre has probably increased to three weeks now due to COVID restrictions on numbers – but this may well revert to the two weekly visits we would ideally prefer. This time span also depends on community wound clinic availability. (b)This would undoubtedly pose a few issues but the number of people being treated with a patch at any one time would probably mean the impact would be minimal. (c)The increase in time and expertise would be the time and skills it takes to take blood and centrifuge the patch. (d) I would say this is an accurate representation. (e)I consider this would not be an issue due to these stated reasons. (f)Not aware of any centres who do this but there is no reason why it would be an issue (g)NICE recommend this care for hard to heal ulcers. However there may be instances where specialist podiatry teams are working in the community (particularly with shared care of ulceration) and there would be no reasons – if the skills of phlebotomy were available – why they could not utilise the patch in these clinics. • E Ricci: (a) No, not in our trust. It depends entirely on the setting and the complexity of the wounds. In our centre the patients with the most complex wounds are seen up to 3 times a week. Most patients with a diabetes foot ulcer will be seen at least once a week for a dressing change. This may be in a shared care arrangement with district nursing or practice nursing teams. Their wounds will not be seen for a full fortnight without someone seeing them (it may not be a specialist though). The arrangements do vary from region to region. The skill mix of the staff also varies from unit to unit. (b) (c)I would say that it does at least to begin with as it takes time to become familiar with using the centrifuge and creating the patch. Once you become familiar with the process however it does become less time consuming. It is not a technology used on high volumes of patients though so it does not create a lot of excess appointment time requirements.

			teams and clinics? c. Is the use of 3C Patch likely to increase the time needed per appointment from the NHS perspective? Please describe the differences between appointments with a 3C Patch dressing change and a standard or other advanced dressing in terms of staff requirements. d. Our understanding is that the centrifuge element of making the 3C Patches takes around 20 minutes. Is it reasonable to assume that this may increase nurse time per	(d) It depends what the baseline appointment time is. In our unit our appointment times are 30 minutes. So it doesn't add any time to our appointments now that we are familiar with the process we can perform all our duties whilst the patch is preparing. It is typical to note that these clinics 90% of the time are operated by Podiatrists not Nurses and this patch would also be used in an MDT environment not a routine clinic environment. (e) This is not a therapy that is used on large numbers of patients as it is for a very small and specific group of patients with diabetes only. In our service there is probably only one patient per week that is suitable to receive it. It is very important to emphasise this. Scheduling is therefore not an issue in my experience (f) I don't know any specialist foot teams that only offer appointments every 2 weeks. (g)Yes ● J Thorpe: :(a) In the trust where I practice-Patients with a DFU are treated weekly in the outpatient clinic. (b) (c)The application of the 3C Patch does not necessarily have to increase the appointment time of the patient-If well managed and patient flow is managed. In the trust where I work-the patient flow is as follows: • Upon arrival - the patient is booked in to reception • The patient is welcomed by the phlebotomist and transferred immediately to the blood room-where their consent is obtained and the device is filled with the patient's blood. • The patient is then transferred back to the foot clinic where their wound is cleaned/debrided whilst the patch is being manufactured in the centrifuge. •If the wound has not obtained required healing, or is healing well and may not require a treatment-the wound is assessed prior to manufacture(This does increase the amount of time spent in clinic). The department has phlebotomists working within the unit-so the treatment plan flows very well. Also the podiatrists are fully trained and aware of the patient flow protocol for the 3c patch within the trust (d)It is a reasonable assumption (e) We do not anticipate vast numbers of patients receiving the 3C Patch, as the criteria for treatment with the patch is specific and very few patients receive the treatment-so the processing aspect of the patch is not an issue-if managed well with the podiatrists and phlebotomy clinic in the unit.

			appointment by around 10 minutes because they would be able to perform other duties whilst the centrifuge is running? e. Are there any practicalities to consider when scheduling outpatient appointments if only one sample can be processed in the centrifuge at a time or would this likely not be an issue because only specific patients with hard to heal wounds would be using 3C Patch and therefore would be mixed in amongst other patients? f. Are you aware of services	(f)No-I am not aware of any evidence of treatment plans for the use of the 3C Patch every two weeks (g)In my opinion yes-Here at Bradford Hospitals we have a specialist hard to heal diabetic foot clinic supported by doctors, nurse specialists and phlebotomy, as the patients with hard to heal DFU-Require a full MDT approach in their care. ● F Game:(a) According to need but fortnightly or less frequently. It would be rare for patients to attend weekly for the whole of their ulcer treatment (b)It would be difficult at first as the clinics are already over capacity, but if it healed patients quicker then that would of course release capacity in the longer term (c)Yes it would. The time taken for phlebotomy, and making a patch followed by the wound dressing would add additional time. Debridement could be done while the patch was being made, but this would usually take less time than venepuncture and making the patch. 18 mls of blood being drawn into the device (or more if 2 patches were being made) was not always a quick process in the trial. (d)It depends whether the “nurse” would otherwise be there. The podiatrist would be doing the debridement and wound dressing. The “nurse” would usually take the blood. So depending on whether both were efficiently working together it could add 10-15 minutes, although my suspicion is that it may be more if the patient was difficult to bleed for example. (e)Scheduling would need to be thought about or it would lengthen some appointments if the centrifuge was in use. But this is not insurmountable (f)I’m not aware of any (g)Yes and yes ● P Chadwick (a)This depends on the patient and service provision. Some mdts do weekly some monthly lots of variables in play. The patient would normally see a healthcare professional (not MDT) at least weekly (b)I think this would be practical there are many reasons why treatment need to be more often than every 2 weeks (c) Yes (d)Yes not necessarily a nurse though probably more likely a podiatrist (e)Not really just need to be flexible and innovative in bookings (f) No not aware (g)Yes

			which have used 3C Patch but only offered an appointment once every 2 weeks? If so, are you aware of the impact of this on efficacy and safety outcomes? g. Are patients with hard to heal ulcers typically managed in specialist diabetic foot clinics as per the Game RCT? Would 3C Patch patients need to be managed in specialist diabetic foot clinics?	• R Berrington (a)Dependant on the wound within our MDFT we see patients weekly to 8 weekly with community podiatry picking up care between visits. (b)Yes, we arranged for the 3C patients to attend earlier to allow time for the patch to be made and ultised spare room so that they could sit and wait, as it is a select group the numbers requiring this treatment at any one time will never be high as we were able to accommodate. (c)Yes appointment times need to be longer and staff need to be able to bleed patients (d) Yes that is very true for most however if they are anticoagulation the appointment will take longer and needs to be factored in. (e)Unlikely to be an issue as not large numbers and can therefore be spaced out accordingly. (f)No (g) No but the podiatrist or D/N would need adequate training if it was to be carried out in a community setting and the equipment • D Russell(a) It would be ideal to see patients at least fortnightly in an MDT clinic, especially those that are failing to meet a healing trajectory. The frequency of debridement needs to be at least fortnightly to maximise healing. Unfortunately, with the prevalence of DFUs our service is currently only able to see most people 3-4 weekly to cope with capacity. (b) In our service, moving to a weekly clinic visit would severely stretch the service. Additional time needed at each visit to collect blood, process the sample and dress the wound would mean that this would further impact on the ability to use the dressing. I do accept that if patients heal more quickly then the active patients in clinic will reduce, and there may therefore be some improvement in capacity with time, depending on the overall increase in healing rates. (c) The standard care for a patient will be similar for those with and without 3C Patch dressings. In addition, a patient with a 3C dressing will need blood taking, blood processing to make the patch, before the dressing can be placed on the wound. Blood taking takes at least 10minutes to set up and perform, and whilst it may be possible to do some standard care whilst the blood is being processed, this will also add some time. There will be additional time if the centrifuge is not kept in the treatment room. Our experience in the Leucopatch trial was that the process may take 40mins or more. Much of this will be in addition to the standard care or need a second health care professional to be involved which would add to the cost. The only NICE approved advanced dressing

				(UrgoStart) takes the same time as a standard dressing. Other advanced treatments with less evidence such as negative pressure wound therapy and dermal substitutes take a similar time to the 3C Patch, although this time can be reduced with the use of disposable NPWT systems. (d)It may be possible to do quick tasks or some documentation, but it would not be possible to start a task that may be expected to take longer than 10mins. (e)I would expect that patients using the patch would be mixed in with other patients, but this would potentially limit the number of patients that could be treated with the patch at any time, particularly as this needs to be used weekly for ≥6 weeks. (f)No. (g)Yes, those ulcers that are hard to heal do tend to be managed in MDT clincs. They have a higher incidence of complications e.g. infection, and often receive higher levels of offloading, revascularisation etc. I would see the 3C Patch being used in specialist clinics.
47.	07/05/2021	**Experts** Q&A via email	Please can you describe how patients with hard to heal ulcers are managed currently? For example: How often are standard dressings replaced? What dressings would likely be used? Would dressing changes be undertaken in an outpatient setting or would they be managed in the community with a visit	• A Musgrove:This varies on the amount of exudate but typically every one to three days. This varies on centres and there is huge variation in dressing choices despite the lack of evidence as to their effectiveness. This is impossible to answer generallybut in our centre we focus on the most simple wound coverings changed regularly.I have known out-patient clinics to carry out all dressing changes but this is very rare. Most are carried out by patient, carer, nurses . Please see above as the dressing change is usually only carried out if the patient actually has an appointment for review in out-patient clinic • E Ricci: Principle management of hard to heal wounds Manage infection Optimise diabetes control Ensure adherence and concordance with offloading strategies Investigation and management of underlying peripheral arterial disease Optimisation of wound bed preparation. Cardiovascular risk modification In our unit dressings are secondary to the principle focus of care which are the items above. As in hard to heal wounds these have the greatest influence over healing rate not the dressing. Dressings regime is based upon the complexity of the wound this can vary from 1-3 changes per week.

			or GP/ GP nurse appointment? What proportion of patients might be managed in each of these settings?	Choice of dressing depends upon the complexity and characteristics of the wound. There is not a 'standard' dressing as such. 60% of the patients are managed in the diabetes foot clinic based in secondary care, 40% with active wounds are managed on our community intermediate care clinics. For approximately 10 percent of the caseload there will be a shared care element for dressings where the district nursing team are involved in at least one of the weekly dressing changes. ● J Thorpe: At my trust-patients standard dressing are replaced twice weekly or on a weekly basis depending on wound aetiology and/or exudate levels. •Again it is dependent on wound aetiology, wound position on the foot and exudate levels – each wound is individual and this is a very difficult question to answer. Hard to heal DFU in Bradford are treated centrally in a specialist outpatient clinic at the hospital •All patients within the Bradford area are referred and treated centrally-there are no hard to heal DFU clinics in the community – so 100% community 0%. If a patient is identified at a community clinic-they are referred to the hospital clinic and seen within 7 days. All patients with previous hard to heel ulcers (that have healed), are not treated in community-they remain under the care of the hard to heel ulcer clinic at the hospital if a wound develops. ● F Game:2-3 times a week •Urgostart for hard to heal ulcers otherwise an inert low cost non-adherent dressing. •About 50% would be done by the patient carer or family member, otherwise patients would attend wound care clinics, district nurses or practice nurses. Dressings only changed in out-patients as part of the specialist foot clinic appointments. •Depends on local policy, but about 50% do their own dressings locally. Otherwise the majority are seen in wound care clinics as our local GP practices will only take on wound care for the first 4 weeks. About 10% of our patients are sufficiently immobile to have district nurse visits. ● P Chadwick 2-3 times per week •Depends on level of exudate normally a low adherent dressing or foam •Usually foot protection team /community podiatry or district nursing •Many variables most would be shared with mdt with a treatment plan ● R Berrington - Daily to 2x weekly, - Urgostart, actilite, kerrmax depends on the wound!,

				- Both - 5% ● D Russell - This depends on the condition of the wound (in particular the exudate levels) and the choice of dressing. Typically, the wounds will be dressed every 2-3 days (2-3 times per week), but this may be daily in a highly exudative wound. - Standard dressings include N/A dressings, inadine, honey or aquacel, usually with a foam secondary dressing. UrgoStart is an advanced primary dressing. - In most MDTs dressing changes are undertaken by practice/district nurses, or in some cases the patient, between MDT clinic visits. Some MDTs see patients for every dressing change. - In our practice all patients with active disease are seen in the MDT clinic, but with dressing changes between clinic visits.
48.	07/05/2021	**Experts** Q&A via email	What proportion of patients in clinical practice might have a large ulcer that would require more than one dressing (more than 5-10cm in size)?	● A Musgrove:I would say the majority of wounds that are hard to heal would be less than this in size. Larger wounds tend to be on amputation sites and these heal more rapidly with best practice. So if pushed I would say 5 – 10 %. ● E Ricci: Do you mean with 3CP? This is hard to gauge as we have a few with quite large wounds but then how many of them have truly hard to heal wounds is difficult to assess as a proportion of caseload. ● J Thorpe: Around 10-15% ● F Game:Very few. Most of our ulcers are <1cm2 ● P Chadwick less than 5 % ● R Berrington Very few ● D Russell It is unusual to get DFUs of this size. Surgical wounds may be this size, but these have often reduced to below this size before becoming static.
49.	07/05/2021	**Experts** Q&A via email	The cost of routine DFU care in outpatient, community and primary care settings (to cover clinical attendances, podiatry, imaging, hospital outreach, NHS transport and orthotics)	● A Musgrove:Both groups would contain hard to heal ulcers but the > 2 scores would most likely be harder to heal. ● E Ricci: It is more likely to be a wound with a SINBAD of >2 that would be hard to heal. However we can see the odd <=2 when it is and old wound i.e has had suboptimal care in a non specialist setting for a prolonged period of time. ● J Thorpe: The 3C Patch is a more expensive/invasive treatment than say a protease modulating dressings. The patient population who would be receiving this treatment is proportionately small, and would only be suggested as a next treatment by a specialist

			as well as the cost of routine care in inpatient settings for those with unhealed ulcers was taken from: Kerr M, Barron E, Chadwick P et al. (2019). The cost of diabetic foot ulcers and amputation to the National Health Service in England. Diabetic medicine 36 (8): 995-1002. Two groups were included, those who have a SINBAD score of <=2 and those that have a SINBAD score >2. Would either of these groups likely reflect costs of those patients considered in this submission i.e. those with hard-to-heal ulcers that have not adequately responded to standard care over a 4-week run in period?	practitioner trained and familiar with the 3 C Patch. It is difficult to align the 3C Patch against these studies. ● F Game: I'm not sure that the SINBAD scores are relevant here. SINBAD scores are an audit tool, they are not a clinical management tools. The point about a SINBAD score is that if you leave an ulcer long enough without good care it will become larger (score 1), become deeper (score another1) and get infected (score another 1). The point of the Kerr paper was to say- if you get patients to specialist services quicker then they get the best treatments (off loading, dressings etc) and then they will take fewer days to heal and cost less. If you leave them they will cost more. Because whatever the healing trajectory a larger ulcer will take longer to heal. ● P Chadwick By definition SINBAD score >2 are more severe and are more difficult to heal ● R Berrington Yes ● D Russell The vast majority of these patients will be SINBAD >2, but the cost of this particularly hard group of patients to manage is likely to be more expensive than a generic group with SINBAD >2 due to the duration of the wound and the increased risk of complications.

50.	07/05/2021	**Experts** Q&A via email	What additional health care resource use might be required when an ulcer becomes infected (other than antibiotics)? (i.e. additional outpatient appointments, x-ray or scans, visits, dressings, inpatient stays etc). If possible, please give an idea of the proportion of patients that may require each of these additional resources.	• A Musgrove: Infected ulcers would necessitate additional out patient appointments to monitor antibiotic and pt response to the drugs. Dressing changes are often more frequent to monitor and control exudate increase. X-rays are frequently carried out. For severe infection admission and associate costs. I think that the research literature would better answer this question than individual clinicians. • E Ricci: Additional appointments Longer duration of appointments In the absence of an onsite prescriber significant delays in accessing a prescriber Xray if suspected osteomyelitis / MRI Surgical consult if Vascular team if suspected peripheral arterial disease involvement / Ortho Pathology labs – microbiology samples, blood tests Admission if spreading Bed Manager Admitting team – clerking Ward Team Inpatient Foot Team As a unit on average we admit 3 patients per week from the clinic. • J Thorpe: All wounds with the suspicion of infection will have a wound swab/tissue biopsy depending on wound aetiology. An x-ray wound can not be performed as a standard treatment for infection-but if the physician suspected possible osteomyelitis or the wound probed to bone an x-ray would be performed. The patient would also attend a wound clinic twice a week for wound assessment and if required would be admitted to hospital for IV antibiotic therapy and vascular assessment if the wound deteriorated/patient deteriorated. It is very difficult to generalise additional resources as each patient is individual. Wound Swab/tissue sample -100% of patients would receive this resource Additional outpatient clinic visit - 100% of patients would receive this resource Additional Dressings – Due to the additional outpatient appointment and wound assessment – 100% of patients would receive this resource X-Ray - @ 30-50% of patients would receive this resource-dependant on physician decision

				In-Patient Treatment - @20-30% of patients would receive this resource-dependant on physician decision/MDT discussion and the patient would require vascular input/intervention i.e. amputation/USS etc… • F Game:10% of ulcer become infected week on week until they heal, and will need antibiotics. 40% of infected ulcers are suspected of having osteomyelitis and get Xrayed. They will get at least 6 weeks of antibiotics and possibly a confirmatory MR scan. • P Chadwick All of the above The NDFA data will give you more accurate figures • R Berrington Surgical debridement, home intravenous antibiotics, amputation, 10-15% • D Russell Approximately 50% of DFUs will develop infection. 3/5 will have soft tissue infection at some stage, requiring antibiotics, of which a proportion (I have been unable to find an exact number) will need admission to hospital and a very small number will need surgery (debridement or amputation). 2/5 will have osteomyelitis. These tend to have more severe infection with a higher incidence of admission to hospital, use of MRI and amputation (up to 30% minor/major amputation).
51.	07/05/2021	**Experts** Q&A via email	In the Game RCT approximately 40% of patients received at least 1 week of treatment with protease modulating dressings and approximately 60% received them as part of standard care in the trial. Does this align with what you would expect to see in practice in those with hard-to-heal DFUs?	• A Musgrove:This varies from centre to centre – we do not use such dressings and I was quite surprised – given lack of evidence – to hear this. Maybe this study is further evidence that they are not effective? • E Ricci: Yes • J Thorpe: Yes it does align with current best practice at Bradford • F Game:I'm surprised at this figure. The CRFs indicate we collected dressing data, as a text field. So if the health economist had the text data they would have needed to be categorised as this was not done by the clinical team at the time. But I cannot find these data anywhere in the database. So I don't know where the data have come from. I would be very, very surprised if 40% of the patients received a protease modulating dressing as these were not widely used at the time. Can you check whether these are trial data or data taken from some other source and assumed to be the case in this study. From my personal clinical point of view this is still a very high figure. • P Chadwick Not traditionally but the "explorer study" and the use of NOSF technology is changing practice • R Berrington Yes • D Russell Yes, protease modulating dressings (UrgoStart) are the only NICE approved advanced dressing for hard-to-heal DFUs and as such are first line for non-healing ulcers in many services.

52.	07/05/2021	Expert F Game contacted via email re questions on 3C Patch specifically relating to Game RCT	The trial protocol for the Game RCT mentions a health economic analysis/cost utility analysis is to be conducted. Please can you confirm whether this has taken place and provide details if so?	[redacted]
53.	07/05/2021	Expert F Game contacted via email re questions on 3C Patch specifically relating to Game RCT	Are you able to share any of the resource use data collected during the Game RCT? For example, the following would be very helpful: - number of 3C patches used per ulcerated week – - district nursing hours for 3C Patch arm and standard care arm for those with unhealed ulcers (per week) - nursing hours and podiatrist hours for 3C Patch arm and standard care arm for those	[redacted]

			with unhealed ulcers (per week) - dressings used in standard care arm, number per patient per week, and proportion of patients on each one	
54.	12/04/2021	F Game was contacted via email regarding data used in the RCT	As part of their submission, the company included the attached file on the dressings used in the RCT. This is where the numbers in our question 8 came from. Based on your response to that question, we'd welcome input on whether you think that the data in the attached file are accurate, or not? If you could send across the data that would be greatly appreciated.	

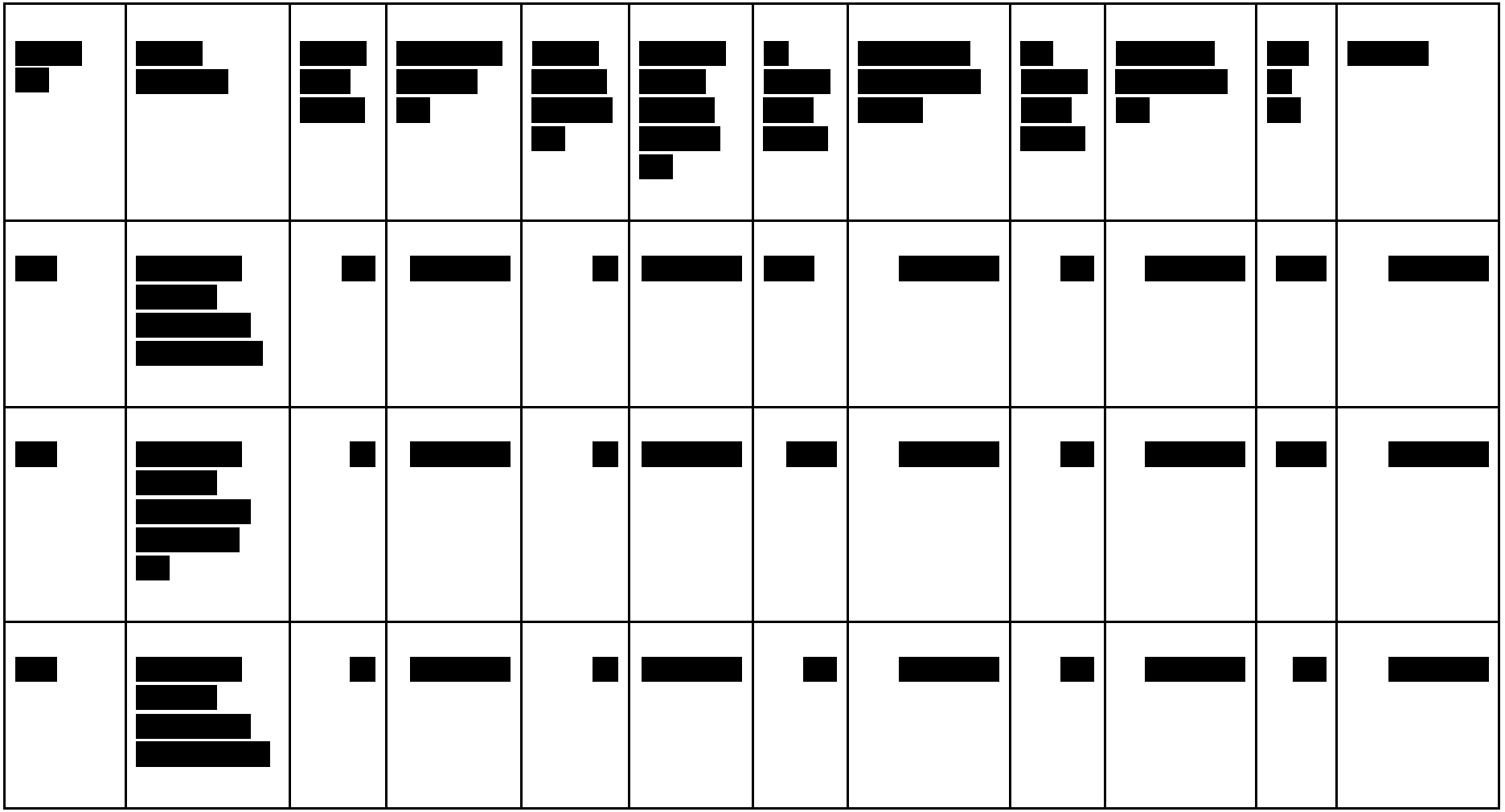
55.	13/05/2021	Experts were contacted via email to gain clarity on their understanding of the “active infection”	We would be grateful if you could please share your understanding of the term "active infection". Taken from the company's instruction for use for the device which states the PRP gel from 3C Patch is contraindicated in those with an active infection.	• A Musgrove: I would say that “active infection” was any ulceration requiring systemic antibiotics but I’m unsure as to their reasoning for this as in the trial if someone developed this whilst undergoing treatment with the patch there was no reason to stop its use. • J Thorpe: Redness/inflammation or purulence around the ulcer – a tissue sample or swab would be taken to confirm if polymicrobial infection present • E Ricci: Active infection would be typical clinical signs of wound infection. • These include. - increased purulent drainage - increased heat - increased swelling - Increasing redness - loss of function • In addition to this we also note within the wound. - new onset of discolouration to the wound bed - increasing wound size - friable breakdown - tunnelling - increased exudate - increasing odour There isn't usually one factor at play but multiple factors combining presenting together. Some are more present that others at any one particular time.
56.	13/05/2021	The company were contacted via email to check minutes taken from the meeting	Please find attached the minutes taken from our meeting on 06.05.2021. Please may you confirm you are happy with the information contained in the minutes.	• Thanks for the notes and for merging with the comments we also sent back so it is all in 1 place! The only comment I would have was for 2 and the IFU. I understand the comment was due to the fact that you had an old IFU and I think it has been resolved now as the company have sent an updated IFU? Maybe add a note to that effect?

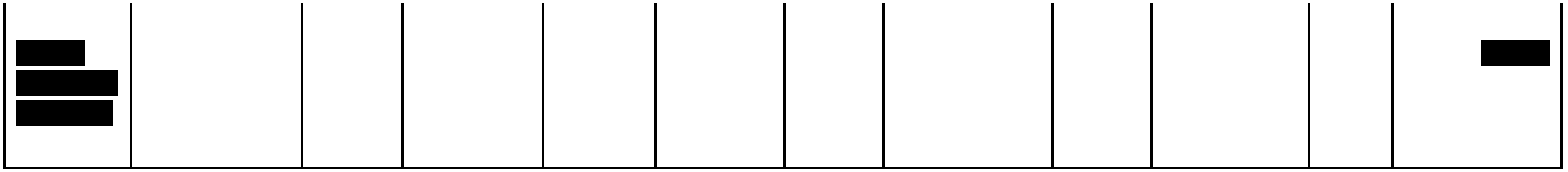
57.	17/05/2021	The company were contacted via email to gain clarity on the IFU	I can't seem to locate an email with an updated IFU attached. The version we have has the date 26.09.18 in the file name. I'm assuming this isn't the updated version you were talking about? Please could you forward me the updated IFU.	• The issue mentioned below – based on the IFU – has been brought to our attention by Juliet last week. She has shared some questions with us (attached) and we are working on the response. In a nutshell: There has been a confusion between the US and the EU/UK IFU unfortunately. Using 3C Patch on infected wounds is not contraindicated in the EU/UK and in the US it only is because FDA clearance was based on an existing product which had this contraindication in the clearance. • Juliet will receive an email with details etc. shortly (before EOB tomorrow) and we hope this will solve the issue. • Again, sorry for the confusion!
58.	17/05/2021	The company were contacted via email to gain clarity on the IFU	Please could the company send across the latest EU/UK IFU?	• I hope this finds you well. Again, sorry for the confusion. I believe there is/was a US and a UK version available for download on our website and it must have been the US one that caused the confusion.Attached is the UK/EU version. • The key differences are: see appendix 1

Appendix 1. During correspondence with the company and experts, additional information is sometimes included as file attachments, graphics and tables. Any questions that included additional information of this kind is added below in relation to the relevant question/answer:

File attachments/additional information from number 38 question 4A:

Table 4a NHS Reference Costs 2017-18, HRGs KB03C-E





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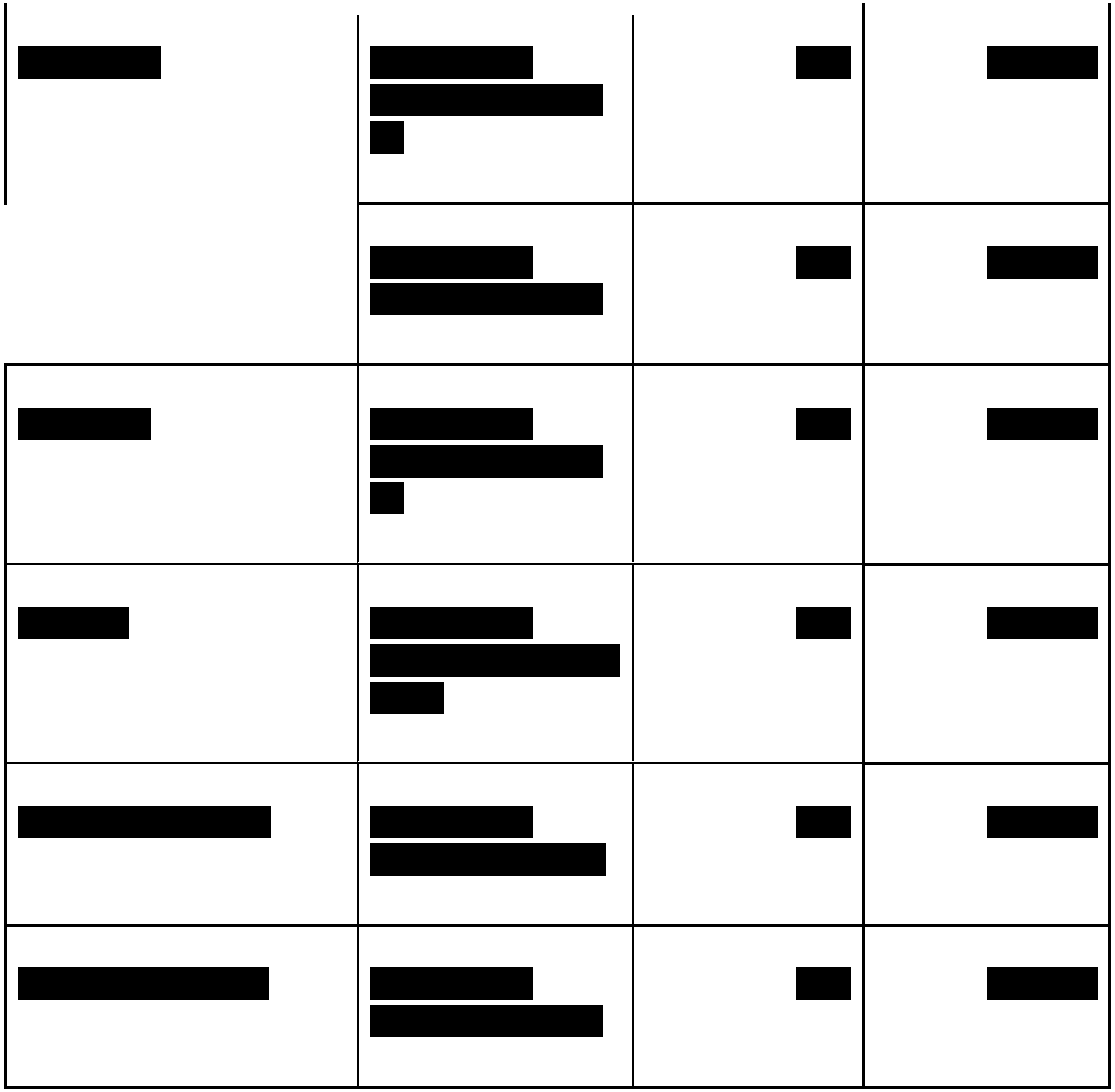

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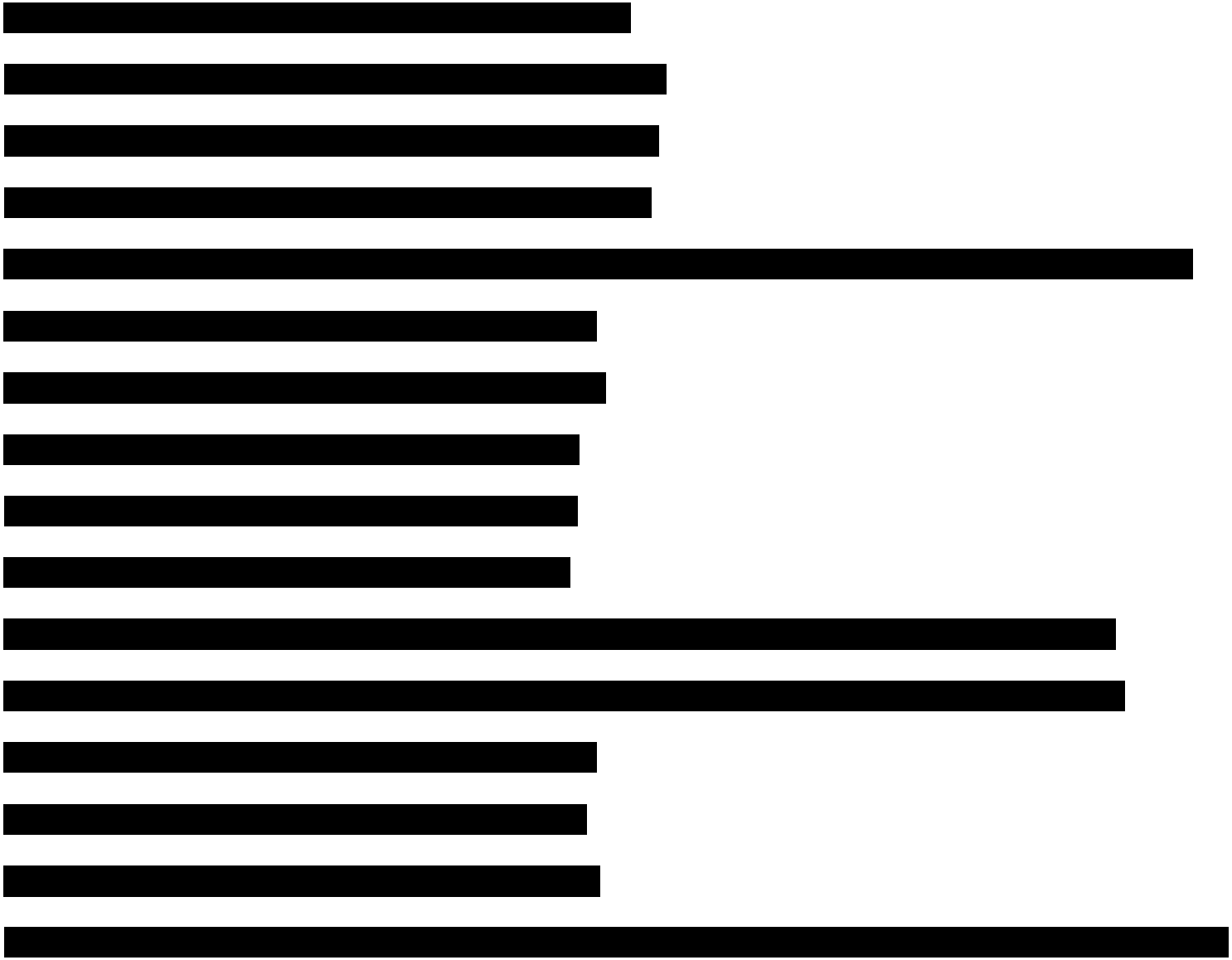

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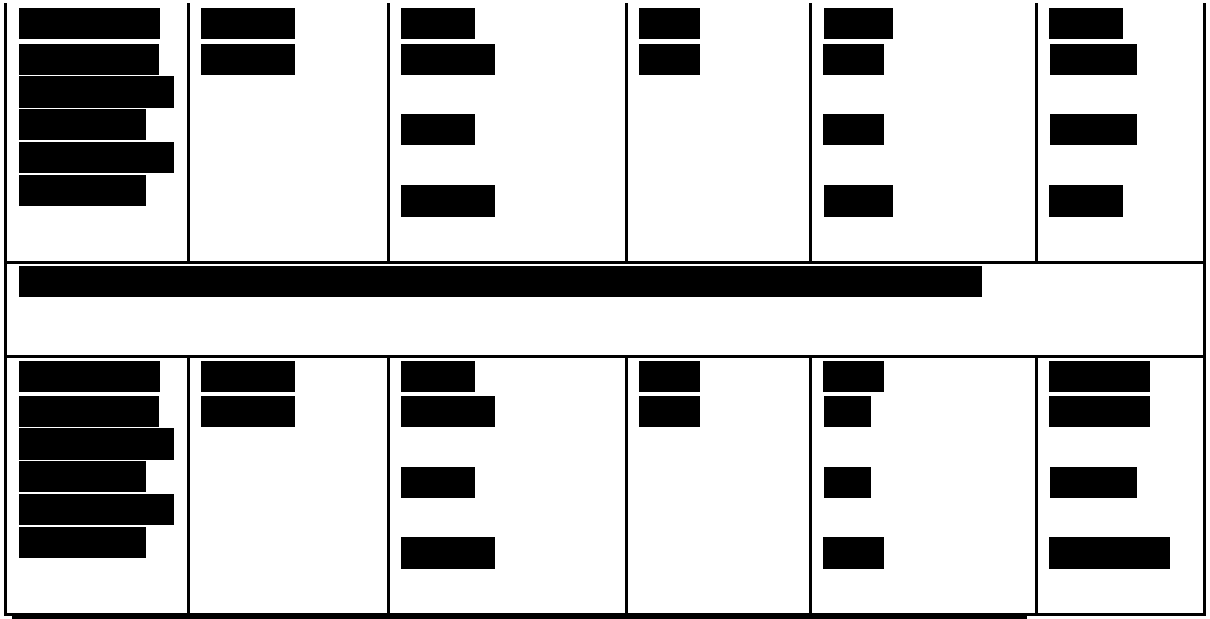

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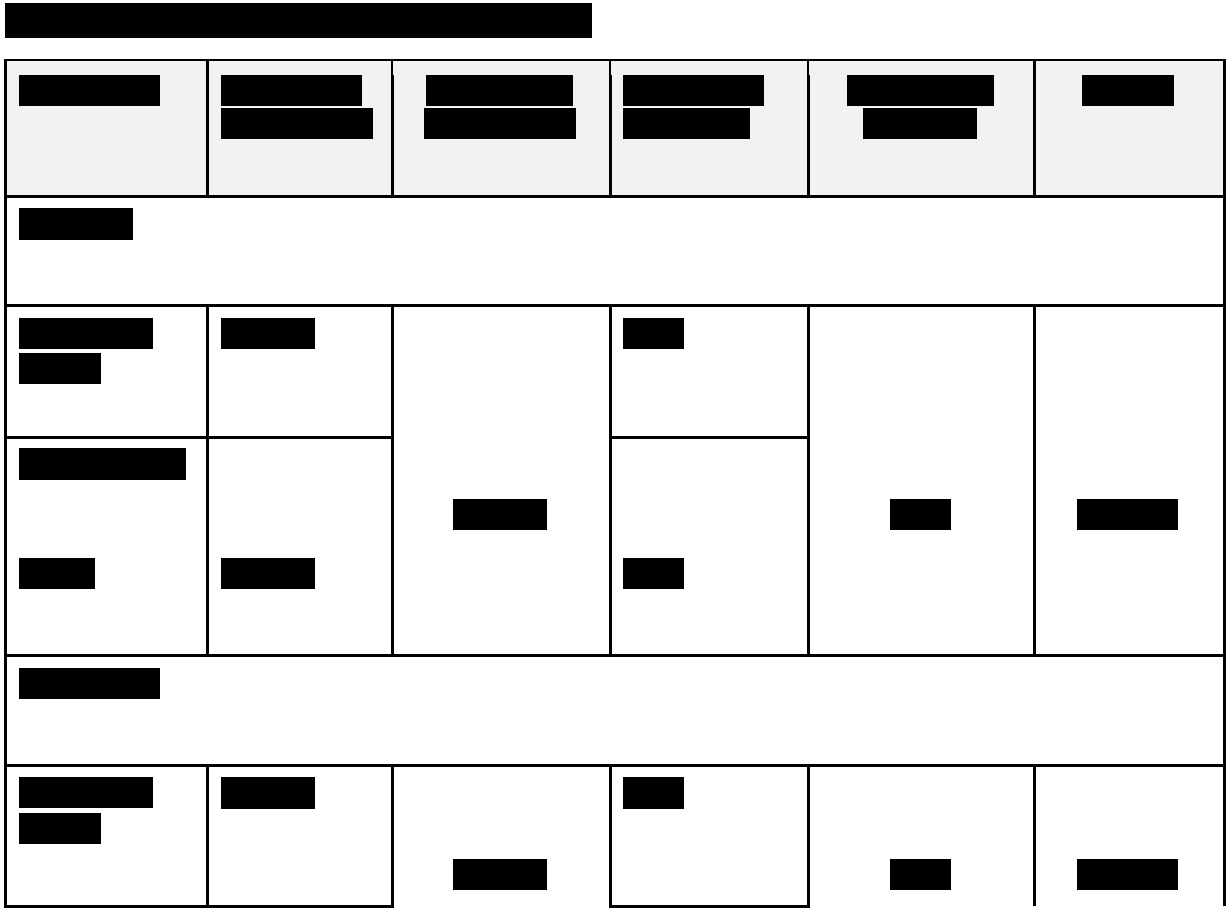

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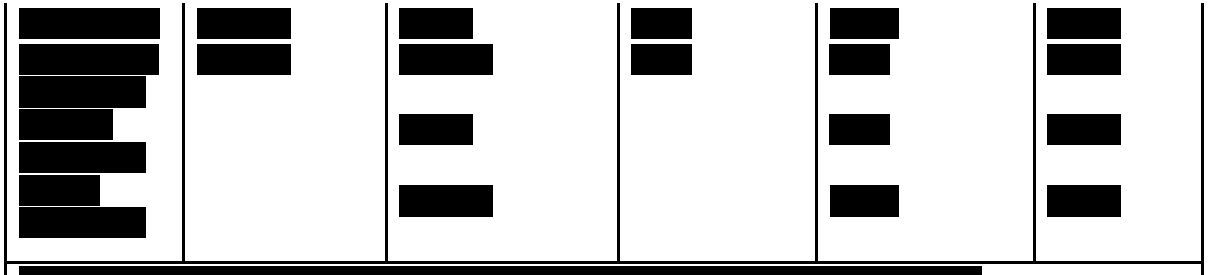

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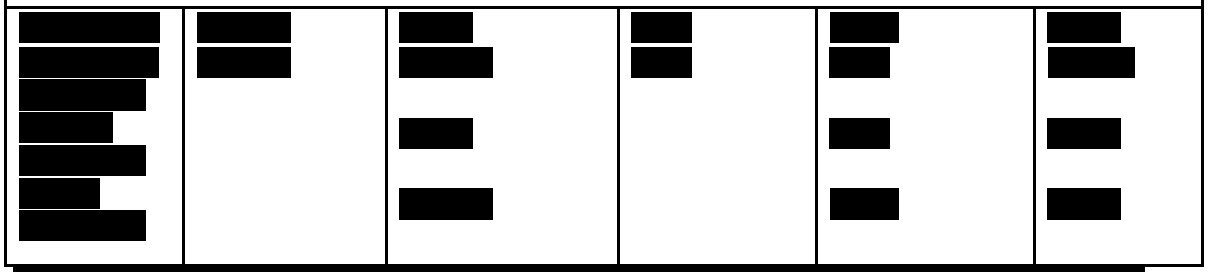

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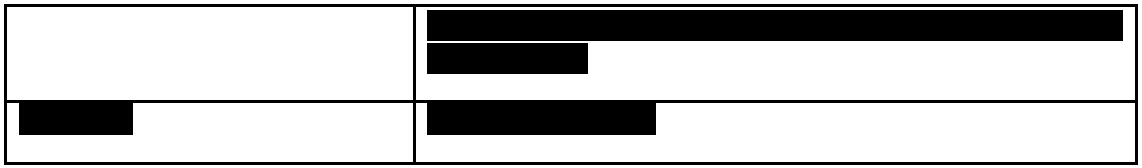

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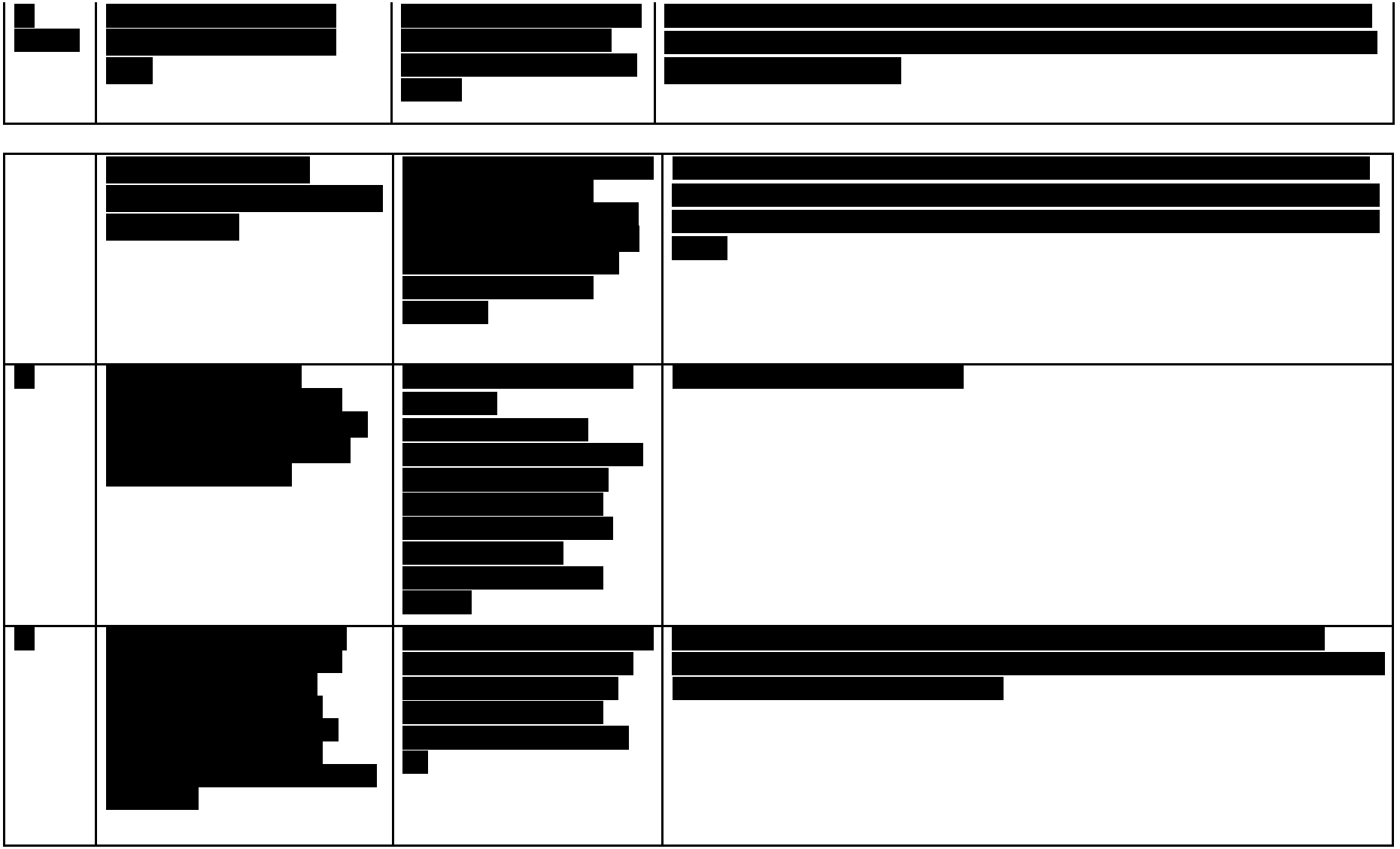

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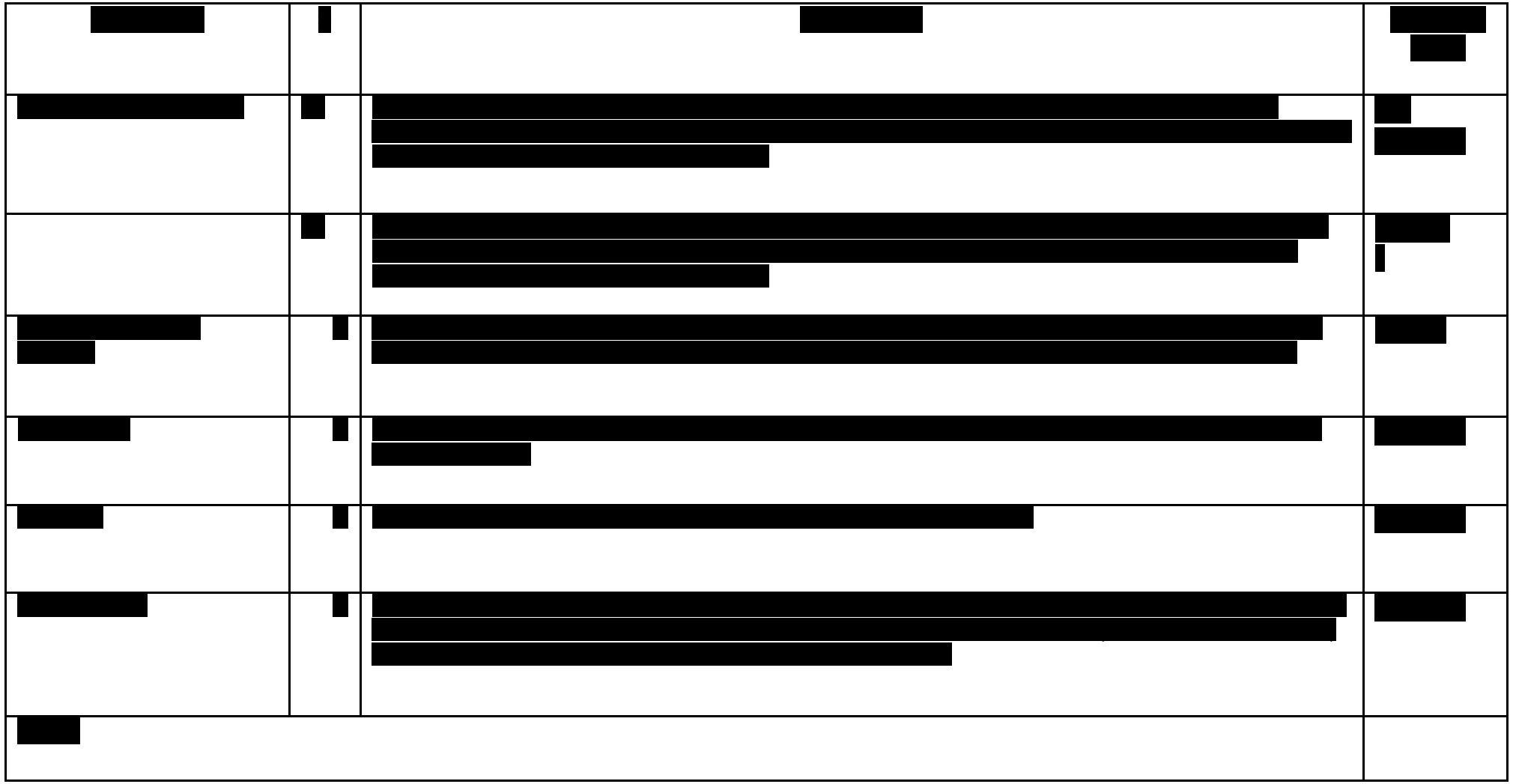

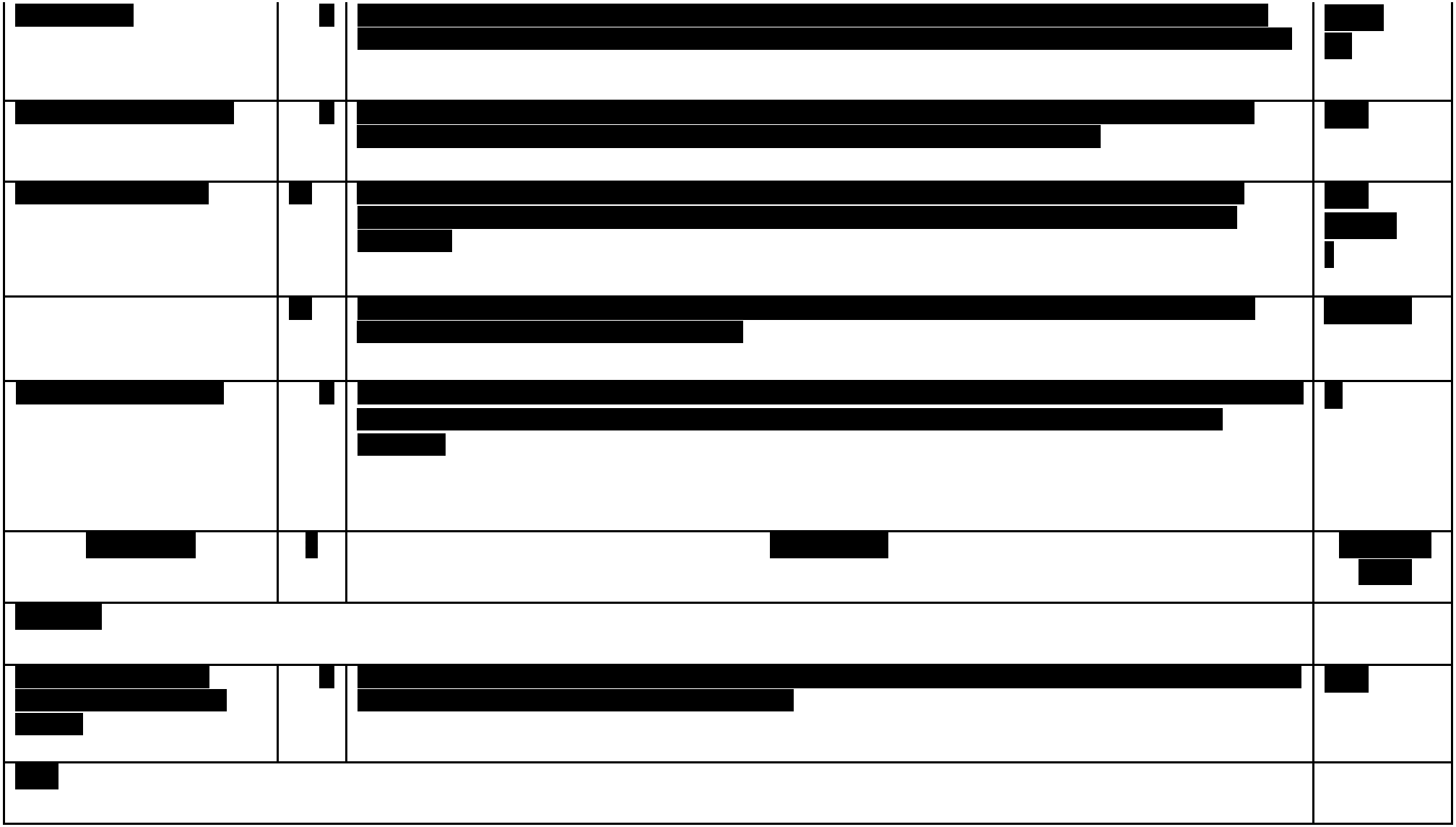

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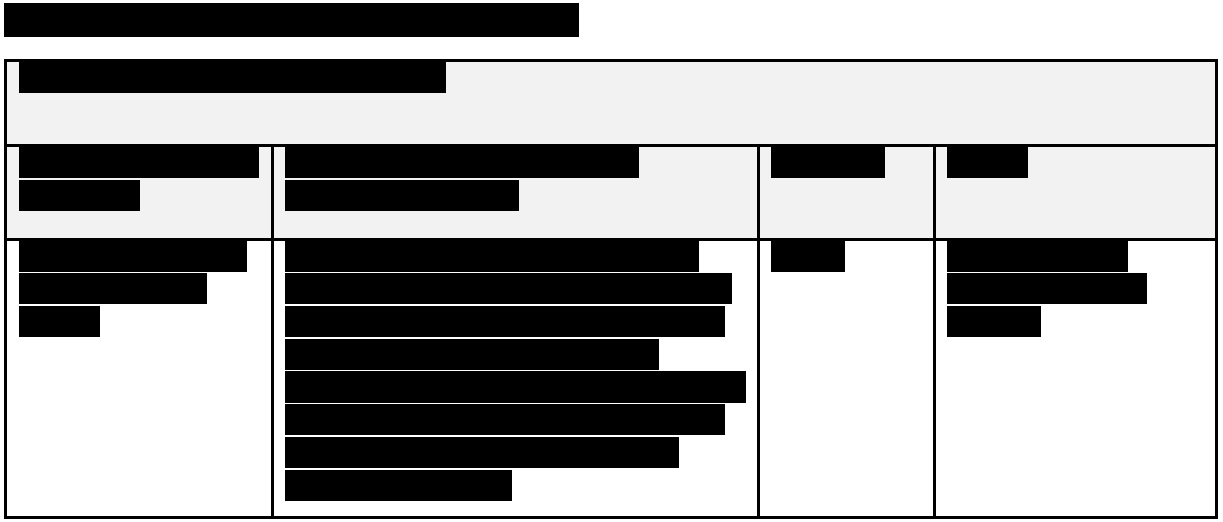

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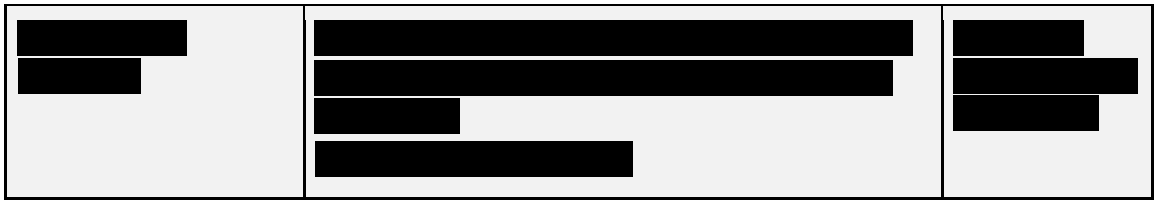

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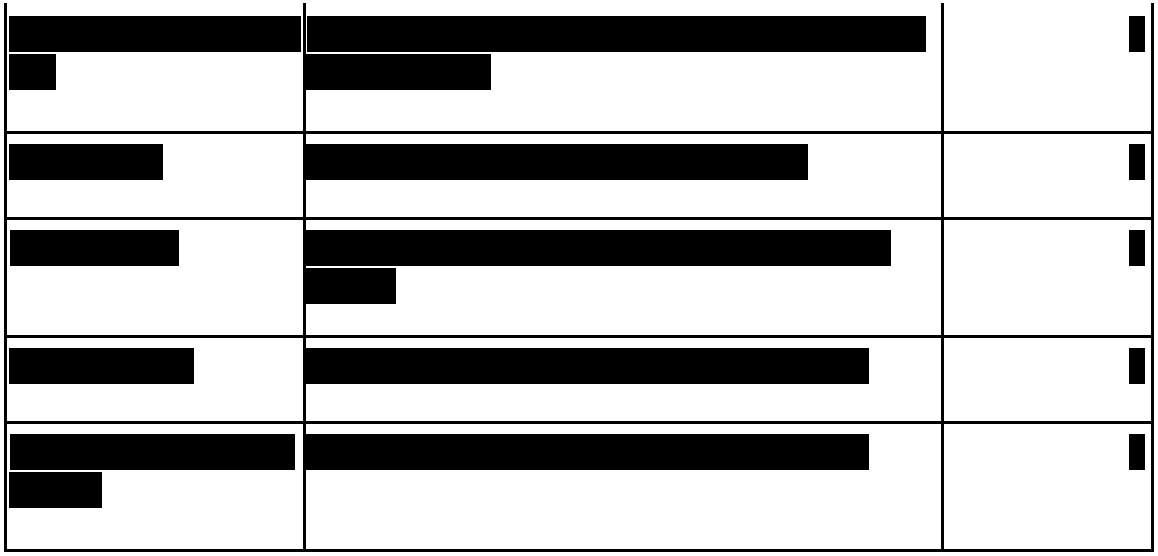

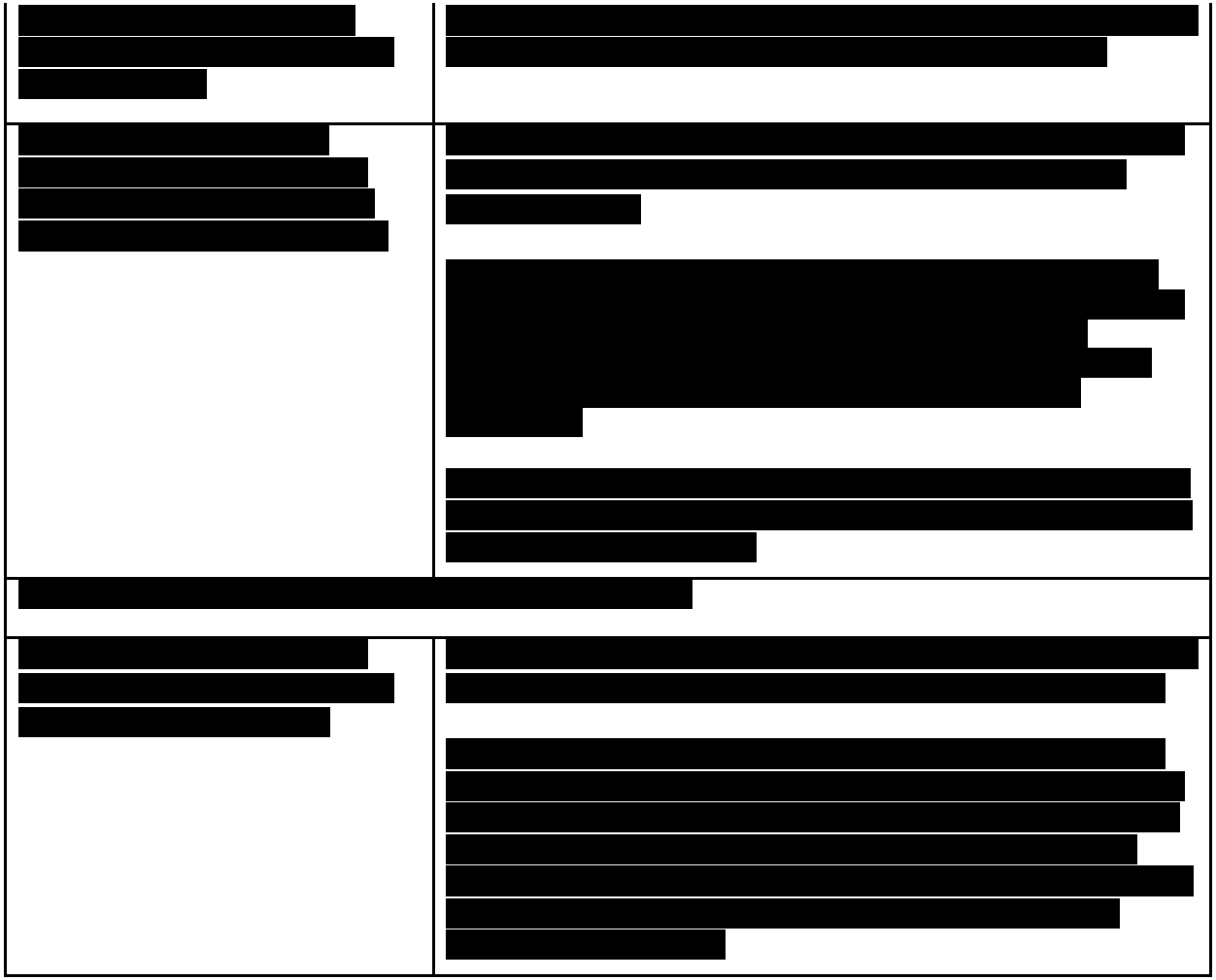

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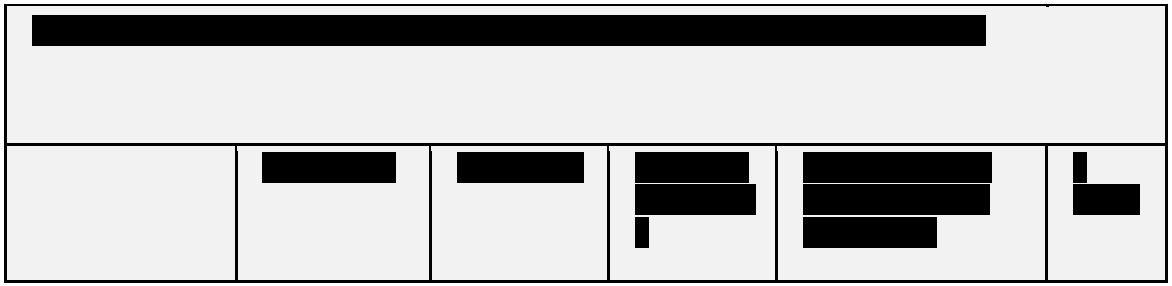

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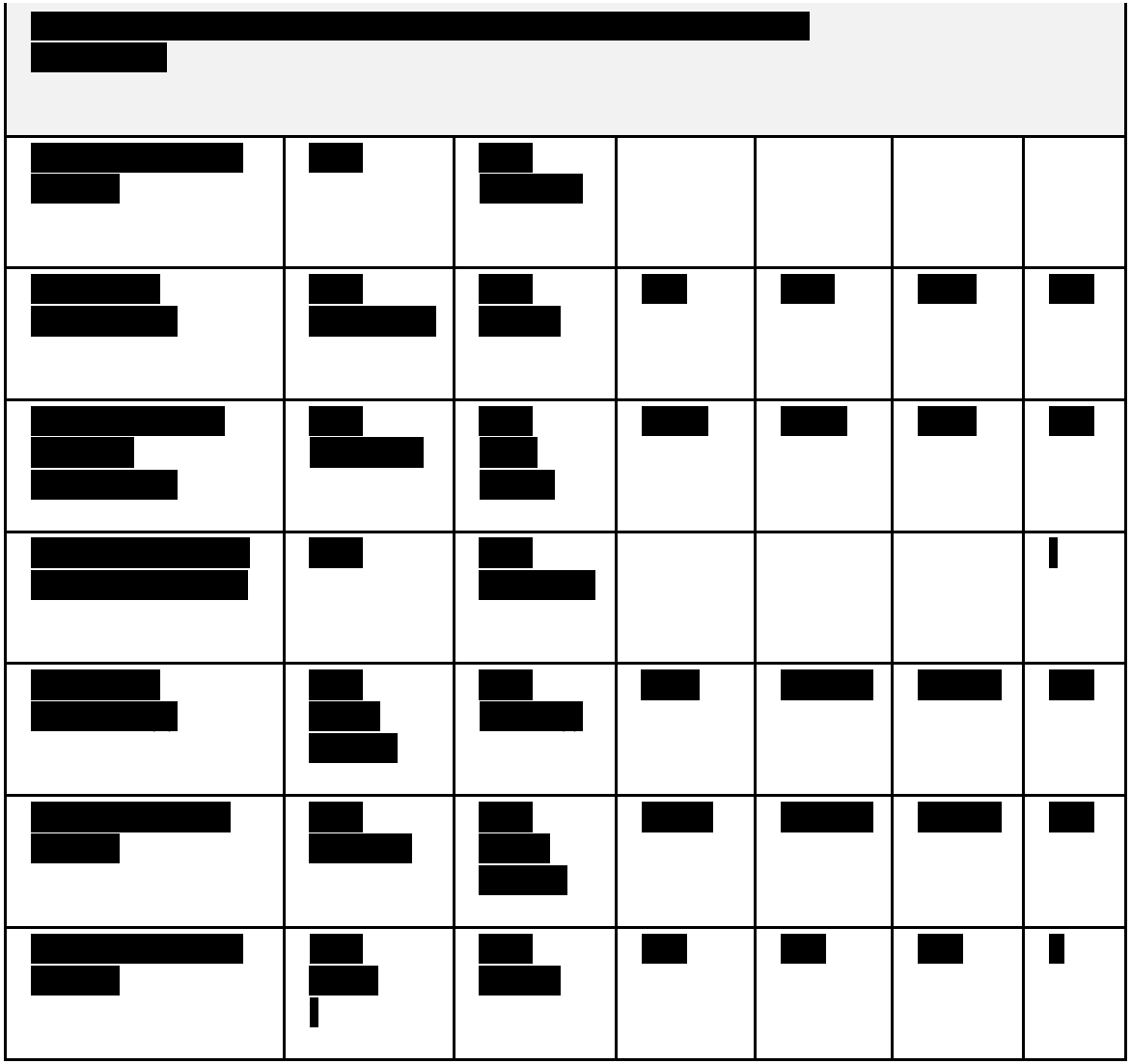

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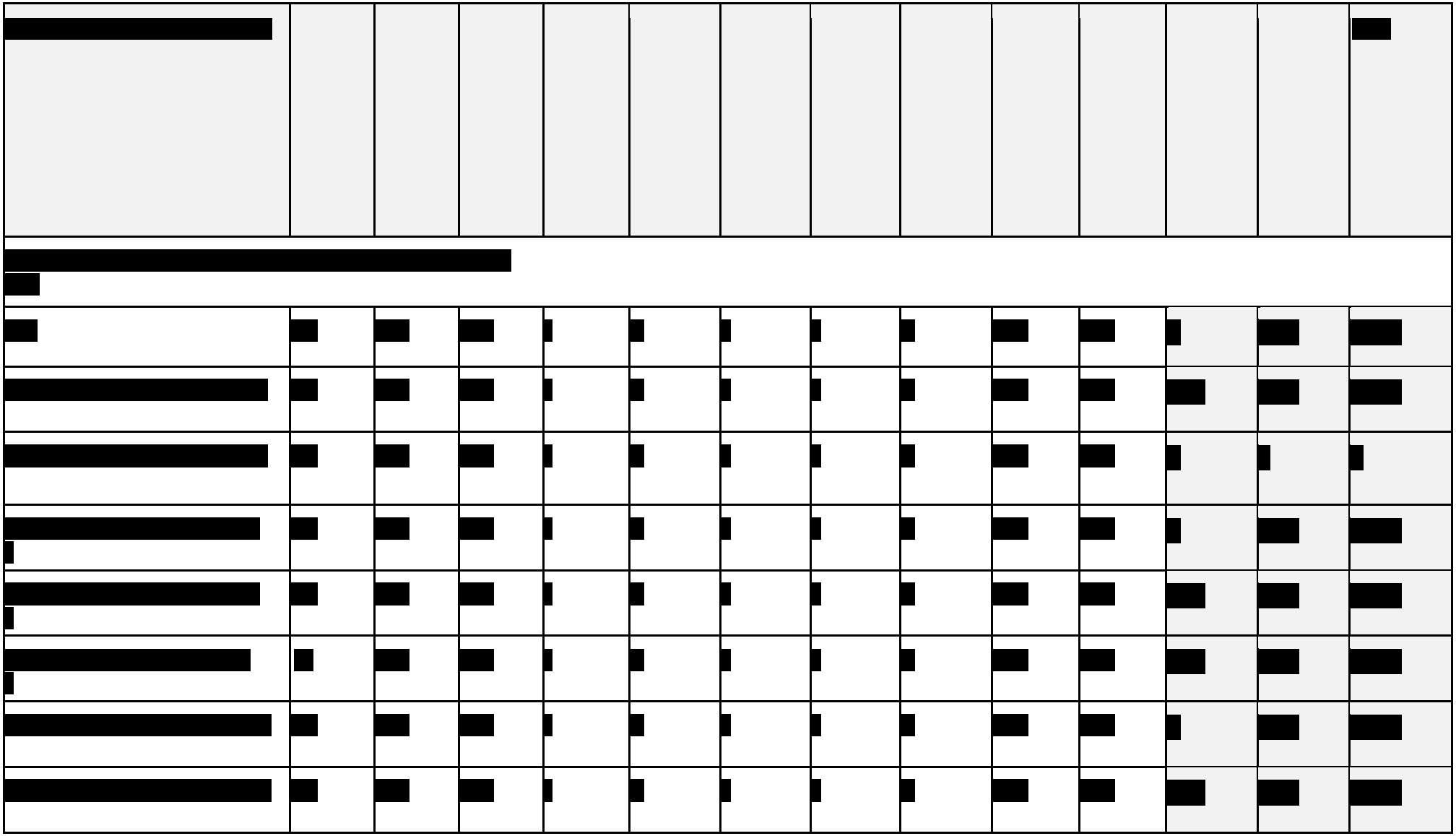

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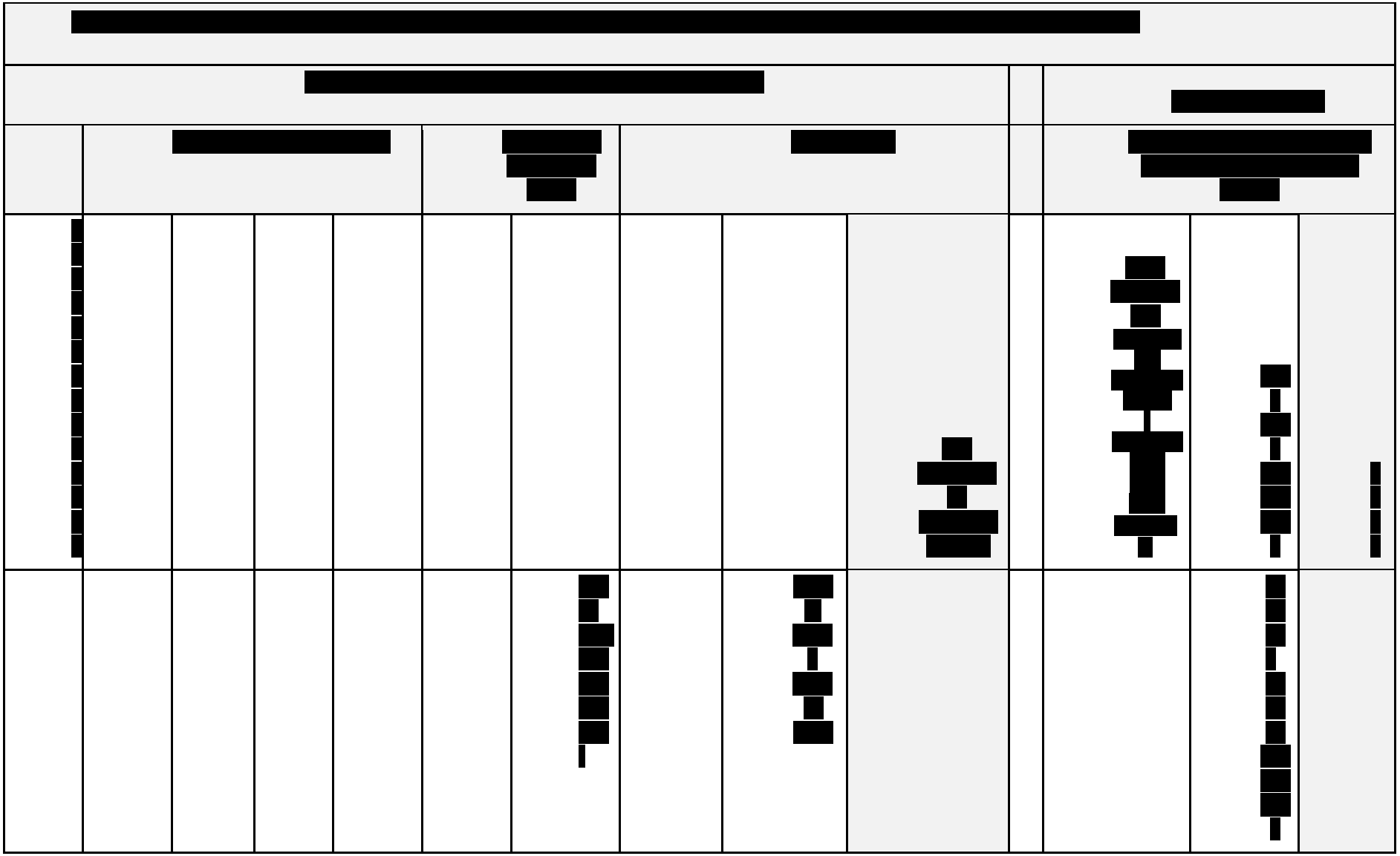

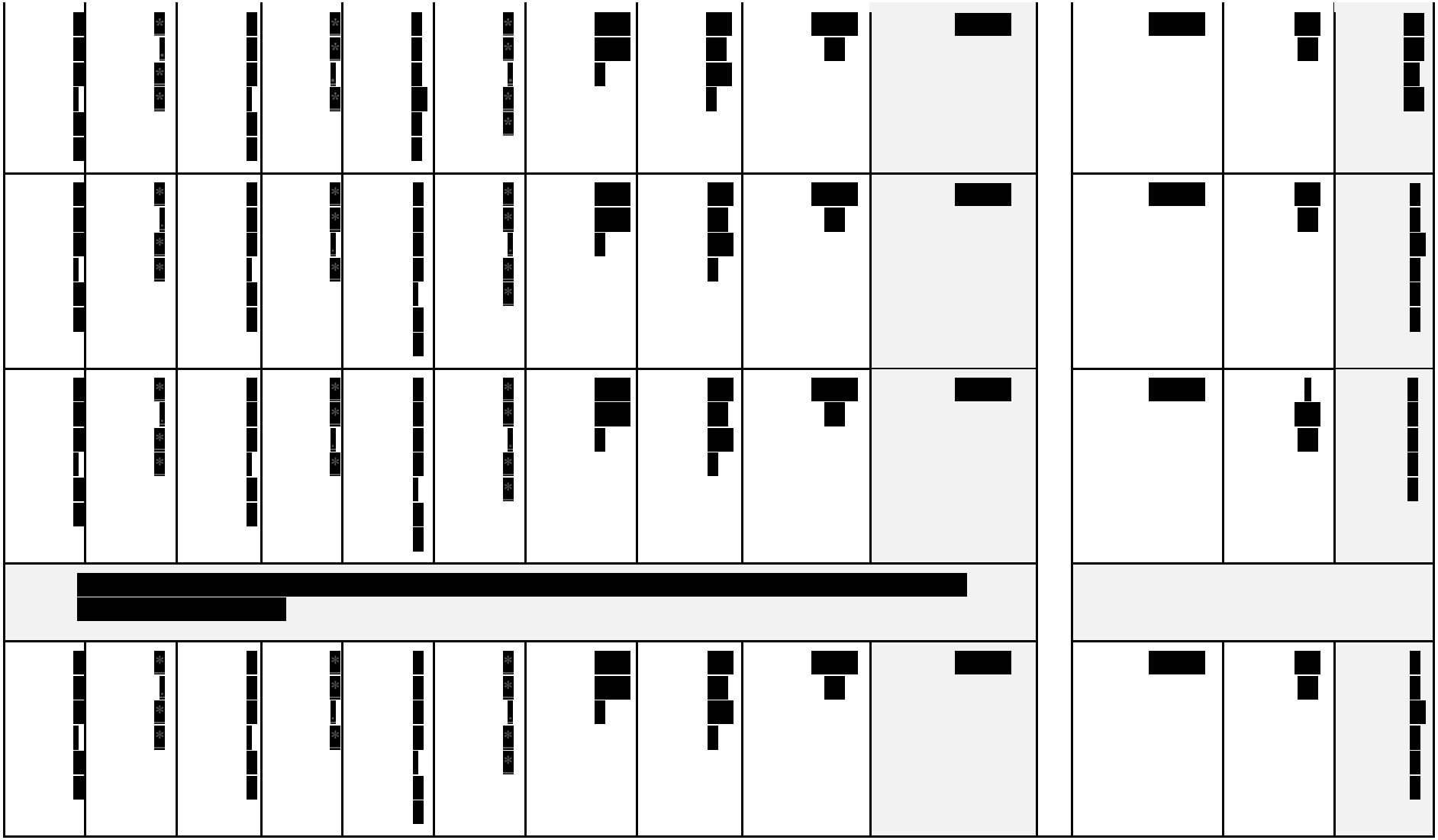

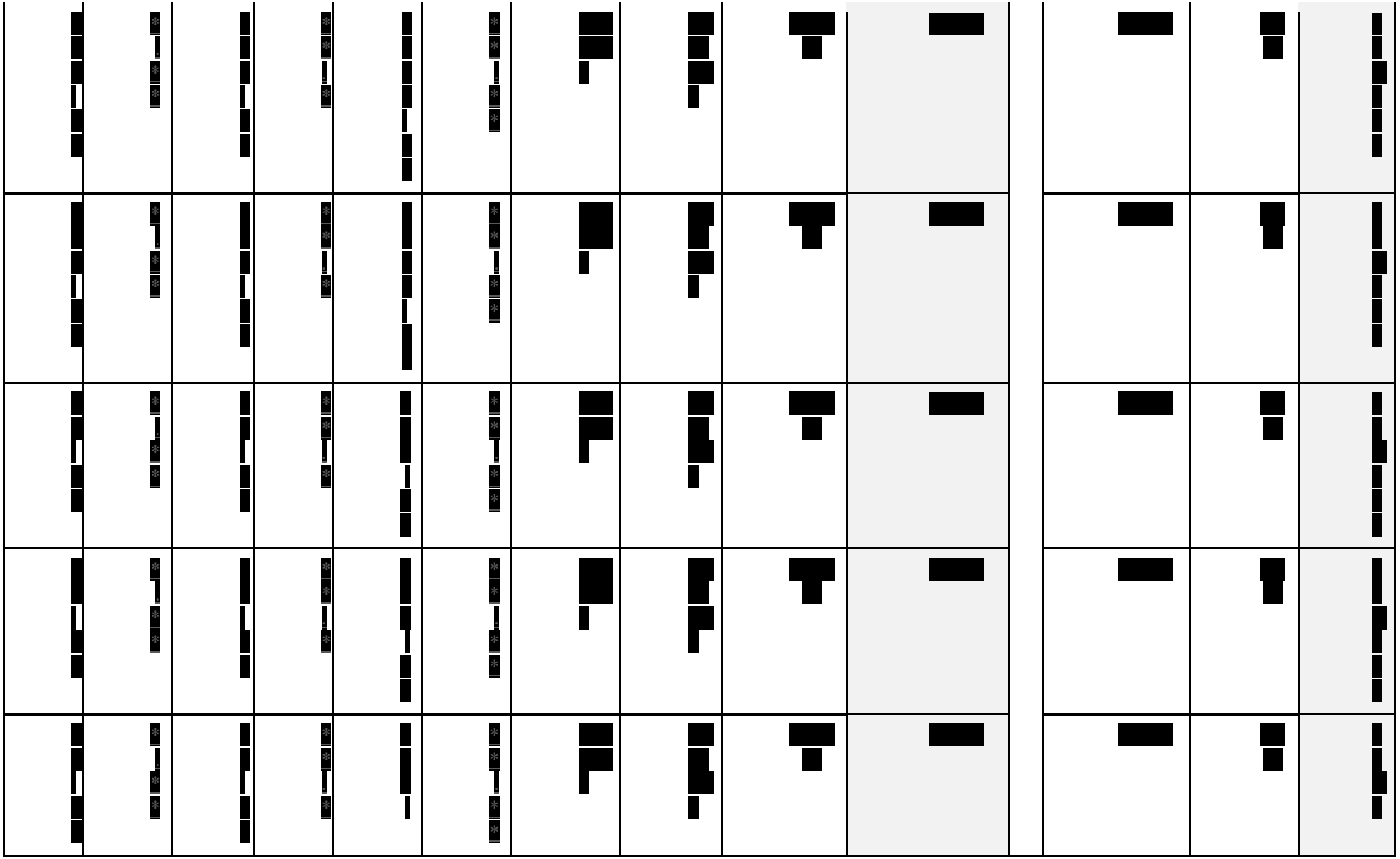

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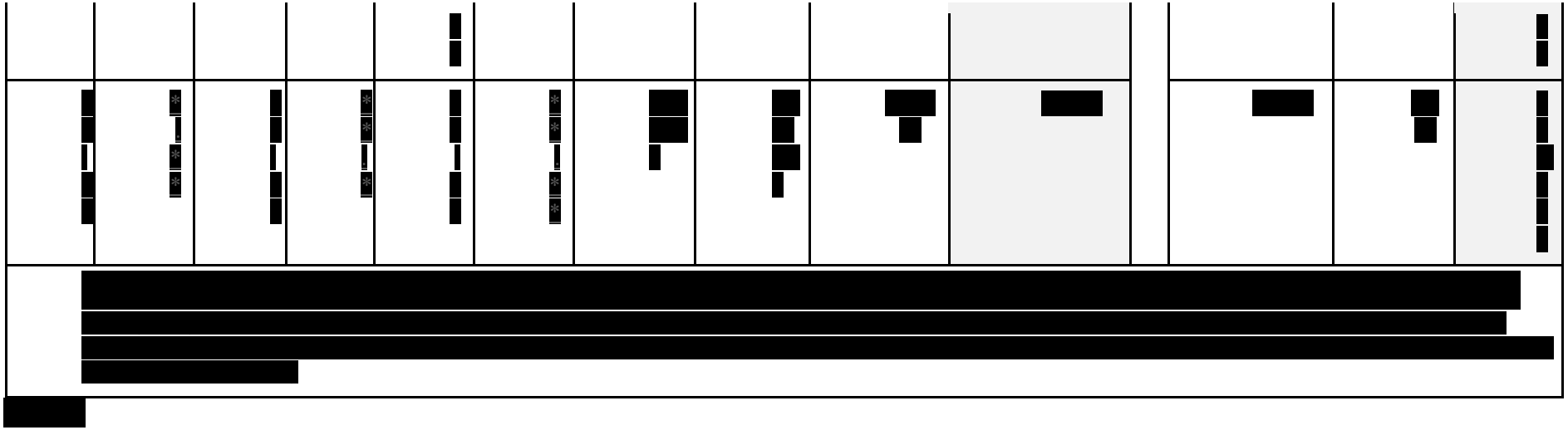

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File attachments/additional information from number 58

former US Version	*Current US version*	***UK/EU Version***

CONTRAINDICATIONS *Do not use PRP gel from the 3C Patch® System on:* ● ***Actively*** *infected wounds* ● *Malignant wounds* ● *Patients with sepsis or bacteraemia* ● *Patients with large wounds, active systemic disorders, and abnormal laboratory tests, such as the following: − Wounds greater than 10cm2 − Coronary artery disease, congestive heart failure, liver failure, and renal failure on hemodialysis, and active gastrointestinal bleeding − Hemoglobin less than 10g/dl, platelet count less than100x109 /L, and serum albumin level less than 2.5g/dl.*	*CONTRAINDICATIONS* *Do not use PRP gel from the 3C Patch® System on:* ● ***Actively*** *infected wounds* ● *Malignant wounds* ● *Patients with sepsis or bacteraemia*	*CONTRAINDICATIONS* *3C Patch® has not been tested on:* *• Actively infected wounds* *• Malignant wounds* *• Patients with sepsis* *• Patients with, haemophilia, sickle cell anemia, thrombocytopenia, leukemia or other blood dyscrasia.* *• Patients being treated for malignant or neoplastic diseases or collagen vascular diseases.*

INSTRUCTIONS FOR USE 3C Patch® System

TABLE OF CONTENTS

SYSTEM DESCRIPTION

The 3C Patch® System consists of:

- 3C Patch® Kit
- Centrifuge Cups (4)
- Counterbalance
- 3CP™ Centrifuge

The 3C Patch®/ 3CP System produces an autologous 3C Patch®.

3C Patch® Kit

The 3C Patch® Kit is individually packed. Each kit contains the following single-use components:

- 1 3C Patch® Device
- 1 3C Patch® Needle Holder

1 Winged blood collection set (G21) with protector

1 Alcohol swab

1 Post-sampling adhesive bandage

1 Primary wound cover dressing (Tricotex)

1 ruler with adhesive,

3CP™ Centrifuge

The 3CP™ Centrifuge is a table-top centrifuge that allows for driving the centrifuge insert at a mean of 3000g. There are optical sensors that allow for complete automation. The optical sensors detect coagulation by measuring the light transmission through the 3C Patch® Device. The transmission will decrease as the fibrin is polymerized. The centrifuge is powered by an external 36-volt power supply (TDK Lamda DT150-C).

3CP™ Counterbalance

The 3CP™ Counterbalance is a non-sterile centrifuge accessory component.

This 3CP™ counterbalance is used with the 3CP™ Centrifuge. It is used to counterbalance the 3C Patch® Device when an odd number of devices (1 or 3) are used.

INDICATIONS FOR USE

The intended use of 3C Patch® device is to produce an autologous platelet-rich fibrin for wound management of recalcitrant wounds.

CONTRAINDICATIONS

3C Patch® has not been tested on:

- Actively infected wounds
- Malignant wounds
- Patients with sepsis
- Patients with, haemophilia, sickle cell anemia, thrombocytopenia, leukemia or other blood dyscrasia.
- Patients being treated for malignant or neoplastic diseases or collagen vascular diseases.

WARNINGS

- In case of increased exudate levels during the 3C Patch ® treatment the secondary dressing type should be adjusted accordingly. If redness, pain and/or wound enlargement occurs the underlying cause should be investigated and treated.
- Manufacturing the 3C Patch® may increase risks of decompensation in patients with the following conditions and disorders: patients receiving blood thinning medication or patients under treatment for malignant diseases or connective tissue diseases; moderate to severe cardiovascular and pulmonary disorders; hematological or lymphoproliferative disorder; systemic infection; moderate to severe malnourishment; immunocompromised conditions; liver and renal failure; active GI bleeding or patients on dialysis.
- Osteomyelitis is a common complication of diabetic foot ulcer. Rule out osteomyelitis prior to treatment with the 3C Patch®. Discontinue the 3C Patch® and treat osteomyelitis if it is diagnosed during management of the wound.
- Patients must be able to donate the required amount of blood.
- Patients receiving anticoagulant therapy may have longer coagulation times; therefor it may be necessary to wait for a longer period prior to second centrifugation.

PRECAUTIONS

Throughout the processing procedure and application of 3C Patch®, use universal precautions as defined by the facility policy and procedure manual.

Do not use the product if the packaging is damaged or the expire date has been exceeded

- The 3C Patch® Device are packed sterile for single use only. Do not re-use. As re-use may lead to infection or illness/injury/death. Discard all unused components at the end of the procedure.
- The 3C Patch® may not be able to be produced due to difficulty in blood sampling and technical device failure.

- Always use UNIVERSAL PRECAUTIONS when handling blood and blood components.
- Patients receiving anticoagulant therapy may have longer coagulation times; therefor visual inspection for coagulation may be necessary prior to the second centrifugation.
- Do not place a label around the body of the device as this can affect the fit of the device in the centrifuge insert and /or affect the centrifugation process. If labelling of the device is required, it is recommended that the initials and/or date of birth of the patient are written on the pink lid on top of the 3C Patch® device with a permanent pen. Alternatively, a small circular label can be placed on top of the device after collecting blood from the patient. (See below).
- 3C Patch® must only be used by qualified personnel that have read and understand these user instructions. Always use aseptic procedures when handling the device.
- If blood drawing takes more than 5 minutes, this could result in poor patch preparation, as the blood will start to coagulate before processing.
- After use, dispose of the 3C Patch® device and its contents as clinical waste as per local procedures.

Complaints:

Report any complaints to Reapplix. In the case of product malfunction, please provide details together with the lot number of the device.

If components must be returned to Reapplix for further investigation, they should always be decontaminated before shipment and a decontamination certificate attached.

INSTRUCTIONS

The 3C Patch® is intended solely for autologous use.

Wound Treatment and Frequency of 3C Patch® Application

1. Use the 3C Patch® in conjunction with good wound care to prepare the wound bed before treatmentand off-load the wound after treatment.
2. Before the first treatment, perform a sharp debridement of the wound using a sharp spoon, scalpel or similar instrument to remove necrotic tissue, and hard fibrin layer. Rinse and/or swab until any bleeding has stopped.
3. 3C Patch® treatment is applied weekly.
4. On subsequent treatments, rinse with water and remove any loose residual 3C Patch®. If the 3C Patch® is integrated into the newly formed granulation tissue, do not remove it**.**
5. Use the 3C Patch® System in conjunction with standard of care procedures for comprehensive wound management tailored to specific cause of the wounds (such as diabetic, venous, surgical) Standard of care may include:

    - Removal of necrotic or infected tissue
    - Off-loading
    - Compression therapy for venous stasis ulcers
    - Establishment of adequate blood circulation
    - Maintenance of a moist wound environment
    - Management of wound infection

- Wound cleansing
  - Nutritional support, including blood glucose control for subjects with diabetic ulcers
  - Bowel and bladder care for subjects with pressure ulcers at risk for contamination
- Management of underlying disease

Prepare the Centrifuge

Reapplix 3CP™ Centrifuge – See separate instructions ("3CP™ Centrifuge User Manual") for fitting the centrifuge with the 3CP™ Centrifuge **Cups**.

Determine the Wound Size.

The number of 3C Patch® Devices required can be estimated from the wound area using the table below:

Wound area (cm^2)				
Number of 3C Patch® devices				

Collect Blood

1. Attach the Winged blood collection set to the 3C Patch® Needle Holder.
2. Wrap a tourniquet proximal to the puncture site and identify the venipuncture site.
3. Prepare the puncture site by cleansing with the alcohol swab.
4. Palpate the vein and perform the venipuncture, inserting the blood collection set needle through the skin into the vein.
5. Once venous access is achieved (blood seen in the tubing line), attach the 3C Patch® Device to the venipuncture set via the 3C Patch Needle Holder and draw blood directly into the appropriate number of 3C Patch® Devices. Turn the device to locking position in the Needle Holder.
6. Remove the device from the Needle Holder before the needle is removed from the arm.
7. Remove the tourniquet and blood collection set needle. Place the protective shield onto the needle and discard in the sharps container.
8. Apply pressure with a gauze pad over the venipuncture site until any bleeding stops. Apply the supplied adhesive hemostatic bandage over the site.

Centrifugation with Reapplix 3CP™ Centrifuge

1. Ensure that the processing commences within 5 minutes after blood collection.
2. Place the filled 3C Patch® Device(s) in the Centrifuge Cup with the guide cams positioned at the tracks marked with a **single red dot (position I). Click** the device gently in the selected track.
3. If using 1 or 3 devices, place 3CP™ counterbalance directly opposite the 3C Patch® Device in the centrifuge.

4. Close the lid. Press Start, and the centrifuge will run the automated process through 3 steps.

The **Centrifugation** step will spin at 6000 rpm for 8 minutes. The centrifuge will then automatically enter into the **Coagulation** step. The speed will be reduced to 1500 rpm, and an optical sensor will start to detect coagulation by measuring the light transmission through the device. When sufficiently coagulated, the **Compaction** step will spin at 6000 rpm – moving the filter to the top of device to form the 3C Patch®. After the compaction step, the processing is complete. The lid can then be open when rotation has stopped, and the device(s) can be removed.

Note: If coagulation has not been detected, the 3CP Centrifuge will stop, and display **"Coagulation Not Complete. User inspection required. Press Open"** In this case, the user must manually inspect the device for coagulation, the display will indicate "**Wait for coagulation and, re-insert in track II. Press START"** to initiate the **Compaction** step. In case the filter has not raised quite to the top of the device restart the process by pressing START and perform second centrifugation in track II

Refer to the "3CP™ Centrifuge User Manual" for complete instructions.

Application

1. Do not open the device before the wound bed is prepared for application.
2. Open the device by turning the lid, then transfer the 3C Patch® to the wound.
3. If the patch is very moist, place the 3C Patch® on a sterile absorbing surface (fibrin side facing down) to absorb any excess fluid before application to the wound.
4. Cut the 3C Patch® to the desired shape and size as necessary before application to the wound.
5. Apply the 3C Patch® to the wound with the surface facing the filter directed to the wound bed.

6. The 3C Patch® may overlap intact skin.

7. Apply the 3C Patch® to the patient's wound within 60 minutes of preparation.

Primary and Secondary Wound Dressings

1. After covering the wound with the 3C Patch®, use the supplied non-adherent cover dressing as a primary dressing. This primary dressing must secure the positioning of the 3C Patch® on the wound and must be fixed with tape to keep it in place.

2. Apply a secondary absorbent dressing (free of choice) in order to control wound exudate (ensure moist wound bed, avoid wet wound bed).

3. Choose secondary dressing(s) to place over the 3C Patch®. Consider the following when making your choice:

- Keep the wound moist and do not allow it to dry out and avoid wet wound bed.
- Use moisture retentive dressings when exudate is minimal.
- In the treatment of venous leg ulcers, compression bandages should be applied according to the therapist's recommendation.
- Wounds with extensive exudate often require additional absorbent dressings over the primary dressing. However, do not use absorbent dressings as a primary dressing as they will absorb the 3C Patch®.
- As the level of exudate may change during treatment, it is essential that the exudate is controlled by appropriate choice of secondary dressings and frequency of changes. After few weeks of treatment exudate volume may decrease.
- If there is a high exudation rate, change the secondary dressing at appropriate time intervals, without changing the primary dressing (unless there are signs of clinical infection). 4. When dressing is complete. document system usage including lot numbers and expiration dates on the appropriate form.

SYMBOLS GLOSSARY

Consult instructions for use		Batch code
Keep away from sunlight		Catalogue number
Do not re-use		Use by
CE marked		Temperature limitation
Latex free	Pat.pend	Patent pending
Do not use if package is damaged		Sterilized using irradiation
Keep dry		Sterilized using Ethylene Oxide
Manufacturer		

Kit components:

All kit components are marked individually except: 3C Patch Needle Holder:

Reapplix A/S, Blokken 45, 3460 Birkerød, Denmark.

NICE National Institute for Health and Care Excellence

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

Pro-forma Response

External Assessment Centre Report factual check

3C Patch for treating diabetic foot ulcers

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

You are asked to check the assessment report from [insert EAC] to ensure there are no factual inaccuracies contained within it. If you do identify any factual inaccuracies you must inform NICE by 12pm, **1st June 2021** using the below proforma comments table. All your comments on factual inaccuracies will receive a response from the EAC and when appropriate, will be amended in the EAC report. This table, including EAC responses will be presented to the Medical Technologies Advisory Committee and will subsequently be published on the NICE website with the Assessment report.

26th May 2021

NICE National Institute for Health and Care Excellence

MT539: 3C Patch Strategic statement

The company has set out a large number of individual issues in the Assessment Report factual check. We do not feel, however, that these issues should be considered in isolation, as there are a number of inter-related problems, in particular with the EAC economic modelling, and it is important for the committee to understand the combined impact of these on the outputs of the EAC model and the conclusions of their report.

There are a number of serious problems with the cost inputs to the economic model. These issues fall into the following broad categories:

- Use of contested and incomplete data from Farr et al. (unpublished) on a [redacted] This is in spite of the fact that:
  [redacted]
  This data is used (along with an inflated unit cost for infection admissions) to derive a 22% uplift in inpatient costs for 3C Patch relative to standard care in EAC Model A.
- Exclusion of a large body of DFU costs from the model – for example, inpatient costs that are not directly related to infection or revascularisation. Study evidence indicates that approximately half of DFU inpatient costs are attributable to extended length of stay in general admissions. It is essential that an economic model of this kind counts all relevant costs.
- Underestimation of inpatient and outpatient standard care costs – outpatient costs in standard care are underestimated by 32% relative to the level supported by the cited source, and inpatient costs are underestimated by 53% (Model A) relative to the level supported by large-scale NHS datasets (e.g. Hospital Episode Statistics, NDFA inpatient activity data, PHE Diabetes Foot Care Profiles) and peer-reviewed papers such as Kerr et al. 2019.
- Use of a differential unit cost for infections for 3C Patch and standard care patients in Model B. The unit cost of infection for 3C Patch is estimated at £2,366 (more than twice the standard care estimate of £1,163). These differential costs are applied to each infection in the model. These figures are estimated on the [redacted] with a flawed adjustment based on inappropriate use of trial infection data. It is very unusual in an economic model to apply a different unit cost to the same event in the two treatment arms. Such an adjustment, if made, should be supported by strong evidence. There is no robust evidence to support the application of a different unit cost in this instance.

As explored in detail in the Assessment Report factual check, there are many other issues of concern regarding costs. The combined impact of these errors is to substantially inflate the cost of 3C Patch, and substantially reduce the cost of standard care. The reduction in the cost of standard care reduces the savings arising from earlier healing with 3C Patch. Thus, there is a two way impact on the overall costs and savings associated with 3C Patch. The costs in the model for standard care cannot be reconciled with published NHS data and peer reviewed study evidence. If these unit costs are correct, it begs the question of how to account for the large body of NHS costs attributable to DFU, as attested by multiple studies. Given the substantial impacts of DFU on quality of life for large numbers of people with diabetes over sustained periods, and very high NHS expenditure on DFU, it is essential that new therapies to alleviate this burden on individuals and the NHS are appraised fairly, in the light of robust evidence and data.

In addition to these very serious concerns about the cost inputs to the economic model, we wish to say that the EAC report repeatedly states that no patients in the 3C Patch RCT could have received or did receive UrgoStart. This is untrue. Patient numbers for UrgoStart were very small, but it is clearly recorded in the trial dataset. One patient in the run-in period was treated with UrgoStart, and one patient in the control arm was treated with UrgoStart throughout the intervention period (and did not heal). We are surprised that the EAC would make such a statement when we have explained that this usage is clearly recorded in the RCT dataset. Further, we would point out that UrgoStart is a protease-modulator, and other protease modulators were used by a substantial portion of patients in the 3C Patch RCT (40% in the run-in period, 60% in the intervention period). There is no evidence to indicate that UrgoStart is more effective than any other protease modulator. No patients in the control arm of the Explorer trial were treated with protease modulators.

Finally, we are concerned that in their base case model the EAC assumes no discontinuation of 3C Patch in cases of insufficient progress. (This was explored to some degree in sensitivity analysis, but not adequately in our view.) The base case approach is at odds with the proposed clinical pathway and majority expert opinion as expressed in the EAC report. We have provided details of healing rates for patients whose ulcers have reduced in size by ≥50% over a 5 week period to inform modelling. While we recognise that experts have expressed differing opinions regarding criteria and timing for discontinuation, all agree that discontinuation would occur. We would hope that NICE will produce guidance to inform future decision-making. The existence of differing opinions in the absence of clear guidance is not a reason to assume no discontinuation at all. It is not possible for NICE to form an opinion on appropriate guidance on the basis of a base case model that is divorced from the proposed pathway and expert opinion.

Issue 1

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
P9 Exec Summary Eligible populations: NHS services are expected to use UrgoStart before 3C Patch but this was not available when the RCT was conducted. Also mentioned on: P11 The EAC notes that patients in the Game et al. (2018a) RCT could not have been treated with UrgoStart as the RCT assessing this technology (Edmonds et al. 2018) was conducted at the same time as the Game et al. (2018a) study. This was confirmed by the clinical experts (EAC correspondence log 2021) who stated that UrgoStart was not part of standard care when recruitment for the Game et al. (2018a) RCT was undertaken. P46 Comparator arm could not include UrgoStart as RCTs were running concurrently.	Please remove the statements asserting that UrgoStart could not have been used or was not used in the Game RCT throughout the paper.	The statements that UrgoStart was not available or not used in the RCT are incorrect and the different parts of the document are somewhat contradictory. The dataset for the 3C Patch RCT included details of all dressings used in the run up to randomisation and during the intervention period, and some patients, albeit a very low number, were recorded by the clinical trial staff as having had an UrgoStart dressing. The EAC acknowledge that they have seen this data in the text on p82, p83 so the different parts of the document do not quite match up. For clarity, the 3C Patch trial recruited patients between Aug 2013 and May 2017. According to the NICE UrgoStart Scope “All UrgoStart products are CE marked as class IIb devices. The CE marks for the different UrgoStart dressings were awarded between 2006 and 2016”. The UrgoStart dressings were new to the market but were available during the 3C Patch RCT, and the	Thank you for this comment and the report has been updated for it.

Also references to UrgoStart on page 82		data clearly indicate that they were used on some patients.	

Issue 2

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
P21 Clinical Context The submission advised that the International Working Group on the Diabetic Foot (IWGDF) Guideline on interventions to enhance healing of foot ulcers in persons with diabetes (Rayman et al. 2020) recommends considering 3C Patch for use in non-infected DFUs that are difficult to heal.	Change 3C Patch to autologous combined leucocyte, platelet and fibrin patch.	In our submission, we give a direct quote from the Rayman article which does not specifically name the 3C Patch but describes it as an "autologous combined leucocyte, platelet and fibrin patch" and then references the Game RCT which used 3C Patch (LeucoPatch).	Thank you for this comment and the report has been updated for it.

Issue 3

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
P25 The clinical experts explained that measuring a '50% reduction in ulcer area', as used by the company to define hard-to-heal DFUs and measure adequate progress to	Change to The clinical experts explained that measuring a '50% reduction in ulcer area', as used by the company (based on current literature as used in the RCT of Game) to define hard-	The company have taken the definition of hard-to-heal DFU from both the clinical input to the Game trial protocol and the available literature (see also Issue 4). This	Thank you for this comment. This section is summarising comments from experts who did not add the text suggested. No change made to report.

support continuing with the 3C Patch, could be difficult and would require specialist equipment to measure the wound accurately.	to-heal DFUs and measure adequate progress to support continuing with the 3C Patch, could be difficult. However, many clinics routinely use this as a method of determining the progress of ulcer healing.	was noted by one of the experts (p25). Whilst we acknowledge that this is derived from expert statement, it appears to be contradicted on P26/27/28 where three out of the eight experts appear to support this; one expert stated that the 50% rule is used routinely and another stated that it was reasonable alongside clinical judgement and a third that this rule is a good predictor of wounds that go on to heal (as evidenced in a number of clinical studies). Many clinicians already use just a standard ruler to determine the size of the wound and it does not require specialist equipment.	

Issue 4

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
P26 The EAC concludes that the experts have a different definition of the eligible population to the company. The experts use clinical judgement, informed by the patient's history and their presentation, to determine who might be suitable for 3C Patch. This	Text should acknowledge that future use would be informed by NICE guidance.	The EAC argues that there are issues of generalisability of the clinical evidence to the likely NHS eligible population, owing to differences of opinion amongst experts as to when they would consider it appropriate to use 3C Patch. Experts will always have differences of opinion regarding the	Thank you for this comment. This is not factually inaccurate. No change made to report.

is probably more consistent with the indicated population in the IFU, being those with recalcitrant wounds. However, as discussed in the next section, the evidence is for patients who meet the company's decision rule. Hence, there are issues of generalisability of the clinical evidence to the likely NHS eligible population.		use of any therapeutic intervention, unless clear guidelines are set out for such use. It is hoped that NICE will set out appropriate guidance to inform clinicians as to the appropriate use of 3C Patch. The company's proposal is for 3C Patch to be considered by clinicians in cases where ulcer area has not reduced by 50% or more during the 4 week period prior to proposed use. This proposal was made after consultation with a number of clinical experts (whose opinions and comments were submitted to NICE). It is also informed by evidence from multiple studies that an area reduction of less than 50% during 4 weeks of treatment is associated with a lower long-term probability of healing (Coerper 2009, Sheehan 2003, Snyder 2010). It is important to stress, however, that this is not proposed as a mechanical "decision rule". The clinical submission makes clear that 3C Patch should be **considered** in cases where ulcer area has not reduced by 50% or more during the 4 week period prior to proposed use. Clinical judgement will be needed to determine whether use is appropriate in individual cases.	

Issue 5

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
P74 However, the clinical experts agreed that the population in the Game et al. (2018a) RCT is broadly representative of the population which would receive 3C Patch if it were to be used in the UK NHS (EAC correspondence log 2021). The EAC notes that further high-quality research is needed to assess whether these preliminary findings are generalisable to a greater proportion of patients with hard-to-heal DFUs (for example, an UrgoStart-experienced population who would be eligible according to the IFU). The EAC concludes that given these discrepancies, the clinical evidence is only partial, and there are considerable uncertainties about generalising the findings to UK clinical practice.	Remove The EAC notes that further high-quality research is needed to assess whether these preliminary findings are generalisable to a greater proportion of patients with hard-to-heal DFUs (for example, an UrgoStart-experienced population who would be eligible according to the IFU). The EAC concludes that given these discrepancies, the clinical evidence is only partial, and there are considerable uncertainties about generalising the findings to UK clinical practice.	The EAC conclusions appear to be somewhat contradictory and at odds with the opinion of the clinical experts. With regard to an UrgoStart-experienced population, it is important to note that 40% of patients in the run-in period received protease-modulating dressings. UrgoStart is a protease-modulator, according to BNF classifications. There is no evidence that UrgoStart is more effective than other protease modulating dressings. The control group in the Explorer trial all received UrgoTul dressings, which is not a protease-modulator. No patients in the Explorer control arm received alternative protease-modulating dressings. The population in the 3C Patch RCT had harder to heal ulcers than the population in the Explorer trial, as outlined in the clinical submission and acknowledged by the clinical experts. Page 83 states “Experts did comment on the differences in	Thank you for this comment. The text is not factually inaccurate and we remain of the view that Game et al. (2018a) provides partial evidence to inform the decision problem because of this issue. No change made to report.

		selection criteria between the UrgoStart trial and the 3C Patch trial and noted that inclusion criteria were more permissive for 3C Patch and therefore it is possible that some patients in the 3C Patch trial would have had ulcers that could be considered 'harder to heal' ulcers than those in the UrgoStart trial. Hence the patient groups in the two trials were different and so this may not have impacted greatly on the outcomes of the Game RCT, with those in Game et al. (2018a) being more representative of a group who have failed on UrgoStart. **Hence the results might be generalisable to UrgoStart experienced patients in the NHS.".**	

Issue 6

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
Page 95 (also P10, P88) the EAC decided to amend the discontinuation rate at 5 weeks with 3C Patch to 0%.	The base case should allow for discontinuation in line with the proposed clinical pathway and expert opinion.	The EAC's summary of expert opinion does not justify setting the discontinuation rate in their base case model to 0. The report notes in several places the consensus view of experts that 3C Patch would be discontinued depending on progress toward healing. All the EAC experts	Thank you for this comment. The reason we set the discontinuation rate at 5 weeks to 0% was because that was consistent with the RCT evidence. The experts did agree with reviewing progress after 4 to 6 weeks and regularly thereafter. They did not

		agreed with the general idea of discontinuation (p. 24/25/26), with at least three supporting using a 50% area reduction as a key guide to continuation. For example: • The EAC report states on page 9 that "NHS clinicians will review healing progress after 4 to 6 weeks of using 3C Patch and regularly thereafter, and decide whether the patch is improving healing rates relative to standard care. This will be more flexible than the rule proposed in the company's clinical pathway and used in its economic model but will still result in some discontinuations, unlike in all the clinical studies. • The EAC reports on pages 25-26 that all experts cited agreed that they would review progress and discontinue 3C Patch if progress was inadequate. • The EAC reports on page 74 that "discontinuation rates are expected to be higher in clinical practice because clinicians will regularly review healing progress and will stop using the patch when this stalls." It is acknowledged that experts expressed differing opinions	agree with adopting the decision rule in the company's proposed pathway. No data were available to model alterative decision rules which are more consistent with the experts' comments. No change made to report.

		regarding appropriate criteria for discontinuation. Experts will always have differences of opinion regarding the use of any therapeutic intervention, unless clear guidance is set out for such use. It is hoped that NICE will set out appropriate guidance to inform clinicians as to the appropriate use of 3C Patch. It is fully within NICE's power to recommend more restrictive use of an intervention if the evidence supports that use. Setting out criteria for continuation would deal with the uncertainty highlighted and ensure that the patch is only used for individual patients where it has the potential to be cost saving. It is also consistent with the IFU (4-6 weeks) and clinical advice (p28) that we received regarding likely use in NHS practice.	

Issue 7

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
P23 Under the Advanced wound dressings heading, the report states: "The experts noted that, from their	Delete "and none were UrgoStart". Acknowledge that the BNF classification of advanced dressings was used, and that the classification	While we do not of course dispute that this is the view of the experts, we used the classification of advanced dressings in the BNF, and this classification is in line with the	Thank you for this comment. No change made to report because we are reporting what the experts noted

perspectives, many of the dressings classified as 'advanced' were not 'advanced' and none were UrgoStart".	is fully in line with the advice given by NICE in the project scope.	NICE advice quoted on page 4 of the project scope: "advanced dressings (such as alginate, film, foam, hydrocolloid and hydrogel dressings)". It should also be noted that the trial dataset indicates that UrgoStart was used on 1 patient in the run-in period and 1 patient in the standard care arm of the trial. It should also be noted that a substantial portion of patients received protease modulating dressings, rather than alginate, foam, hydrocolloid or hydrogel dressings in both the run in and intervention periods. 40% of patients received protease-modulating-dressings for at least 1 week in the run-in period, rising to 60% for the control arm during the trial intervention period.	to us. This is not factually inaccurate.

Issue 8

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
P30 of the report states: "The NICE guidance recommends all people with hard-to-heal foot ulcers are managed by a multidisciplinary foot care service but does not define whether this service should be in	Multidisciplinary foot care services (MDFTs) are generally located within secondary care. Therefore, according to NICE guidance, patients with hard to heal foot ulcers	Multidisciplinary foot care services (MDFTs) are generally located within secondary care, as this is where the required specialists are located.	Thank you for this comment. We agree with the company that MDFTs will generally be located in secondary care. However, the NICE guidance was careful to avoid defining the settings for these

primary or secondary care. Using 3C Patch would seem to require all patients to attend a secondary care setting to access the device and practitioners able to do venipuncture. Currently, many services do not have this skill set and would need to expand their interdisciplinary working."	should currently be managed in secondary care.	NICE lists in section 1.2.3 of NG19 the skills required for an MDFT: - Diabetology. - Podiatry. - Diabetes specialist nursing. - Vascular surgery. - Microbiology. - Orthopaedic surgery. - Biomechanics and orthoses. - Interventional radiology. - Casting. - Wound care. Many of these specialties are not available in primary or community settings. It is not possible for primary care to provide the range of specialist inputs specified by NICE for care of hard to heal ulcers.	services. Hence our wording was quite deliberate. This is not factually inaccurate. No change made to report.

Issue 9

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
P36 DFUs with a duration of at least 6 weeks and a positive probing to	DFUs with a duration of at least 6 weeks and a positive probing to	Patients were not treated in Birkerød, Denmark (this is the address of Reapplix)	Thank you for this comment.

bone test (Wagner grade 3 or more), treated at Lund, Sweden and Birkerød, Denmark.	bone test (Wagner grade 3 or more), treated at Lund, Sweden.		Report has been changed in line with proposed amendment.

Issue 10

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
P42 Katzman et al. (2014) Lund, Sweden and Birkerød, Denmark Diabetes,2014, 63, A581	Katzman et al. (2014) Lund, Sweden Diabetes,2014, 63, A581	The references provided are inaccurate.	Thank you for this comment. Report has been changed in line with proposed amendment.

Issue 11

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
P60 The point estimate of OR 1.47 reflects a relative increase of almost 50% in the percentage of people healing, which is a clinically and statistically significant benefit in this population of people with hard-to-heal ulcers.	The point estimate of OR 1.58 (ITT) reflects a relative increase of almost 60% in the percentage of people healing, which is a clinically and statistically significant benefit in this population of people with hard-to-heal ulcers.	The ITT OR of 1.58 is most appropriate.	Thank you for this comment. Report has been changed in line with proposed amendment.

	The following section should be adjusted accordingly.		

Issue 12

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
P71 of the report states in relation to claimed benefits (Reduced need for follow-on treatment including amputation and associated rehabilitation): "The numbers of amputations was not statistically significantly different between the groups in the Game et al. (2018a) RCT".	It should be acknowledged that increased healing as demonstrated in the trial is likely to reduce amputation incidence over the longer term.	The claimed benefit is a longer term impact arising from reduced time at risk of amputation, owing to the reduced ulcer duration demonstrated in the RCT. Patients with healed ulcers will not require amputation. Amputations are rare events so a statistically significant difference in amputation rates would not be expected in a trial of this kind. However, the increased healing rate demonstrated in the RCT directly leads to reduced time at risk of amputation.	Thank you for this comment. We are only able to describe if the submitted evidence and any identified by the EAC, supports the company's claim and the current evidence does not. The evidence is accurately reported. No change made to report.

Issue 13

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
P73 of the report states: "Thus. the EAC agrees with the company's submission that using the RCT	Acknowledgement of evidence for the claimed benefits of reduced demand for ulcer care, reduced	The company believes they have provided evidence of other claimed benefits, specifically reduced	Thank you for this comment.

protocol, the 3C Patch can heal diabetic ulcers more rapidly than standard care but did not find evidence to support the other claimed benefits.”	need for follow-on treatment including amputation and associated rehabilitation, increased quality of life and reduced costs.	demand for ulcer care, reduced need for follow-on treatment including amputation and associated rehabilitation, and increased quality of life. Each of these follows directly from the reduced ulcer duration demonstrated in the RCT. Patients with healed ulcers will not require continued ulcer care, amputation, or associated rehabilitation. Reduction in demand for ulcer care, amputation and rehabilitation will reduce NHS costs for these very expensive aspects of care. Multiple studies have indicated that DFUs are associated with substantial decrements in quality of life (Ragnarson Tennvall and Apelqvist 2000). Earlier healing of DFUs as demonstrated in the RCT therefore leads to improved quality of life. The EAC report acknowledges that the clinical experts support the connection between early healing with 3C Patch and the other claimed benefits. The report states (page 14) “The clinical experts advised that time to complete healing is the most important outcome. It is associated with fewer clinic visits and dressing changes, a lower risk of infection and amputation, and it reduces the	As we note in the assessment report, the need for subsequent resources such as future appointments, dressings and offloading devices is likely to be less with patients who are healed following use of 3C Patch but company has not provided data to support these assertions. No change made to report. In respect of quality of life, on page 71 we report in full the data provided by the company to our question on quality of life. These were from 20 patients. The company added that these data are NOT an estimate of the impact of 3C Patch. This is not factually inaccurate. No change made to report.

		loss in quality of life (EAC correspondence log 2021)." The EAC acknowledges in a number of places positive QoL impacts with 3C Patch relative to standard care (p61 para 3 & p69 and expert opinion on p14). The report also comments that there are likely to be beneficial resource impacts (pp14, 29, 72 and 76).	

Issue 14

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
P77-78: The EAC notes inconsistencies about the mean expected treatment duration with the 3C Patch: • The IFU states that 3C Patch can be used weekly but does not specify the maximum number of treatment weeks for which 3C Patch can be continued. • The mean treatment duration in the RCT was 17.1 weeks.	This section should be deleted.	We do not agree that these are inconsistencies. The purpose of an IFU is to inform users of a device's intended purpose and proper use and of any precautions to be taken. The proposed clinical pathway and company submission do not contradict the IFU, but provide supplementary information, based on expert clinical advice. There is no inconsistency between saying that initial treatment is	Thank you for this comment. We note the company disagrees with our description of the differences across the IFU, RCT and clinical pathway as inconsistencies. Hence, we have edited the text in respect of the RCT to add that it had a maximum treatment period of 20 weeks, to bring out the difference between the IFU and the RCT.

• The company submission states the initial treatment with 3C Patch is recommended for between 4 and 6 weeks (with treatment continuing for patients who demonstrate adequate improvement). The EAC notes that the company submission also states that 3C Patch can be used once per week for up to 20 weeks at the discretion of the treating healthcare practitioner. According to the company submission, expert opinion indicates that treatment with the 3C Patch would be unlikely to continue for up to 20 weeks in routine practice. These inconsistencies give rise to concerns about generalising from the RCT protocol to clinical practice.		recommended for 4-6 weeks, with treatment continuing only for patients who demonstrate adequate improvement, and saying that maximum treatment duration should be 20 weeks. It is acknowledged that the RCT did not include discontinuation at 4-6 weeks. However, the economic modelling submitted by the company was based on the proposed pathway, using the trial data to demonstrate the impact in the trial population of stopping 3C Patch for patients whose ulcers had not reduced in area by ≥50% at 5 weeks.	

Issue 15

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
P78 The experts advised they would manage patients failing on 3C Patch with other aspects of standard care	We would advise to add the experts opinion on which wound treatment to use if 3C Patch fails as the aspects mentioned here are not an alternative to 3C Patch or any wound treatment but adjunctive	Offloading, infection control and vascular interventions are NOT alternatives to 3C Patch. They are part of best standard of care and	Thank you for this comment. We concur that the interventions listed are not dressings but are components of standard care, and will be used in conjunction with

(offloading, infection control or vascular interventions)."	measures that have to be taken in addition to the wound treatment itself.	need to be done IN PARALLEL to the actual wound therapy.	dressings. Hence, we have added these components will be used together with appropriate dressings.

Issue 16

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
P81: The analysis is subject to limitations given that it is unpublished. It does, however, report being reviewed by both the trial team and Reapplix. Comments from Reapplix on the final version of the report and authors responses to these are provided as an appendix.	Delete Comments from Reapplix on the final version of the report and authors responses to these are provided as an appendix. Replace with Comments from Reapplix on a draft version of the report and authors' responses to these are provided as an appendix but Reapplix did not receive replies to concerns raised regarding data quality and accuracy of the draft report, and was not aware of the existence of the final report.	The final report was not commented on by Reapplix - an early draft V1 was. Although Reapplix was a funder, it was not aware of the existence of a final report. As noted in the comments on the report Reapplix believe there are a number of issues with the quality of the data used and the accuracy of the report. Reapplix never received responses to the concerns it raised in relation to data quality in version 1. The data quality and accuracy issues raised by Reapplix were not corrected in the final version of the report. This incomplete and inaccurate data has been used as a key driver of the EAC model. See issues raised below in relation to inpatient cost estimation, infections and antibiotic costs. In addition, we do not believe it is appropriate for the EAC to present	Thank you for this comment. We note the company's concerns and have updated the report to note: 'Reapplix advises it did not receive replies to their concerns and was not aware of the existence of the final report.' We have not marked this as CiC. We have retained the ICERs as these are not factually inaccurate.

		the [redacted]	

Issue 17

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
P88 (and also P94 and P96) of the report states: "raw data from the trial were not provided and therefore the EAC could not assess that the correct figures were used from the trial or assess the appropriateness of the post hoc analysis".	It should be acknowledged that the company was informed by NICE that they would not expect to receive raw data from the trial, but that the results of supplementary analysis of the trial dataset could be used in the submission, and would be acceptable.	The company was advised by NICE that they would not expect to receive this data. Had we known that analysis of this data would be discounted if the data itself was not provided, we would have taken steps to make the appropriate data available.	Thank you for this comment. We have edited the report at pages 89, 95 to note that the company had been advised it was not expected to submit raw data.

Issue 18

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
P94 of the report states: "Half cycle correction was applied in the EAC model although this change would have had negligible impact on the results."	Half cycle correction is inappropriate and should not be used.	We did not consider it appropriate to use half cycle correction for this model. Much of the cost of ulcer care is in weekly units (e.g. clinic visits). Where this is not the case, costs have been estimated from disaggregated data and averaged across weeks of ulceration for the	Thank you for this comment. This is not a factual inaccuracy and no change has been made. In any Markov model (regardless of the cycle length) without a half cycle correction an assumption is made that transitions happen at the start or end of the cycle. The half cycle

		patient group, thereby already reflecting any part week resource use (e.g. medications and dressing changes). This follows the principles in the YHEC online glossary: "In economic models that use Markov-type processes, it is generally recommended that a 'half-cycle correction' be built into the analysis, to account for the fact that events and transitions can occur at any point during the cycle, not necessarily at the start or end of each cycle. For example, if we know that 100 people are alive *at* month ten, and then 90 people are alive *at* month eleven, we do not necessarily know at what point those 10 patients died *between* months ten and eleven. In such cases, it is usual to assume that the event occurred at the mid-point of the cycle. However, for many health events, the implications of the event may not actually become apparent until the next cycle. For instance the increased costs associated with disease progression may not occur until progression is clinically confirmed, which may only happen at regular routine follow-up visits (i.e. at the start or end of a cycle). Likewise, if packs of medicine are prescribed on a monthly basis,	correction accounts for the fact that in reality transitions will happen on average halfway through the cycle. For example, if a person's ulcer becomes infected or they require amputation this would happen on average halfway through the weekly cycle (rather than always at the start or end of the cycle). A case could be made for excluding some costs, e.g. the cost of 3C Patch (and application), from the half cycle correction as this happens to all individuals on entry to the model. It is unclear if this would be the case in the first cycle only. The cost of the 3C Patch is applied as part of a health state costs with other costs that should be half cycle corrected (e.g. other dressings). Hence, a simplifying assumption is made to half cycle correct all costs. Taking the 3C Patch out of this correction would mean that 3C Patch is slightly more cost incurring. The impact of applying the half cycle correction to all costs within the model is small and no change has been made to report.

		then a monthly cost to the healthcare system would occur in full, no matter what point the person died within the cycle. **Therefore, it is usually recommended that half cycle correction is applied carefully, and only to those aspects where the timing of the event and its consequences are not known."**	

Issue 19

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
P89 states "further costs could be incurred by the healthcare system as a result of an infected ulcer, such as additional staff time, inpatient admissions or appointments which may not be fully captured within the company's model". Also, P123, table 9.12.	The line on page 89 should be removed and the reference to "not included" under infection in Table 9.12 should be changed to N/A.	This is incorrect. The cost of relevant infections is fully captured in the company model. Antibiotic use for infections related to the index ulcer, and staff time for IV and IM administration of these medications were costed at patient-level and applied to the model. There was no significant difference in infection rates between the two treatment arms in the RCT. Other costs associated with treating infection were included in the outpatient and inpatient costs in both arms.	Thank you for this comment. Edit made to Table 9.12. No change made to p89 as having the separate health state enables other costs to be included; it is not a judgement on the completeness of the company's costs. No change made to report.

Issue 20

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
P104 Table 9.6 Company does not state the additional annual staff training required.	This line should be deleted	The company provided details of annual staff training requirements. See pages 25-26 of the company economic submission, under the heading “NHS staff time for training sessions”.	Thank you for this comment. We agree with proposed amendment and justification. Edit made to add the grades, hours and source of unit costs.

Issue 21

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
P103 Table 9.6 And P105 Table 9.7 “The company did not include revascularisation costs.”	This line should be deleted.	This is incorrect. Revascularisation costs are included in inpatient costs derived from Kerr et al. 2019, and applied to both treatment arms in the model.	Thank you for this comment. The EAC reviewed the codes used in the supplementary material in Kerr (2019) but did not judge any explicitly captured vascularisation inpatient costs. Hence the EAC concluded that the company did not explicitly capture revascularisation costs. To address this gap, the EAC extracted unit cost values for the same NHS reference cost codes as used in the Farr economic

			evaluation (unpublished). The codes are YQ10A to YQ12D. It may be that other non-specific codes are used to capture revascularisation, but it is not clear which codes would represent this. No changes made to the report.

Issue 22

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
P103 Table 9.6 "The company used a cost per infected DFU derived from Kerr et al. (2019). The same value was applied across both treatment arms."	Delete the reference to infected DFU.	This is incorrect. The estimate of the cost of inpatient care is a mean weekly cost for all ulcers. It is not specific to infected DFUs.	Thank you for this comment. Edit made to advise cost was for all ulcers.

Issue 23

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
P104 Table 9.6 3C Patch: Antibiotics to manage infections. (Model A) EAC value £1.14	Change value in model from £1.14 to £7.13.	The EAC estimate is based [redacted]	Thank you for this comment. As the company states the EAC has not included an [redacted]

		[redacted] The company analysis estimates costs for all antibiotics prescribed for infection related to the index DFU, taking into account the number of days of administration, and the costs of IV/IM administration where appropriate. It is considered a more complete and accurate estimate.	[redacted] We did not include any staff costs for administration of these medicines because we did include the cost of all district nurse visits across the 20 weeks. The reasons for such visits were not stated by Farr or Game et al. (2018a) but we assumed would include administering these medications. We thus do not accept the case to add in further costs. No change made to report.

Issue 24

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
P106 Table 9.7 Standard care: Medications cost for antibiotics to manage infections. (Model A) £2.59	Change value in model from £2.59 to £9.70.	The [redacted] The company analysis estimates costs for all antibiotics prescribed for infection related to the index DFU, taking into account the	Thank you for this comment. As the company states the EAC has not included an explicit cost for intravenous or intramuscular administration, but [redacted] We did not include any staff costs for administration of these because we

		number of days of administration, and the costs of IV/IM administration where appropriate. It is considered a more complete and accurate estimate.	did include the cost of all district nurse visits across the 20 weeks. The reasons for such visits were not stated by Farr or Game et al. (2018a) but we assumed would include administering these medications. We thus do not accept the case to add in extra costs. No change made to report.

Issue 25

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
P105 Table 9.7 Standard care: Ulcer inpatient cost for severe infections and revascularisation (Model A) £43.06	The model should include all inpatient costs associated with DFU, not just those attributed to severe infection and revascularisation. The unit cost used for DFU admissions is incorrect and should be adjusted. Relevant activity should be estimated based on NHS datasets and peer-reviewed papers rather than on contested and [redacted]	This cost estimate is based on: - An underestimate of inpatient care related to DFU - A substantially overestimated unit cost of each admission. The net effect is a substantial underestimate of weekly costs for inpatient care associated with DFU in standard care, as evidenced by large-scale NHS datasets and peer-reviewed studies. [redacted] Further details are provided below:	Thank you for this comment. The EAC has used the data from the RCT for [redacted] and applied unit costs for admission consistent with those used in NICE guideline on Diabetic foot problems (NG, 2015). Revascularisation costs were taken from NHS reference costs. We note the concern from the company that the cost from NG (2015) is for a foot ulcer which may include multiple admissions. However, we refer to page 14 of NG (2015) that states: '*This analysis*

		The EAC model focuses only on inpatient care for severe infections and revascularisation. It is unclear why other inpatient costs are excluded. It is known that DFU entails substantial costs arising from extended length of stay in admissions where ulceration is not the primary cause. (See for example Kerr et al. 2019, which estimates that approximately half of DFU inpatient costs arise in this way.) This leads to a substantial underestimate in the model of inpatient costs in standard care. The lead author in Kerr et al. has indicated that the unit costs in her report and in NICE NG19 have been misinterpreted by the EAC. The unit cost estimated in the NICE costing report (£6,249 in 2015) is for all inpatient care *per ulcer,* not for an individual ulcer admission. In the NICE costing report, this cost is not specific to severe ulcers, nor to ulcers that have deteriorated, but is rather an estimate of the total mean cost of inpatient care over the duration of an ulcer. The estimated cost of an individual admission is very much lower than the estimated total cost of *all* admissions during an ulcer episode. Many ulcers are of very long duration and some never heal. During the course of a long	*generated a unit cost per admission detailed in Table 12.'* Table 12 states £6,249. This value per admission is used by the EAC, being updated to 2021 prices and [redacted] We also note the company's comment that [redacted] The EAC notes the protocol specified that: 'SAEs will be collected until Visit 26 (end of study visit, 26 weeks), or 30 days past the last device usage (whichever is sooner). Indeed all patient-related outcomes (e.g. amputation, pain, and new anaemia) were to be collected to week 26. Hence the 26 week data were collected. However Farr et al. state clearly that they [redacted] This is consistent with their responses to a question posed by the company on the draft report. [redacted] Company: [redacted]

		period of ulceration some patients will have many DFU-related hospital admissions. It is not acceptable to use an estimate of all inpatient care during ulceration as an estimate of the cost of an individual admission. The unit cost of admission used in the model is approximately double the level supported by NHS data and peer-reviewed studies. Large-scale NHS datasets and peer reviewed studies provide more robust sources for estimating the weekly cost of inpatient care for DFU. For example, NDFA data based on 33,155 ulcers in England and Wales in 2015-18 indicate that there were on average (mean) 2.82 inpatient bed days in foot disease-related hospital admissions per ulcer within 6 months of first expert assessment. Using the weighted average bed day cost from HRGs KB03C-D (Diabetes with lower limb complications) in NHS Reference Costs 2017-18 (inflation-adjusted), £456.63, to provide an illustrative cost, and estimating mean ulcer duration at 13.58 weeks during this 6 month period, based on reported healing and death rates in NDFA (72.7% of patients have healed or died within 24 weeks – weekly probability assumed constant and applied over 26 weeks) the average	Farr response: [redacted] We also note the [redacted] We highlight two questions asked by the company about the accuracy of data for serious adverse events (SAEs). Company: [redacted] Farr response: [redacted]

		cost of these admissions per ulcerated week is estimated at £94.34. This is likely to be a more robust estimate of inpatient costs associated with DFU than the approach used in the EAC model. The estimate used in the company's model (£92.51) is derived independently, from Kerr et al. 2019, and is very close to the calculation based on NDFA. Either of these estimates is considered more robust than that used by the EAC. The company's economists have analysed the RCT dataset and cannot replicate the figures produced in Farr et al [redacted]	[redacted] Hence, we assume all SAEs were related to a DFU. Company: [redacted] Farr response: [redacted] Hence due diligence appears to have been conducted before data were provided to the health economics team. We see no reason to sustain the company's challenge to the veracity of the data on event rates as reported by Farr (unpublished).

		[redacted] Since receiving the EAC report, the company has asked the RCT CI, Prof. Game, about these admissions. [redacted]	No change made to report.

Issue 26

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
P103 Table 9.6 3C Patch: Inpatient cost for severe infections and revascularisation. £52.51 (Model A)	The model should include all inpatient costs associated with DFU, not just those attributed to severe infection and revascularisation. The unit cost used for DFU admissions is incorrect and should be adjusted. Relevant activity should be estimated based on NHS datasets and peer-reviewed papers rather than on contested and unvalidated	As indicated in relation to issue 25, above, this cost estimate is based on: - An underestimate of inpatient care related to DFU - A substantially overestimated unit cost of each admission. All the issues raised in relation to issue 25 apply also to this estimate.	The EAC response to issue 25 addresses the issues raised here including the accuracy of the data reported by Farr. We cannot comment on the advice provided by Prof Game that the data used by Farr were at 26 weeks, other than to state the economic evaluation is transparent about the

	summary data in Farr et al. on a [redacted] during the 3C Patch RCT, for which no details to support cost analysis are provided. There is no evidence of a significant cost difference for inpatient care between 3C Patch and standard care.	In addition, the difference in unit costs in the EAC model between treatment arms is entirely based on summary data on [redacted] published in Game et al. 2018. which states that *"The most common serious adverse event (SAE) was diabetic foot infection; there were 24 events in the LeucoPatch group (24% of all SAEs) and 20 events in the standard care group (27% of all SAEs; table 2, appendix). Of these diabetic foot infections, 16 infections (67%) in the LeucoPatch group (16% of all SAEs) and 12 infections (60%) in the standard care group (16% of all SAEs) were attributed to the index ulcer."* As all admissions were classed as SAEs (but not all SAEs were	[redacted] We note the company advises the changes in costs were not statistically significant in the economic evaluation. The RCT was not powered to detect statistically significant differences in this parameter. Hence that the difference in costs is not statistically significant is unsurprising. No change made to report.

		admissions), it is impossible to reconcile the statement in Game et al. that there were in [redacted] The company's economists have analysed the RCT dataset and cannot replicate the figures produced in Farr et al [redacted] It does not seem reasonable to attribute admissions for conditions such as critical renal disease or severe peripheral arterial disease to ulcer deterioration, or indeed to 3C Patch versus standard care. The company contested these [redacted]	

		[redacted] Since receiving the EAC report, the company has asked the RCT CI, Prof. Game, about these admissions. She has indicated that the [redacted]	

Issue 27

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
P 108 Table 9.9 Subsequent ulcer costs: Model A £176.65 Model B: £169.03	These costs are underestimates and should be corrected.	These are substantial under-estimates of the mean weekly cost of care for DFUs. All the points made in relation to costs for standard care apply also to subsequent ulcers. See Issue 25.	The EAC response to issue 25 addresses the issues raised here including the accuracy of the data reported by Farr. No change made to report.

Issue 28

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
P106 Table 9.7 Standard care: Infection cost (one off cost). (Model B) £1,162.99 In model B, the cost of severe ulcer deterioration (£7052.56) from (NG19 [NICE 2015b] from Kerr et al. (2014) was weighted by the proportion of infections that were [redacted] to current prices using BNF (2021) and [redacted]	This cost is inaccurate and should be corrected.	As noted above, in relation to issue 25, the lead author in Kerr et al. has indicated that the unit costs in her report and in NICE NG19 have been misinterpreted by the EAC. The unit cost estimated in the NICE costing report (£6,249 in 2015) is for all inpatient care *per ulcer,* not for an individual ulcer admission (or infection). In the NICE costing report, this cost is not specific to severe ulcers, nor to ulcers that have deteriorated, but is rather an estimate of the total mean cost of inpatient care over the duration of an ulcer. It is not acceptable to use an estimate of all inpatient care during ulceration as an estimate of the cost of an individual infection episode. In addition, in the EAC's Model B the cost of severe ulcer deterioration is applied to the proportion of infections considered to be severe. [redacted] and apparently dividing this by the number of patients who developed a new infection during the 20 week trial period presented in	The EAC response to issue 25 addresses the issues raised here including the accuracy of the data reported by Farr. The final comment by the company stems from the company's belief that the Farr data are at [redacted] weeks. Hence it claims the EAC has used infection data at [redacted] weeks from Farr as the numerator but data from Game et al. (2018a) at 20 weeks as the denominator. This is untrue. The EAC has only used data at [redacted] weeks to calculate the transitional probabilities used in the model. No change made to report.

		Game et al, 2018 (although no source is given for this by the EAC). We do not consider either of these components to be appropriate. With regard to the numerator: as explained under Issue 25 above (3C Patch: Inpatient cost for severe infections and revascularisation), the company's economists do not accept that [redacted] (see issue 25 above for fuller detail). It is noted in particular that the RCT CI, Prof. Game, has indicated that the [redacted] With regard to the denominator: as some patients had more than one infection during the RCT, it is not appropriate to use the number of affected patients to estimate the proportion of infections that were severe. Furthermore, the infected health state in the EAC model is designed to capture moderate and severe infections only as "It was judged that the 3C Patch may continue to be used for mild infected ulcers" (page 93 of the EAC report), whereas the number of patients with new infections used here includes all infections. Finally, and most	

		significantly, the probability of infection used in Model B was estimated using a different source for infection numbers (without reference to these patient numbers), introducing an inconsistency into the model which penalises 3C Patch (as described under Issue 29 below).	

Issue 29

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
P104 Table 9.6. 3C Patch: Infection cost (one off cost). Model B.	This cost is inaccurate and should be corrected.	The unit cost of infection for 3C Patch is estimated at £2,366 (more than twice the standard care estimate of £1,162.99). It is important to emphasise that this is an estimated unit cost, applied in the model to each infection. This estimated difference in [redacted] Additionally, the RCT CI, Prof. Game, has indicated that the [redacted] These data are wholly	Thank you for this comment. For the sake of completeness we repeat the EAC used data from Farr which are [redacted] Hence the data used by the EAC are the values of 51 and 63 for 3C Patch and standard care respectively, taken from the middle column of the

		inappropriate as a basis for deriving differential unit costs of infection for the two trial arms. In addition, as described under Issue 28 above, there are [redacted] The denominator used for these estimates is the number of patients who developed a new infection during the 20 week trial period presented in Game et al, 2018. This is not appropriate, for the reasons described above (issue 28). The most significant issue is that <u>different</u> numbers of infections were used to derive the probability of infection applied in the model. This introduces an inconsistency into the model which unfairly penalises 3C Patch. The [redacted] not the 20 week intervention period. These are <u>higher</u> for 3C Patch than standard care which leads to more patients incurring the cost of infection in the 3C Patch arm of the model (and they are inappropriate). In contrast, the infection numbers used in the denominator to estimate the proportion of infections that are severe are <u>lower</u> in 3C Patch, (and	table presented by the company. As the heading notes, these are at 20 weeks. The EAC notes the results of the [redacted] The EAC has conducted sensitivity analysis to test the sensitivity of the base case results to no difference in inpatient costs (see Table 9.11 and Figures 9.2 and 9.3). These inpatient costs were not one of the top 15 drivers of the results. The model and report have been updated such that in model B weights are no longer applied to antibiotic costs. This is because the cost of antibiotics to manage people with mild infections have now been captured in health states related to an index ulcer, with the infection state only capturing the costs related to managing people contracting moderate to severe infection.

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<td>are from the 20 week intervention period). This drives up the proportion of severe infections in the 3C Patch arm and therefore the unit cost. This produces a discrepancy between the two arms in the cost of infection applied in the model which is inconsistent with the relative rates of infection and unsupported by the data.
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<td>Number of patients who developed new infection within 20 weeks (Table 2, Game et al, 2108) – apparently used as the denominator to calculate the proportion of infections in the infected health state that are severe</td>
<td>Serious AEs (infection, gangrene, sepsis) over 26 weeks (Appendix, Game et al, 2018) - used to calculate the probability of infection</td>
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		<table><tr><td>3C Patch</td><td>51</td><td>27</td></tr><tr><td>Standard Care</td><td>63</td><td>24</td></tr></table> It is very unusual in an economic model to apply a different unit cost to the same event in the two treatment arms. Such an adjustment, if made, should be supported by strong evidence. There is no evidence to support the application of a different unit cost in this instance.	

Issue 30

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
P100 Table 9.5 Weekly probability of moderate/severe infection with 3C Patch 1.99% Weekly probability of moderate/severe infection with standard care 1.49%	The infection model is not supported by robust data. If an infection model is to be used it should be supported by robust data.	The weekly probabilities of moderate/severe infection with 3C Patch and with standard care were estimated using data on serious adverse events from the supplementary appendix to Game et al. (2018a). All events categorised as DFU infections, infections, gangrene and sepsis in this data were included in the calculation and this resulted in weekly probabilities of infection of 1.99% for 3C Patch	Thank you for this comment. The crux of this concern from the company is whether the [redacted] As noted in response to issue 25, Farr has responded to this challenge as follows: Company [redacted]

		and 1.49% for standard care. However, this includes infections that were not related to the index foot ulcer. Additionally, the RCT CI, Prof. Game, has indicated that the [redacted] For all these reasons, we do not consider these data an appropriate basis on which to drive different costs in the two arms. The number of serious AEs in each arm categorised as diabetic foot infections and attributed to the index ulcer are quoted in the main text of the paper and are much lower (see table below). In addition, the difference between the two arms is not statistically significant. [nested table: Serious AEs (infection, gangrene, sepsis) (Appendix, Game et al, 2018) used to calculate the probability of infection for Model / Serious AEs classified as diabetic foot infections in the index ulcer (Results, Game et al, 2018)]	Farr response:   Hence, we assume all SAEs leading to hospitalisation were related to their index DFU. Table 9.15 reports a scenario analysis assuming the same infection rates across both arms. The costs fell by £80 per patient and hence the results are not sensitive to this parameter. No change made to report.

	B – 26 weeks	– 26 weeks
3C Patch	27	16
Standard Care	24	12

Other indicators of infection rates are lower for 3C Patch compared with standard care, including:

- Number of patients who developed new infection
- Percentage of visits at which infection was reported as a proportion of total visits,
- Total number of days of antibiotic therapy.

All these indicators are reported in Table 2, Game et al 2018. While it is recognised that these figures include mild infections, severity will to some extent be reflected in duration of infections captured by the percentage of visits with infection and total days of antibiotics.

We do not believe there is sufficient evidence to model differential infection rates between the two arms (particularly as the cost of mild infections, which would presumably be higher in the standard care arm

		under the assumptions applied by the EAC is not included anywhere in the model).	

Issue 31

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
P110 Infection costs No infection costs are included for mild ulcers in Model B	Reconsider infection model.	Infection costs in the EAC model are limited to severe and moderate infections. No cost is included for mild infections. As described above, the method used to derive the probability of severe/moderate infection results in an estimated higher rate of infection in 3C Patch patients despite other measures indicating less infection in 3C Patch patients (Number of patients who developed new infection, Percentage of visits at which infection was reported as a proportion of total visits, and total days of antibiotic therapy, all reported in Table 2, Game et al 2018). On this basis, the cost of treating mild infections would be expected to be higher in standard care and therefore excluding these penalises 3C Patch. The company provided a detailed analysis using patient level data of all expenditure	Thank you for this comment. We had included mild infection costs within the infection health state in model B but only those with moderate/severe infection enter that state (and stop 3C Patch). This was because some community prescriptions will be for people post discharge. In light of these comments we have changed approach and now the cost of infection in the moderate/severe state only includes hospital costs. The report has been updated for these results and edited accordingly.

		on antibiotic care for both treatment arms. This is considered a more robust foundation for analysis of costs relating to infection.	

Issue 32

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
P105 Table 9.7 Standard care: Ulcer outpatient attendance cost £78.29 Company used a weekly cost for outpatients and the community derived from Kerr et al. (2019). EAC assumed weekly standard care comprised of alternating outpatient appointments and podiatry in the community (EAC correspondence log [2021]). Outpatient cost was £111.66 (see Table 9.6). The podiatry appointment was £44.92 (from NHS reference costs [A09A]). These are summed and divided by 2 for a weekly cost.	Change value in model from £78.29 to £115.36, and change description of costs to acknowledge that patients with DFU receive a range of care across community, outpatient and primary care settings, not confined to outpatient attendances.	These costs are labelled as "outpatient attendance cost". However, patients with DFU receive a wide range of care inputs in community, outpatient and primary settings, in line with NICE guidance. These include orthotics and offloading, imaging etc. It is essential that an economic model of this kind takes into account all relevant aspects of care. The lead author in Kerr et al. 2019 is of the view that the cost adjustments in the EAC model are based on a misunderstanding of the data in Kerr et al. 2019 and are inappropriate. The cost estimates in Kerr et al. 2019 are based on standard care for DFUs in the NHS in England. They are not based on the assumption of weekly outpatient appointments. As the EAC points out, some care is provided in community settings	Thank you for this comment. The company used a weekly cost of £135.97 (2021 prices) from Kerr (2019) and added additional hospital nurse and phlebotomy costs to arrive at a weekly cost of £157.45 for 3C Patch arm. Separately, they included a saving in district nurse time from fewer visits to patients receiving 3C Patch. The cost of £135.97 was applied to all standard care appointments. These rotate weekly between community care and outpatients (OP). The EAC considered alternative sources to Kerr for the cost of standard care (being an OP appointment alternating with weekly attendance at a community podiatry service plus support from a district nurse). This was to avoid the

		rather than in secondary care. This is already built into the cost estimates in Kerr et al. The estimated costs in Kerr et al., as used in the company's economic model, are for a wide range of outpatient, community and primary care provided for DFUs (apart from dressings and medications, which are costed separately in both the company's and the EAC models). The costs cover inputs such as orthotic provision, imaging, NHS transport and hospital outreach services, as well as outpatient appointments. These are averaged across all weeks of care. The approach taken in the EAC model effectively reduces by half the cost of inputs such as orthotic provision, imaging, NHS transport and hospital outreach services for an ulcer in standard care. This is not reasonable. As the cost estimate of £135.97 is based on standard care in the NHS, this is the appropriate cost for the standard care arm of the model. The EAC has indicated that it wishes to deduct the cost of district nurse inputs from this estimate, and include them separately in the model. If so, the appropriate deduction is £20.61 (as set out in detail under issue 33 below) and the	potential of double counting costs. As the company notes in its comments, Kerr bundles the costs to deliver care across a mix of treatments and settings. Options considered included: ● PSSRU. Outpatient attendance average cost: £135 (£141.03 in 2021 prices). This was the value used in the UrgoStart assessment and hence had the merit of consistency. ● NHS reference costs: Diabetic medicine outpatient cost (Service code 307) = £142 (£148.35 in 2021 prices) ● Kerr (2019) follow up outpatient attendance, non-consultant led £116 (2015 prices, £129.78 in 2021 prices). The 2018/19 Reference costs did not report costs against such a code. Hence, we discounted this source. The two other sources each reported a higher cost than Kerr (2019), as adopted by the company. To be conservative we decided to use the Kerr (2019) cost but remove the cost of the district nurse element (£28.21) as we had included the district nurse as a specific cost line. This gave a cost for a standard OP appointment

		adjusted weekly cost estimate for standard care is £115.36. Supplementary note: The Reference Cost used to estimate the cost of podiatry appointments in the EAC model is A09A Podiatrist, Tier 1, General Podiatry. This is the lowest cost community podiatry appointment. It is not considered appropriate for hard to heal diabetic foot ulcers. As indicated above, it is not appropriate to adjust the outpatient costs in the model, as these already reflect standard care. However, if an adjustment were appropriate, it would be important to use the correct NHS Reference Cost. A09C Podiatrist, Tier 3, Management of at Risk Complex Foot is a more suitable reference for these complex hard to heal ulcers. The cost of A09C in 2020-21 prices is £56.24, while the cost of A09A is £44.92.	for a DFU of £111.66 (vs £135.97 as used by the company). We note the company advises the deduction should be £20.61 (not £28.21) but the data informing this lower cost are not in the public domain (see issue 33 for more detail). In terms of the podiatrist cost, the EAC accepts that people with a DFU will be managed by a range of services in the community including those provided by tier 3 services. With hindsight we should have used a weighted average cost of services across tiers 1 and 3 and not just tier 1 (but what weights?). However the difference is £54 for A09C Podiatrist, Tier 3, and £43 for tier 1 services. Adopting a slightly higher cost for this element would have a marginal impact on the results. The company and EAC have also adopted slightly different estimates of inflation to 2021. We used the NHS cost index reported by PSSRU to 2019/20 and assumed the 2019/20 annual rate applied in 2020 and 2021. This must give a slightly higher index value than used by the company. This accounts for the differences in our calculation of the £111.66. No change made to report.

Issue 33

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
P103 Table 9.6 3C Patch: Outpatient consultation Company used a weekly cost for outpatients and the community derived from Kerr et al. (2019). The EAC used same source but deducted the cost of a district nurse (£28.21) to avoid double counting this.	Change deduction for district nurse inputs to £20.61, and total outpatient consultation cost to £128.94. Change description of costs to acknowledge that patients with DFU receive a range of care across community, outpatient and primary care settings, not confined to outpatient consultations.	These costs are labelled as "outpatient consultation". However, patients with DFU receive a wide range of care inputs in community, outpatient and primary settings, in line with NICE guidance. These include orthotics and offloading, imaging etc. It is essential that an economic model of this kind takes into account all relevant aspects of care. The estimated costs from Kerr et al. are for a wide range of inputs to DFU care across outpatient, community and primary settings. These include orthotic provision, imaging, NHS transport and hospital outreach services, as well as outpatient appointments. The numbers given are not consistent with the description provided. It is stated that £28.21 has been deducted from the weekly cost of £135.97, resulting in an adjusted cost of £111.66. However, the difference between £135.97 and £111.66 is £24.31.	See issue 32 above for most of the responses. The EAC only has access to published data by Kerr; the lead author (Kerr) has provided supporting information to the company which are not public domain. Hence the EAC could not have derived the £20.61 value for a district nurse. Rather we used the value in Kerr (2019) (£28.21). The additional £13.58 assumed by the EAC for patients attending for a 3C Patch is related to the longer outpatient appointment. This is not capturing differences in the number of appointments, rather each 3C Patch appointment is assumed to be 10 minutes longer as advised by the experts. We do not understand the final point which the company is making about the intermediate appointments. In essence our approach assumes that the cost of ancillary care provided in addition to the care provided by a

		The lead author in Kerr et al. 2019 is of the view that the deduction of £28.21 is not supported by her paper. Kerr et al. 2019 reports that patients with severe ulcers (SINBAD score ≥3) had mean district nurse weekly cost of £28.52 in 2014-15 (£31.50 in 2020-21 prices). Patients with less severe ulcers had fewer district nurse dressing changes (estimated mean district nurse weekly cost of £11.83 in 2020-21 prices). The distribution of severe and less severe ulcers is assumed to be as observed in NDFA (44.61% severe). The weighted average district nurse cost is £20.61 in 2020-21 prices. If a deduction is to be made for district nurse inputs, this is the amount that should be deducted. This adjustment reduces the cost of community, outpatient and primary care inputs from £135.97 to £115.36. As noted in relation to outpatient costs for standard care, above, it is not reasonable to reduce the weekly cost of outpatient care for standard care, as the cost estimate from Kerr et al. 2019 is based on standard care, and already takes into account the standard care distribution of appointments across secondary and community settings. It is accepted that with 3C Patch patients will need to have the patch	district nurse plus weekly attendances at outpatient and/or podiatry clinical appointments is the same in each arm. This is consistent with the data collected by Game et al. (2018a) and used by Farr. No change made to report.

		replaced weekly at a clinic with 3C Patch capability, and that this is more likely to be in secondary care. The EAC has assumed that standard care patients will have weekly appointments, alternating between outpatient and community podiatry settings. It is appropriate therefore to adjust the cost of 3C Patch to allow for any marginal additional inputs associated with these intermediate appointments for 3C Patch taking place in secondary care rather than community podiatry settings. NHS Reference Costs 2018-19 indicate that the mean weekly cost for WF01A Non-Admitted Face-to-Face Attendance, Follow-up, Podiatry is £51 (£53.11 in 2020-21 prices). This is lower than the cost recorded for the most relevant community podiatry HRG (A09C Podiatrist, Tier 3, Management of at Risk Complex Foot, £56.24). No addition should therefore be made to 3C Patch costs to allow for the fact that these intermediate appointments for patch replacement take place in secondary rather than community podiatry. It should be noted that the EAC model has already added additional weekly outpatient costs of £13.58 to 3C Patch to allow for additional	

		nurse and podiatry time. No further adjustment is justified.	

Issue 34

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
P106 Table 9.7 Standard care: Dressing cost and Standard Care Dressing cost when infected (Model B)	Cost should be changed from £7.62 to £12.47.	The EAC has changed the estimate of dressings cost from £12.47 to £7.62, stating that they have used costs from NHS Supply Chain to replace the costs from BNF used in the company model. The company's estimate was based on individual costing of every dressing used during the 20 week intervention period of the 3C Patch RCT. The EAC did not request data on the quantity of each dressing used. It is unclear therefore how their cost estimate was produced.	Thank you for this comment. The EAC was provided with raw data from Game et al. (2018a) by Prof Game This provided patient level data on the dressings or combinations of dressings used over the 20-week period of the RCT. This information was not included in the Correspondence log as advised by NICE (email L Berry 24 May 2021). In general NHS supply chain prices are materially lower than BNF prices used within the company submission. The EAC opted to use NHS supply chain costs on the advice of NICE and, in order to be consistent with previous submissions which are in a similar medical area. No change made to report.

Issue 35

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
P107 Table 9.8 Healed DFU The company assumed there would be a podiatrist appointment every 6 weeks for a check-up. This is costed as a band 6 podiatrist, equivalent to 15 minutes working time from PSSRU (Curtis and Burns 2020). The EAC used the cost of podiatry outpatient attendance of £54, updated to 2021 prices (NHS England 2019; NHS reference costs service code 653) divided by 6 to adjust to weekly visits, consistent with company and experts opinion (EAC correspondence log [2021]).	Use consistent and appropriate unit costs.	It is noted that a more expensive Reference Cost service code is used here than in the EAC estimate of intermediate weekly podiatry appointments for standard care hard to heal ulcers. The impact of this is to increase costs for 3C Patch relative to standard care, owing to higher healing rates in 3C Patch. If anything, it is likely that more senior and expensive podiatry inputs would be required for care of hard to heal ulcer than for routine check-ups on patients whose ulcers have healed.	Thank you for this comment. The cost used here is an outpatient cost for podiatry. This is the valid setting to conduct a review of progress post amputation. The weekly podiatry cost was for a community setting. The experts advised every 2 weeks the patient would be seen in the community under current standard of care. No change made to report.

Issue 36

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
P108 Table 9.9 All index ulcer, infection, healed DFU and subsequent ulcer costs.	These costs should be corrected.	As outlined above, there are multiple problems with the inputs to these health state costs, all of which inflate 3C Patch costs and reduce standard care costs. The resulting health state	Thank you for this comment. This is a summary table and links unit costs to health states. We have updated the table to report the updated health state costs, reflecting the

		unit costs are inconsistent with the known resource use and costs associated with DFU care, as evidenced by multiple large-scale NHS datasets (e.g. NDFA, PHE Foot Care Profiles) and peer reviewed studies (e.g. Kerr et al., 2014, Kerr et al. 2019, Guest et al. 2018). These issues need to be addressed and health state costs adjusted accordingly.	change in treatment of antibiotic costs.

Issue 37

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
P116-120 Table 9.11 DSAs: 3C patch week 5 index ulcer 3C to ulcer 3C discontinued weekly transition probability and 3C patch week 6-19 index ulcer 3C to ulcer 3C discontinued weekly transition probability Tornado plots on pages 126-7	Take out DSAs varying discontinuation rates.	It is not appropriate to vary the discontinuation rate without also adjusting the healing rate. This does not make sense clinically and is not a reasonable test of uncertainty. While this is acknowledged with a further two-way sensitivity test, we do not think the results of the single way tests should be presented.	Thank you for this comment. This is not factually inaccurate. No change made to report.

Issue 38

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
P96 Table 9.4 Threshold analysis – Total weekly cost of standard care.	Review the conclusions of this threshold analysis.	The discussion misrepresents the impact of the cost of standard care. It is not just the difference between the cost of 3C Patch and standard care that is relevant, but also the absolute cost of standard care as this is the cost incurred for patients whose ulcers are unhealed and who continue to need treatment after 20 weeks in both arms of the model. This is a key driver of savings from 3C Patch as more standard care patients are still ulcerated at 20 weeks and need continuing treatment. As explained above, standard care costs are very substantially underestimated in the EAC model.	Thank you for this comment. The company refers to Table 9.14 not 9.4. The text is factually accurate based on the analyses undertaken. No change made to report.

Issue 39

Description of factual inaccuracy	Description of proposed amendment	Justification for amendment	EAC response
P135 Scenario analysis on Model B.	Remove or revise these scenarios.	Both these scenario analyses are inappropriate. If patients continue to receive 3C Patch during infection,	Thank you for your comment. Additional text has been added into this section to explain the limitation

		there should not be a separate health state in the model as this distorts the costs and healing rates. The RCT healing rates and resource use take account of infection and these are reflected in the company's model. The second scenario models the same infection rate in both arms. We support this, but this scenario still uses differential costs for the two arms which are wholly inappropriate as explained in issue 28/29.	of the scenario analyses. The analyses themselves remain as they provide additional information that these scenarios do not impact on the results of the analyses.