York Health Economics Consortium

NICE

Topical antimicrobial dressings for infected leg ulcers in people aged 16 and over (GID-HTE10041): late-stage assessment

Final Protocol

Hayden Holmes, Associate Director, YHEC

Lavina Ferrante di Ruffano, Project Director, YHEC

Mick Arber, Senior Information Specialist, YHEC

Mary Edwards, Senior Research Consultant, YHEC

Angel Varghese, Senior Research Consultant, YHEC

Sarah Medland, Senior Research Consultant, YHEC

Laura Kelly, Senior Research Consultant, YHEC

Ben Hyde, Research Assistant, YHEC

Sam Woods, Research Assistant, YHEC

Monica Garrett, Research Assistant, YHEC

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Abbreviations

AMD	Antimicrobial dressing
CRD	Centre for Reviews and Dissemination
DACC	Dialkylcarbamoyl Chloride
DSU	Decision Support Unit
EAG	External Assessment Group
EMC	Electronic Medicines Compendium
HTA	Health Technology Assessment
ICER	Incremental Cost Effectiveness Ratio
IWII	International Wound Infection Institute
LSA	Late-stage Assessment
NHB	Net Health Benefit
NICE	National Institute for Health and Care Excellence
NMB	Net Monetary Benefit
PA	Protocol Amendment
PHMB	Polyhexamethylene Biguanide
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
QALY	Quality Adjusted Life Years
RFI	Request For Information
YHEC	York Health Economics Consortium

1 Background

Antimicrobial dressings (AMDs) used to treat infected leg ulcers have been identified by NICE for late-stage assessment (LSA). As described in the NICE scope, the aim of this LSA is to assess whether price variations between AMDs using different agents are justified by their incremental differences, in order to understand which technologies represent value for money. This document was prepared in response to the NICE Scope and presents the methods that the external assessment group (EAG) commissioned by NICE will undertake to produce the LSA.

1.1 Summary of terms

Throughout this protocol, the term "**dressing agent"** refers to the active ingredient in the dressing.

Dressing "categories" are based on clinical indication, while **dressing "type"** refers to the dressing medium, as set out in Table 1.1.

Table 1.1: Categories and types of dressing

Category of dressing (based on clinical indication)	**Dressing types included**
Dressings for exuding wounds, to absorb whilst maintaining a moist environment	Alginate, gelling fibre, absorbent fibre
Dressings for moderate to high exuding wounds	Foams, absorbent pads
Dressings for superficial or partial thickness wounds	Wound contact layers, e.g. gauze
Dressings for deeper wounds and wounds requiring debridement of thick slough	Ointments, hydrogels, gels or pastes containing the antimicrobial agent, or ribbons made from one of the materials from another category
Dressings to aid debridement of devitalised tissue	Hydrocolloid

1.2 Decision problem

The following sections summarise the decision problem as stated in the NICE Scope [1].

Population

The decision problem aims to assess the use of AMDs in the following population:

- People aged 16 and over with a leg ulcer that shows signs and symptoms of local wound infection. Leg ulcers will be defined as ulcers on the lower leg (between knee and ankle) that have not healed in two weeks [2].

If the evidence allows, the following subgroups may be considered:

- Type of leg ulcer (venous, vascular, phlebolymphoedema).
- Location of ulcer.

- Complexities that may impact treatment of leg ulcer infections.
- Wound presentation.

The decision problem excludes:

- People with (1) contamination or colonisation without signs and symptoms of local wound infection or (2) spreading or systemic infection.
- People at risk of infection who may be using AMDs as prophylaxis.

Intervention

Interventions within the scope of the decision problem are AMDs available to the NHS on Part IX of the Drug Tariff, using one of the following active antimicrobial or bacterial-binding agents:

- Honey.
- Iodine.
- Silver.
- Chlorhexidine.
- Copper.
- PHMB (polyhexamethylene biguanide).
- DACC (dialkylcarbamoyl chloride).
- Enzyme alginogel.
- Chitosan.
- Octenidine.

Any other interventions are outside the scope of the decision problem.

Comparator

Eligible comparators will consist of antimicrobial dressings that are considered current standard of care in the NHS (e.g. based on clinical expert advice and clinical evidence). In most cases the comparator will not feature the additional agent included in the intervention. The comparator may differ between subgroups.

Comparison assumes that clinical reasoning has been completed by the nurse, and the choice they need to make is between agents rather than dressing categories or types. Good wound bed preparation, including debridement, is also assumed.

Outcomes

The performance of AMDs will be assessed using the following outcomes.

- Intermediate outcomes:
    - Reduction in signs of local infection (including malodour).
    - Changes to wound bed condition and condition of peri-wound skin.
    - Reduction in wound size or area.
    - Frequency of dressing changes.
    - Reduction in laboratory-confirmed microorganisms.
- Clinical outcomes for infection:
    - Complete infection healing.
    - Time to healing.
    - Infection recurrence.
    - Prescription of antibiotics.
- Clinical outcomes for wound healing:
    - Complete wound healing.
    - Time to healing.
    - Wound recurrence.
    - Prescription of antibiotics.
    - Scar formation.
- Pain and discomfort levels (patient reported outcome)
- Quality of life (patient reported outcomes)
    - Health related quality of life (HRQoL).
    - Functional status.
- Adverse events
    - Allergic reaction (including sensitivity and irritation).
    - Increased pain due to dressing.
    - Skin discolouration.
    - Negative impact on antimicrobial stewardship.

- Other intervention-related adverse events.

- Resource use
  - Cost of the technology.
  - Cost of other resource use including healthcare professional appointments or visits, costs associated with managing wound infection related complications, costs of wound care due to underlying conditions or diseases.

1.3 Research questions

This LSA aims to identify and assess evidence for the clinical and cost effectiveness of AMDs for people with infected leg ulcers being treated in the NHS, to assess whether differences between antimicrobial agents used in AMDs justify price variations. The outcome(s) of the assessment will support NHS procurement and commissioning decisions. To do this, the LSA will address the following research questions:

- What is the clinical effectiveness and safety of different antimicrobial agents and innovative features of AMDs for treating people aged 16 and above with a leg ulcer showing signs and symptoms of local infection? Specifically, what is the comparative effectiveness of different agents:
  - Regardless of dressing type?
  - According to wound presentation (agents within the dressing category regardless of the dressing type in that category)?
  - According to other subgroups as specified in the decision problem?
- Do differences between antimicrobial agents and innovative features of AMDs bring additional benefits and are these worth the cost?
- What is the economic evidence for AMDs in treating adults with a leg ulcer showing signs and symptoms of local infection?

In accordance with Section 4.8 of the NICE interim methods and process statement for LSA [3], we will undertake a rapid evidence review taking a pragmatic approach. A systematic search for relevant published evidence will be conducted, and any relevant evidence supplied by manufacturers as part of NICE's request for company information will be incorporated into the evidence base. The identified evidence will be screened, after which any eligible documents will be prioritised by completeness of outcome data, quality of study conduct, and relevance to an NHS setting.

Relevant data will be extracted from the eligible documents and synthesised, with relevant clinical and health-related quality of life (HRQoL) data informing the parameters of an Excel-based economic model.

At the time of protocol preparation, the possibility of accessing real-world primary care data from the Clinical Practice Research Datalink (CPRD) was raised. The CPRD does not

distinguish between the use of AMDs prophylactically or for infected leg ulcers. Given that prophylactic AMD use is not included in the scope, it is unlikely primary analysis will produce outcomes of interest to this evaluation. We will therefore appraise the real-world registry data provided by NICE and consider whether the data is in scope, and if so, whether it can feasibly be incorporated into the economic model.

The findings of this LSA will inform procurement decisions by establishing whether there are differences in outcomes between different agents used within AMDs, and whether their costs justify these differences.

2 Evidence Review

A rapid evidence review will be conducted to identify evidence relevant to the first three research questions, using methods that conform to the NICE late-stage assessment interim statement [3].

While this is a rapid evidence review rather than a full systematic review, the search will be conducted systematically, using a methodical and pre-planned approach that is transparent and reproducible. The review will be undertaken according to the principles of systematic reviewing published by the Centre for Reviews and Dissemination (CRD) [4].

2.1 Eligibility Criteria

The eligibility criteria for including studies in the evidence review are summarised in **Error! Not a valid bookmark self-reference.** and reflect the decision problem as set out in the NICE Scope.

Table 2.1: Summary of the review eligibility criteria

	Inclusion Criteria	Exclusion Criteria
Population	Studies of people aged≥16 years old with a leg ulcer showing signs and symptoms of local infection. Leg ulcers will be defined as ulcers on the lower leg (between knee and ankle) that have not healed in two weeks [5]. The following subgroups are of interest: People with a comorbidity and whose comorbidity exacerbates an existing leg ulcer infection (herein defined as complex wounds). The type of leg ulcer: venous, vasculitic or phlebolymphoedema The location of the ulcer across the leg. Wound presentation. Studies in mixed populations will be included if at least 80% of the population meet the inclusion criteria for the review, or if results are reported separately for the eligible population.	Children or young people (<16 years old). People with a leg ulcer with systemic or spreading infection (i.e. not localised, as per IWII 2022) [6] People with a leg ulcer at high risk of local infection, but without current infection People with a foot ulcer (including diabetic foot ulcers), who may or may not show signs and symptoms of local infection (see also PA#1) Studies in mixed populations will be excluded if less than 80% of the study population meets the inclusion criteria for the review.
Setting	Primary and community care settings in any country.	Secondary care settings.

	Inclusion Criteria	Exclusion Criteria
	Studies reporting economic evaluations outcomes must be set in the UK or countries with comparable healthcare systems.	Studies reporting economic evaluations outcomes set in other countries.
Intervention	Studies assessing AMDs, available to the NHS on part IX of the drug tariff [7]. Eligible interventions will be categorised by dressing type and by antimicrobial or bacterial binding agent, rather than by individual brand name. The nine eligible agents are: Active antimicrobial agents: Honey Iodine Silver Chlorhexidine Copper PHMB (polyhexamethylene biguanide) Enzyme alginogel Chitosan Octenidine Non-active antiseptic agents with a physical mode of action: Dialkylcarbamoyl chloride (DACC) Eligible categories will include: 1. Alginate, gelling fibre, absorbent fibre 2. Foams, absorbent pads 3. Wound contact layers, gauze, 4. Ointments, gels, hydrogels 5. Hydrocolloid For studies reporting health-related quality of life and/or resource use outcomes, non-interventional primary studies will also be eligible.	Any AMDs not listed.
Comparators	Either: An AMD that is considered current standard of care in the NHS (e.g., based on clinical expert advice and clinical evidence). In most cases the comparator will not feature the additional agent included in the intervention. The comparator may differ between subgroups. These could be comparisons **between** agents, **within** a given category, for example: Alginate honey vs alginate silver	None.

	Inclusion Criteria	Exclusion Criteria
	Gauze DACC vs gauze iodine Comparisons of a standard dressing with an antimicrobial agent, for example: Alginate honey vs alginate Or: No comparator (single arm studies) Comparative studies with only one eligible arm: in this case only the eligible arm will be included in the review	
Outcomes	All outcomes listed in the NICE final scope. https://www.nice.org.uk/guidance/gid-hte10041/documents/final-scope (see also PA#2, Appendix C)	Studies not reporting outcomes listed in the NICE final scope https://www.nice.org.uk/guidance/gid-hte10041/documents/final-scope
Study design	For clinical effectiveness and safety data: RCTs. Cross-over RCTs if data presented at time of cross-over. Non-randomised comparative studies. Single-arm evidence, such as registry data, evaluating at least 10 patients. For economic evaluations data: Cost-effectiveness analyses (including cost-utility analyses). Cost-benefit analyses. Cost-consequence analyses. Cost-minimisation analyses. HTA reports investigating the cost-effectiveness of treatments.	Case series of fewer than 10 patients Case reports Reviews, both systematic and non-systematic.; Any retrieved relevant systematic reviews published in the last 5 years will have their included studies lists checked to identify any relevant studies that may have been missed in the searches
Limits	Studies in the English language only Unpublished studies/reports submitted by companies in confidence Abstracts and conference posters	Studies not in the English language News items, opinion pieces and editorials Preprints Conference abstracts without an accompanying poster or slide presentation, or without an associated full-text publication from the same study (see also PA#3, Appendix C)

2.2 Identifying Relevant Studies

A single set of searches will be conducted to identify evidence on clinical, safety and economic outcomes.

Reflecting the NICE interim methods and process statement for LSA, search methods (including strategy design, selection of search resources and approach to strategy translation) will incorporate some pragmatic elements, as appropriate to the LSA timeline and resource context. Searches will be conducted systematically (the searches will be conducted in a methodical pre-planned way, will be appropriately transparent and reproducible, and will be designed to be appropriately robust for the project context).

2.2.1 Search strategy

A MEDLINE (OvidSP) search strategy designed to identify studies of dressings that use eligible antimicrobial or bacterial-binding agents in patients with leg ulcers is presented in Appendix B. The search strategy is not restricted by outcome or study design and is therefore appropriate for identifying evidence on clinical, safety and economic outcomes.

The strategy comprises three main concepts:

Leg ulcers (search lines 1 to 28).

Non-specific antimicrobial/bacterial-binding dressings (search lines 29 to 38).

Eligible agents (search lines 39 to 105).

The concepts are combined as follows: leg ulcers AND (non-specific antimicrobial/ bacterial-binding dressings OR eligible agents).

The strategy was devised using a combination of subject indexing terms and free text search terms in the Title, Abstract and Keyword Heading Word fields. The search terms were identified through discussion within the research team, scanning background literature, browsing database thesauri and use of the PubMed PubReminer tool (http://hgserver2.amc.nl/cgi-bin/miner/miner2.cgi).

Studies with a leg ulcer population may just refer to a non-specific venous, vasculitic or phlebolymphoedemic ulcer context in the database record. The search terms for the leg ulcers concept are therefore designed to retrieve database records that explicitly refer to either an explicit **leg** ulcer context (search lines 1 to 16) or to non-specific venous, vasculitic or phlebolymphoedema ulcers (search lines 17 to 27).

The search terms for the non-specific antimicrobial/bacterial-binding dressings concept (search lines 29 to 38) are included to retrieve studies on eligible agents where the database record does not explicitly refer to the specific agent. The terms are designed to retrieve database records that refer to antimicrobial/bacterial-binding terms in close association with terms relating to dressings (for example dressing, alginate, film, foam, gauze, hydrogel, hydrocolloid) or topical application.

The search terms for the eligible agents concept (search lines 39 to 105) includes generic terms and brand name terms for each specific agent. A pragmatic approach was used to identify the list of brand names for inclusion. The approach and list of included brand names were agreed with NICE.

The strategy excludes animal studies from MEDLINE using a standard algorithm (search line 109). The strategy also excludes some ineligible publication types which are unlikely to yield relevant study reports (editorials, news items and case reports) and records with the phrase 'case report' in the title (search line 110).

Reflecting the eligibility criteria, the strategy is restricted to studies published in the English language (search line 112). No date limits are applied.

The final Ovid MEDLINE strategy will be peer-reviewed before execution by a second Information Specialist. Peer review will consider the appropriateness of the strategy for the review scope and eligibility criteria, inclusion of key search terms, errors in spelling, syntax and line combinations, and application of exclusions.

2.2.2 Resources to be searched

We will conduct the literature search in the databases shown in Table 2.. The resources include sources of both clinical and economic studies.

Table 2.2: Databases and information sources to be searched

Resource	Interface / URL
Databases	
MEDLINE(R) 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 Ultimate	EBSCOhost
NHS Economic Evaluation Database (NHS EED)	https://www.crd.york.ac.uk/CRDWeb/HomePage.asp
EconLit	OvidSP
Trials Registers	
ClinicalTrials.gov	https://clinicaltrials.gov/
WHO International Clinical Trials Registry Platform (ICTRP)	https://trialsearch.who.int/
Reference list checking	n/a (see below for details)
Company Submission Evidence	n/a (see section 0 for details)

The trials register sources listed above (ClinicalTrials.gov and ICTRP) will be searched to identify information on studies in progress. A number of data providers provide data to WHO for inclusion in ICTRP, including the EU Clinical Trials Register (EU-CTR).

Sources for identifying potentially eligible grey literature include Embase (for conference abstracts), CPCI-S, ClinicalTrials.gov, WHO ICTRP, HTA Database, reference-list checking

and company submission evidence. Reflecting the eligibility criteria, records that are indexed as preprints will be excluded from Embase search results.

We will also check included studies lists of any retrieved relevant systematic reviews published in the last 5 years for any eligible studies that may have been missed by the database searches.

For details of how we will use company submission evidence to identify eligible evidence, see Section 5.

2.2.3 Running the search strategies and downloading results

We will conduct searches using each database or resource listed in the protocol, translating the agreed Ovid MEDLINE strategy appropriately. Translation includes consideration of differences in database interfaces and functionality, in addition to variation in indexing languages and thesauri. The approach taken to strategy translation may incorporate some pragmatic elements, as appropriate to the LSA timeline and resource context. The final translated database strategies will be peer-reviewed by a second Information Specialist. Peer review will consider the appropriateness of the translation for the database being searched, errors in syntax and line combinations, and application of exclusions.

We will document all search strategies and search results and we will provide this in the final report to meet standard requirements for clear formal reporting of the search process. The report of search methods will be informed by the PRISMA-S (Preferred Reporting Items for Systematic reviews and Meta-Analyses literature search extension) checklist [8] and the PRISMA 2020 statement [9, 10].

Where possible, we will download the results of searches in a tagged format and load them into bibliographic software (EndNote) [11]. The results will be deduplicated using several algorithms and the duplicate references held in a separate EndNote database for checking if required. Results from resources that do not allow export in a format compatible with EndNote will be saved in Word or Excel documents as appropriate and manually deduplicated.

2.3 Study selection

Record assessment will be undertaken using pragmatic methods in line with the NICE interim methods and process statement for LSA [3].

A single researcher will assess the search results for relevance to the review and will remove the obviously irrelevant records such as those about ineligible diseases or in children. Where identified, studies in ineligible indications will be grouped for later use in case of a paucity of evidence.

A single reviewer will assess the titles and abstracts of remaining records for relevance against the eligibility criteria, with the first 10% completed in duplicate by an independent second reviewer to ensure consistency.

We will obtain the full text of potentially relevant studies. A single reviewer will assess the full text documents for relevance against the eligibility criteria, with the first 10% completed in

duplicate by an independent second reviewer to ensure consistency (see also PA#4, Appendix C).

We will record the number of records included and removed at each selection stage in the PRISMA flow diagram. We will list studies excluded after assessment of the full document in an excluded studies table, with the reasons for exclusion.

We will obtain electronic or paper copies of potentially relevant full documents meeting the evidence review's eligibility criteria.

Where results for one trial are reported in more than one paper, all related papers will be identified and grouped together to ensure that participants in individual trials are only included once.

2.4 Study prioritisation

If the number of studies identified is large, then we will prioritise clinical studies for inclusion based on the most relevant evidence within each class/category of AMD. We will prioritise:

- Studies reporting prioritised outcomes.
- Studies reporting comparative evidence, and using the most relevant comparators.
- Studies conducted in the UK.

As the relevant healthcare setting is primary and community care, real-world evidence is of significant interest and the search is not restricted by study type or design.

Equally, if few eligible studies are identified we will consider adding broadly relevant evidence identified by the searches but excluded at full text for not meeting all PICO criteria (see also PA#1 and PA#2, Appendix C). This is most likely to consist of including evidence in populations with mixed indications that also include people who are not the target of the NICE Scope, such as people with infected foot ulcers or infected wounds in other locations. We note that since the literature searches were necessarily not designed to retrieve studies in these populations, any evidence from these broader populations will be summarised with caveats regarding the potential for having missed other studies within these broader populations.

For the rapid review of economic evaluations, studies will be eligible if they report total costs, effectiveness (for example QALYs), incremental analyses (for example ICERs) or other economic evaluation outcomes, or measure any relevant cost or resource use (within the economic evaluations) associated with the use of AMDs. Recent studies and those conducted in a UK NHS setting will be prioritised. Reasons for the prioritisation or deprioritisation of evidence will be summarised in the assessment report.

2.5 Data extraction

One researcher will extract data from the included studies and a second researcher will check a random 20% sample of the extracted data.

We will extract data into standardised data tables, with pilot extraction conducted on four studies before progressing to full data extraction.

2.5.1 Clinical Effects and Safety

Data extraction will be targeted. Key patient and study details will be extracted, including bibliographic details, details of study design, and key patient characteristics (including patient age, gender, race / ethnicity (where reported), type and size of ulcer, and healthcare setting). Details of the intervention and comparator assessed will be extracted (dressing agent, category and type), along with the duration of treatment and details of any concomitant treatments.

For each outcome extracted, the timepoint of measurement will also be extracted, along with the authors' description of the outcome.

2.5.2 Economic evaluations

Data extraction will be high-level and will include methods of analysis, model structure, (including health states, time horizon, cycle length, treatment arms and treatment sequencing), main model sources used, model summary outputs including total QALYs, total costs and incremental outcomes if relevant to a UK setting, key scenario analyses, and any major study limitations.

2.6 Quality assessment strategy

One reviewer will assess the risk of bias of the eligible studies in a population with infected leg ulcers using a validated tool specific to the study's design. A second reviewer will check all formal risk of bias assessments. For all other included studies, we will include discussion of any concerns regarding study reliability due to study designs used, and consequently how any risk of bias might have affected key outcomes. The report will also discuss the transferability of results across clinical practice in the NHS.

We will summarise the results of formal risk of bias assessments in a table and provide a detailed assessment in an Appendix to the main report.

For economic evaluations, we will assess the structure of all relevant models to identify those that could be used to inform the modelling approach for this LSA. If we identify multiple models as appropriate, researchers will perform a formal quality assessment of those models using the CHEERs checklist [12]22]. We will not perform formal quality assessment of other relevant models.

2.7 Methods of analysis/synthesis

2.7.1 Clinical Effects and Safety

Studies will be summarised in tables providing data on their methods and results. We will provide a narrative summary exploring the quality of the studies, the relationship between studies and patterns that have been discerned in the data, particularly comparing different antimicrobial agents in AMDs. A comparison of branded dressings of similar type and the same antimicrobial agent is not within scope for this LSA.

We will meta-analyze effect estimates of included studies, should study methods and characteristics be considered similar enough to produce clinically meaningful pooling. We will provide an overall assessment of the strength of the research evidence in relation to the research question.

2.7.2 Economic Evaluations

The methods and results of economic evaluations will be summarised in tables accompanied by a short narrative summary. Utility, cost and resource use outcome data will be passed directly to the EAG modelling team conducting the early model.

2.8 Protocol Amendments

Any essential protocol amendments or clarifications will be recorded in Appendix C. Changes will be made to the text of the protocol and flagged with [PA#].

3 Economic Modelling Methods

3.1 Draft decision problem

We will develop an economic model to evaluate antimicrobial agents used in topical AMDs for people aged 16 or over with a leg ulcer that shows signs and symptoms of local wound infection.

The model will be developed in line with NICE process and methods [13]. The draft decision problem is presented in the table below.

Table 3.1: Key decision elements

Population	People aged 16 or over with a leg ulcer that shows signs and symptoms of local wound infection
Subgroups	If the evidence is available, the following subgroups will be considered: ▪ By aetiology of leg ulcer: venous, vasculitic, phlebolymphoedema. ▪ By wound presentation ▪ Location of ulcer. ▪ Complexities (e.g., comorbidities or medical history) that may impact treatment of leg ulcer infections.
Healthcare setting	Primary and community care settings
Intervention*	AMD available to the NHS on Part IX of the Drug Tariff.
Comparator(s)*	An AMD that is considered standard of care in the NHS identified through evidence review. In most cases the comparator will not feature the additional agent included in the intervention. The comparator may differ between subgroups.
Time horizon	To be confirmed, based on available clinical evidence. The time horizon will be long enough to reflect all important differences in costs or outcomes between the technologies being compared. Note that existing CEMs for leg ulcers have varying time horizons (2 weeks to 12 years) [14]. A common time horizon is 1 year with a cycle length of 1 week.
Measuring and valuing health effects	Health effects (e.g., pain and HRQoL) should be expressed in QALYs. The EQ-5D-3L is the preferred measure of health-related quality of life in adults. A key efficacy outcome highlighted in the scoping workshop was reduction in signs of local infection.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit. This aligns with the NICE health technology evaluations manual. Section 6.2.19 which states that '*medical technologies evaluated through the medical technologies evaluation programme, the concept of a quantitative QALY weight is not applicable'*.
Evidence on resource use and costs	Costs should relate to NHS primary care and community costs.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)
Model outcomes	Probabilistic and deterministic total and incremental costs; quality adjusted life years (QALYs), and life years. Probabilistic and deterministic incremental cost effectiveness ratio (ICER); net monetary benefit (NMB); net health benefit (NHB) Probabilistic and deterministic fully incremental analysis Additional outcomes of interest to be confirmed in order of importance.

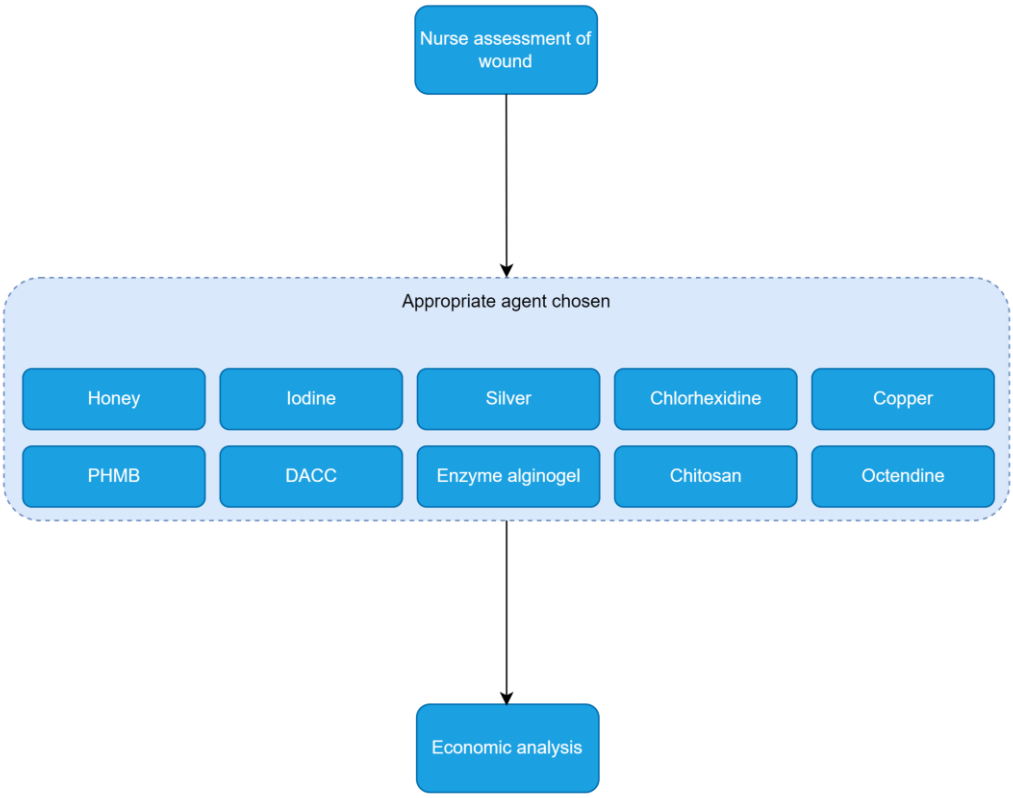
Abbreviations: AMD, antimicrobial dressings; HRQoL, health related quality of life; ICER, incremental cost effectiveness ratio; NHS, National Health Service; NHB, net health benefit; NICE, National Institute for Health and Care Excellence; NMB, net monetary benefit; QALYs, quality adjusted life years.

The model will be built using Microsoft Excel because this is a format that can be easily accessed by all users of the model.

3.2 Intervention and comparators

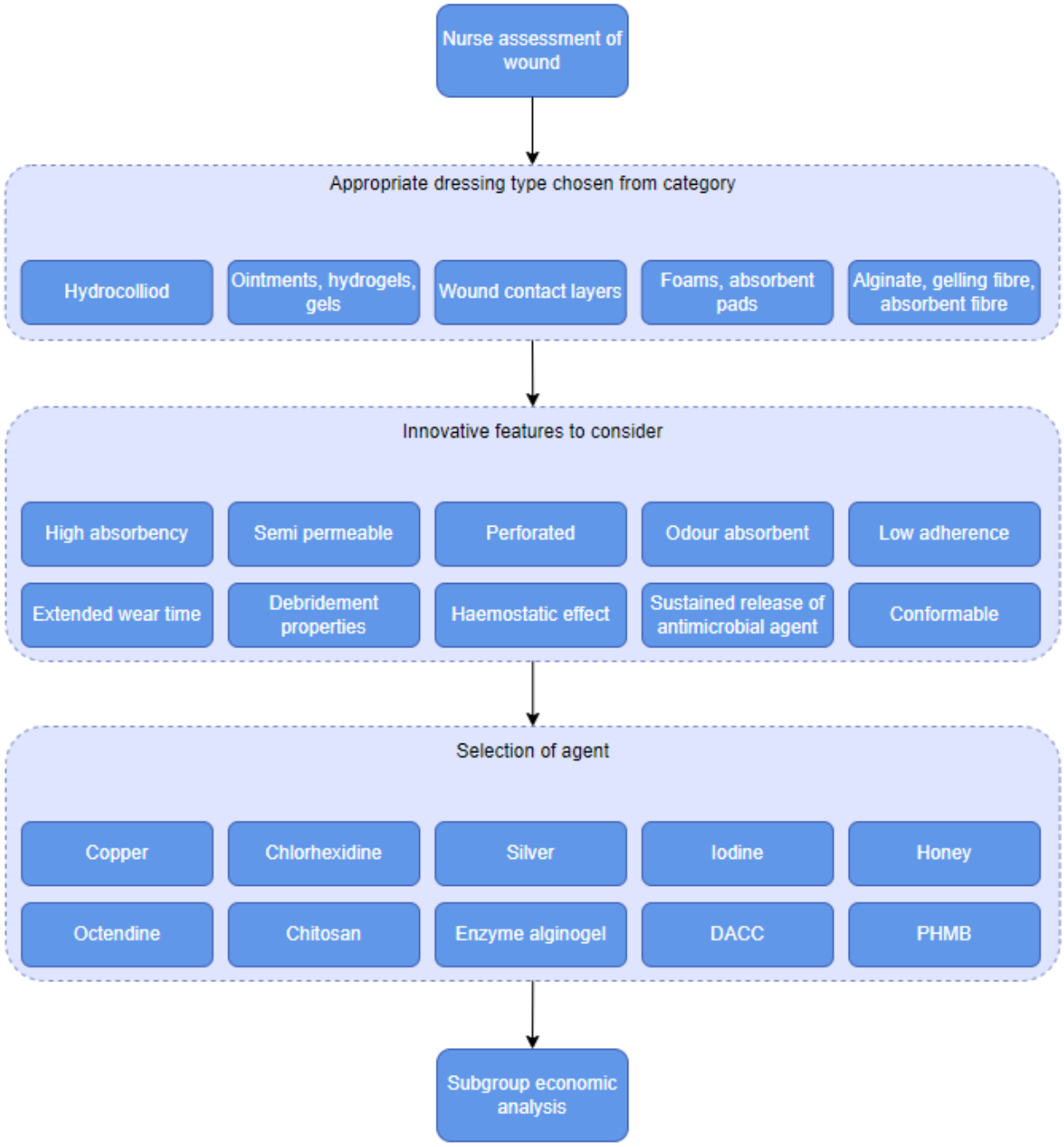
The principal population of interest comprises all people aged 16 and above with a local leg ulcer infection. The economic analysis will therefore aim to answer the research questions in the first instance by comparing all antimicrobial agents. This is outlined in Figure 3.1.

Figure 3.1: Flow diagram illustrating the principal economic analysis of antimicrobial agents in the total population of people aged 16 and above with a leg ulcer showing signs and symptoms of local wound infection.



In a clinical practice setting, it is expected that, before selecting the antimicrobial agent, a clinician will assess the wound, considering the aetiology of the leg ulcer; the location; the wound presentation and complexities. Based upon the clinical assessment, the clinician will select an appropriate type of AMD from one of five categories. If evidence allows, the economic model will conduct subgroup analyses to compare the antimicrobial agents within the dressing types with consideration to any innovative features. See Figure 3.2 for a flow diagram illustrating the types of dressing within each of the five categories, the innovative features and the antimicrobial agents that will be compared.

Figure 3.2: Flow diagram illustrating the economic analysis of antimicrobial agents in subgroups determined by the type of dressing and any innovative features.



3.3 Model structure

Prior to the model being built, we will undertake a development period whereby available data from the existing model structures and from the evidence review will be reviewed to determine an appropriate model structure. At the end of the scoping phase, we will meet with clinical experts to discuss the final structure of the model to be developed and ensure that it reflects NHS practice.

It is anticipated that there may be insufficient data to model some interventions. Published evidence will be used to inform the economic model. The use of real-world evidence from registries, such as CPRD, will be considered if it is found to be appropriate for the decision problem, feasible to include, and within scope.

Any changes in the economic evaluation after this scoping period will be discussed with the NICE team in advance.

The modelling aspects presented here are based on the final scope https://www.nice.org.uk/guidance/gid-hte10041/documents/final-scope and a brief targeted review of literature; this may be subject to change following a wider review of evidence available.

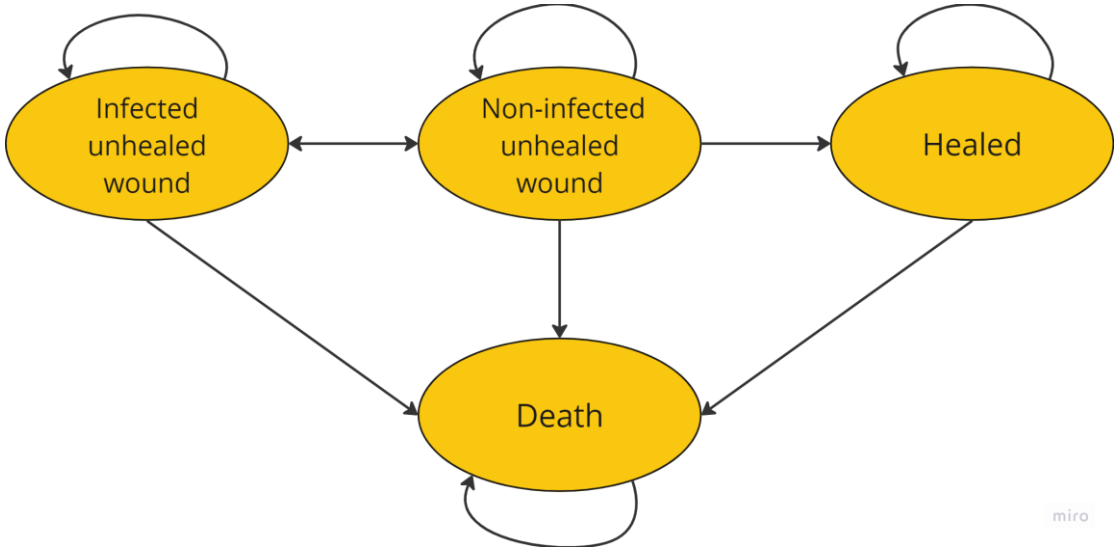
The primary benefit of dressings is infection resolution. The population considered here is people with a leg ulcer with signs or symptoms of local infection with an unhealed wound is likely an appropriate consequence of an unmanaged infection. Therefore, we propose a cohort-based modelling approach using a Markov structure with health states informed by the typical healing pattern of leg ulcers which also incorporates the presence or absence of infection. This suggested approach is also consistent with previous model structures. Please note that the health state definitions will be informed by an appropriate clinical efficacy measure of infection resolution to be confirmed during the scoping phase and validated by clinical experts.

We anticipate that the model structure will include health states that capture non-infected unhealed wound, infected unhealed wound, healed wound and death (see Figure 3.3). Within these states we will capture relevant outcomes conditional on evidence, including short term outcomes such as adverse events and complications of infections.

The method used to determine how the cohort will move between health states (for example, transition matrix or regression model) will be confirmed following a wider review of evidence.

The model structure and all key assumptions will be validated by clinical experts.

Figure 3.3: Preliminary model structure



3.4 Model inputs

Populating a model involves a synthesis of data from multiple sources. All model inputs will be clearly referenced for clarity.

The clinical (for example, dressing effectiveness in reducing infection and adverse events) and HRQoL model parameters will be populated where possible using data from studies such as clinical trials identified during the evidence review (see Section 2.5.2). This data will be supplemented with a targeted search if necessary.

The model will adopt a health service and personal social service cost perspective. Therefore, the main costs are expected to include:

- Acquisition costs of the dressings.
- Drug acquisition costs for antibiotics.
- Healthcare resource use such as community/tissue viability nurse appointments, GP appointments and testing.

Published evidence and all potentially relevant studies identified in the economic review will be assessed for use in the model.

Unit costs to be applied to the resources in each model will be compiled from the latest publicly available sources. Typical sources for the England and Wales include the:

- Part IXA of NHS drug tariff which provides costs for each type / size of dressings [15].
- NHS Reference Costs which provide case payments for hospital-based care [16].

- The Unit Costs of Health and Social Care which provide costs for health and social care resources [17].
- Drugs and pharmaceutical electronic market information tool (eMIT) which provides details on drug acquisition costs and dosing respectively [18].
- The electronic medicines compendium (EMC) which provides details on dosing [19].

3.5 Model outcomes

Probabilistic analysis will be presented as the reference case results of the economic model reference case results as per the NICE processes and methods handbook [13]. This will quantify the level of confidence in the output of the analysis, in relation to uncertainty in the totality of model inputs. In a deterministic analysis, the point estimate of each input parameter value is used. In the probabilistic analysis, these input parameters are represented as distributions around the point estimate. Each distribution will be summarised using specific data outputs (such as mean and standard deviation for a normal distribution). A set of input parameter values will be drawn by random sampling from an appropriate distribution and the model is 'run' to generate outputs (cost and health outcomes). This is repeated many times (typically 1,000 to 10,000 with the exact number of iterations selected based upon a test for stability of results within the model), resulting in a distribution of outputs that can be graphed on the cost-effectiveness plane and inform conclusions.

The key outcome from the probabilistic analysis will be the net health/monetary benefit (NHB/NMB) and incremental cost-effectiveness ratio (ICER), presented as an incremental cost per quality adjusted life year (QALY) gained. This result will be compared against the pre-established NICE cost-effectiveness threshold of £20,000 per QALY gained in a fully incremental analysis to establish which agents are the most efficient use of health care resources.

The results of the probabilistic analysis will be reported as averages per person and their associated confidence intervals. These averages will be used for the fully incremental analysis. The probability of an AMD being cost-effective will also be reported for a range of cost-effectiveness thresholds in a cost-effectiveness acceptability curve (CEAC). The model will also include a deterministic summary of results, a deterministic sensitivity analysis and a deterministic scenario analysis.

The model will output a detailed breakdown of costs and a breakdown of additional efficacy outcomes of interest (both probabilistic and deterministic). Specific efficacy outcomes of interest will be confirmed in the final scope https://www.nice.org.uk/guidance/gid-hte10041/documents/final-scope.

3.6 Quality assurance

Once the model is finalised, it will be subjected to our internal quality assurance procedure, which includes a technical validation and cross validation. The model will be validated by a member of staff completely independent of the project.

The technical validation will focus on checking the formulae to ensure that they are correct and appropriately applied. We will use a standard checklist as a starting point for validation of the model. Any issues or errors noted in the reviews will be documented and will be addressed in the final version of the models. We will also provide the ‘model review checklist’, which is used for the pressure testing of models. In addition to the use of a checklist a cell-by-cell check of the models will be conducted. This will involve error checking each calculation within the model to ensure that there are no functional errors.

Cross validation involves providing a comparison between the results of the models developed for this analysis and any other published models with a similar decision problem that are identified in the evidence review. This type of validation can increase confidence in the results generated by the model. The validation of the analysis will follow the good practice guide as set out by the ISPOR Modelling Task Force [20]. In addition, all outputs are quality assured and signed off by a senior member of the modelling team.

4 Additional information sources

We will consult with clinical experts identified by NICE during the assessment process to provide clarification and guidance on interpreting and prioritising evidence that has been identified as relevant to the assessment, where necessary. Clinical experts may also be asked to contribute opinions on key points of uncertainty that arise from the clinical evidence review and the economic modelling.

5 Handling Information

We will consider any data or evidence supplied by the companies or stakeholders involved. If the data meet the inclusion criteria for the review, they will be considered. It may not be possible to include data received later than 26th July 2024.

Company RFI evidence will be screened against the eligibility criteria outlined in Section 2 and prioritised, data extracted, and quality assessed alongside the identified published literature. Evidence that is supplementary to a study found in the literature searches will be considered as part of the quality assessment for that study.

Any ‘commercial in confidence’ data provided and specified as such will be highlighted in blue and underlined in the assessment report. Any ‘academic in confidence’ data provided will be highlighted in yellow and underlined in the assessment report. Any ’depersonalised data’ (DPD) in the assessment report document will be underlined and highlighted in pink.

If confidential information is included in any economic models produced, then a version using dummy data or publicly available data in place of confidential data will be provided.

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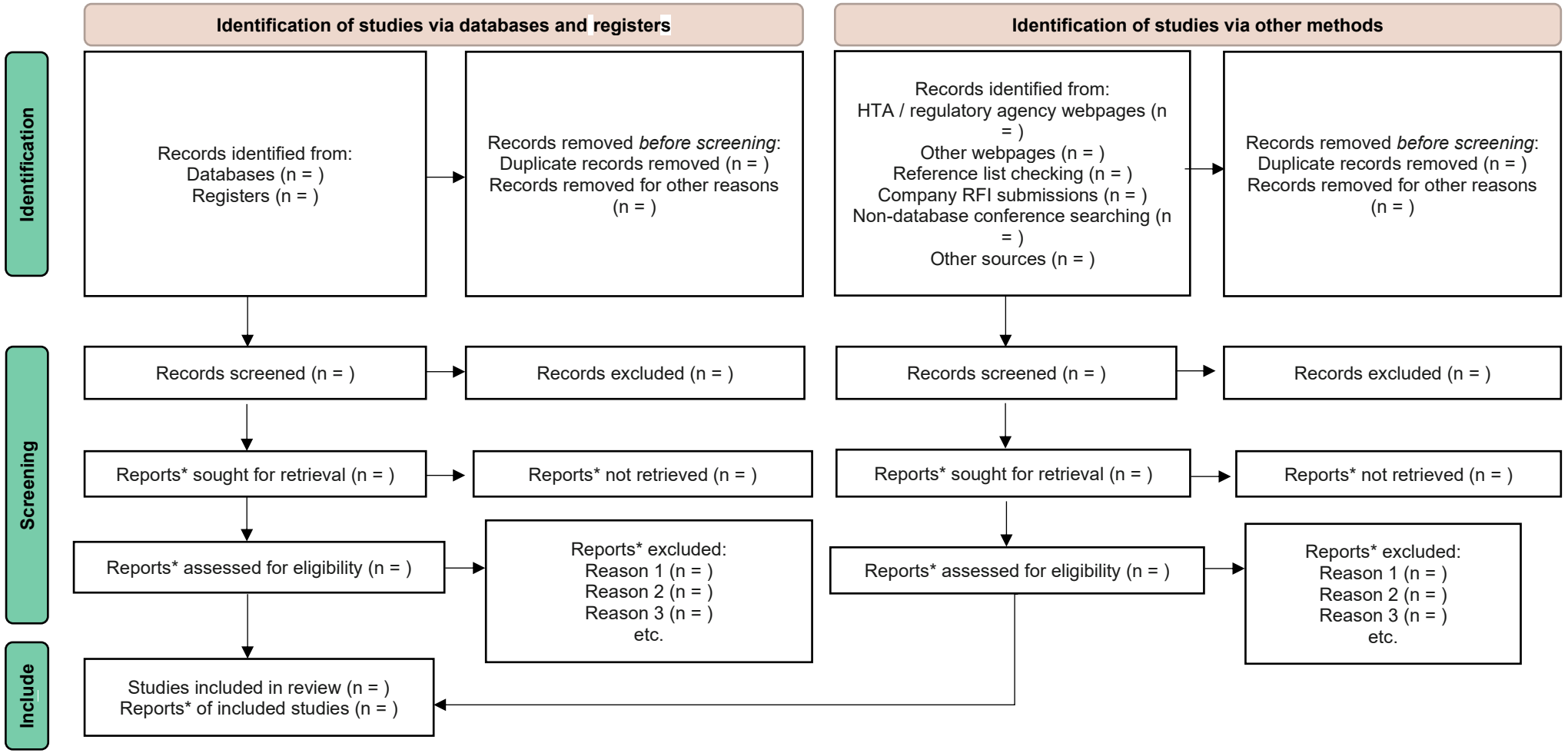
Appendix A – PRISMA Record Selection Process

Figure A.1: PRISMA flow diagram of record selection process [10]



* "Note that a "report" could be a journal article, preprint, conference abstract, study register entry, clinical study report, dissertation, unpublished manuscript, government report or any other document providing relevant information": https://www.bmj.com/content/372/bmj.n71.

Adapted from: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Appendix B – Medline Search Strategy

Figure B.1: Search strategy for Ovid MEDLINE® ALL

1	Leg Ulcer/ (8995)
2	leg/ and (ulcer/ or skin ulcer/ or buruli ulcer/ or pressure ulcer/ or pyoderma gangrenosum/) (1052)
3	(ankle/ or knee/) and (ulcer/ or skin ulcer/ or buruli ulcer/ or pressure ulcer/ or pyoderma gangrenosum/) (122)
4	((leg or legs) adj10 (ulcer* or ulcus)).ti,ab,kf. (9869)
5	((leg or legs) adj10 (bedsore* or decubital or decubitus or sore or sores)).ti,ab,kf. (215)
6	((leg or legs) adj10 ((chronic* or longterm or long term or longlasting or long lasting) adj6 (lesion or lesions or wound or wounds))).ti,ab,kf. (544)
7	((acruris or crural or cruris) adj10 (ulcer* or ulcus)).ti,ab,kf. (628)
8	((acruris or crural or cruris) adj10 (bedsore* or decubital or decubitus or sore or sores)).ti,ab,kf. (12)
9	((acruris or crural or cruris) adj10 ((chronic* or longterm or long term or longlasting or long lasting) adj6 (lesion or lesions or wound or wounds))).ti,ab,kf. (12)
10	((ankle* or calf or calves or gaiter* or knee or knees or shin or shins) adj10 (ulcer* or ulcus)).ti,ab,kf. (1266)
11	((ankle* or calf or calves or gaiter* or knee or knees or shin or shins) adj10 (bedsore* or decubital or decubitus or sore or sores)).ti,ab,kf. (106)
12	((ankle* or calf or calves or gaiter* or knee or knees or shin or shins) adj10 ((chronic* or longterm or long term or longlasting or long lasting) adj6 (lesion or lesions or wound or wounds))).ti,ab,kf. (189)
13	(lower adj3 (extremit* or limb or limbs) adj10 (ulcer* or ulcus)).ti,ab,kf. (3033)
14	(lower adj3 (extremit* or limb or limbs) adj10 (bedsore* or decubital or decubitus or sore or sores)).ti,ab,kf. (91)
15	(lower adj3 (extremit* or limb or limbs) adj10 ((chronic* or longterm or long term or longlasting or long lasting) adj6 (lesion or lesions or wound or wounds))).ti,ab,kf. (368)
16	or/1-15 (18264)
17	Varicose Ulcer/ (5473)
18	((stasis or varicos* or varix or vein* or venous) adj10 (ulcer* or ulcus)).ti,ab,kf. (8481)
19	((stasis or varicos* or varix or vein* or venous) adj10 (bedsore* or decubital or decubitus or sore or sores)).ti,ab,kf. (309)
20	((stasis or varicos* or varix or vein* or venous) adj10 ((chronic* or longterm or long term or longlasting or long lasting) adj6 (lesion or lesions or wound or wounds))).ti,ab,kf. (710)
21	(vascul* adj10 (ulcer* or ulcus)).ti,ab,kf. (3956)
22	(vascul* adj10 (bedsore* or decubital or decubitus or sore or sores)).ti,ab,kf. (86)
23	(vascul* adj10 ((chronic* or longterm or long term or longlasting or long lasting) adj6 (lesion or lesions or wound or wounds))).ti,ab,kf. (686)
24	((lymphedem* or lymphoedem* or phlebolymph*) adj10 (ulcer* or ulcus)).ti,ab,kf. (169)
25	((lymphedem* or lymphoedem* or phlebolymph*) adj10 (bedsore* or decubital or decubitus or sore or sores)).ti,ab,kf. (4)
26	((lymphedem* or lymphoedem* or phlebolymph*) adj10 ((chronic* or longterm or long term or longlasting or long lasting) adj6 (lesion or lesions or wound or wounds))).ti,ab,kf. (49)
27	or/17-26 (14698)
28	16 or 27 (26767)
29	(anti-infective agents/ or anti-bacterial agents/ or disinfectants/ or antisepsis/) and exp Bandages/ (2808)
30	((antibacter* or anti bacter* or antibiofilm* or anti biofilm* or antibiotic* or anti biotic* or antiinfect* or anti infect* or antimicrob* or anti microb* or antimycobacter* or anti mycobacter* or antisep* or anti sep* or bacteriocid* or bactericid* or biocid* or microbicid*) adj6 (dressing or dressings)).ti,ab,kf. (3178)
31	((bacteria* or microb* or mycobacteria*) adj3 bind* adj6 (dressing or dressings)).ti,ab,kf. (14)
32	((antibacter* or anti bacter* or antibiofilm* or anti biofilm* or antibiotic* or anti biotic* or antiinfect* or anti infect* or antimicrob* or anti microb* or antimycobacter* or anti mycobacter* or antisep* or anti sep* or bacteriocid* or bactericid* or biocid* or microbicid*) adj6 (alginat* or balm or balms or bandage* or bead or beads or bioactive or biomaterial* or biosynthetic* or cellulose* or cloth or cloths or collagen* or cotton* or cream or creams or disc or discs or disk or disks or elastin* or fabric or fabrics or fiber or fibers or fibre or fibres or fibrous or film or films or fluid or fluids or foam or foams or gauze* or gel or gels or gelling or gelatin* or hyaluronic or hydrocellular* or hydro

	cellular*or hydrocolloid* or hydro colloid* or hydrofiber* or hydrofibre* or hydrogel* or hydropolymer* or irrigat* or lint or lints or liquid or liquids or matrice* or matrix* or membrane* or mesh* or ointment or ointments or packing* or pad or pads or paste or pastes or patch or patches or plaster or plasters or polyamide* or polyester* or polymer* or polysaccharid* or polyurethane* or powder* or rayon* or ribbon* or rope or ropes or sachet or sachets or seaweed* or sea weed* or sheet or sheets or silicon* or sleeve or sleeves or solution or solutions or sponge or sponges or strip or strips or swab or swabs or tape or tapes or tulle or tulles or wash or washes or wrap or wraps or wrapping*)).ti,ab,kf. (52588)
33	((bacteria* or microb* or mycobacteria*) adj3 bind* adj6 (alginat* or balm or balms or bandage* or bead or beads or bioactive or biomaterial* or biosynthetic* or cellulose* or cloth or cloths or collagen* or cotton* or cream or creams or disc or discs or disk or disks or elastin* or fabric or fabrics or fiber or fibers or fibre or fibres or fibrous or film or films or fluid or fluids or foam or foams or gauze* or gel or gels or gelling or gelatin* or hyaluronic or hydrocellular* or hydro cellular*or hydrocolloid* or hydro colloid* or hydrofiber* or hydrofibre* or hydrogel* or hydropolymer* or irrigat* or lint or lints or liquid or liquids or matrice* or matrix* or membrane* or mesh* or ointment or ointments or packing* or pad or pads or paste or pastes or patch or patches or plaster or plasters or polyamide* or polyester* or polymer* or polysaccharid* or polyurethane* or powder* or rayon* or ribbon* or rope or ropes or sachet or sachets or seaweed* or sea weed* or sheet or sheets or silicon* or sleeve or sleeves or solution or solutions or sponge or sponges or strip or strips or swab or swabs or tape or tapes or tulle or tulles or wash or washes or wrap or wraps or wrapping*)).ti,ab,kf. (703)
34	anti-Infective agents, local/ (18282)
35	(anti-infective agents/ or anti-bacterial agents/ or disinfectants/ or antisepsis/) and (administration, topical/ or administration, cutaneous/) (4255)
36	((antibacter* or anti bacter* or antibiofilm* or anti biofilm* or antibiotic* or anti biotic* or antiinfect* or anti infect* or antimicrob* or anti microb* or antimycobacter* or anti mycobacter* or antisep* or anti sep* or bacteriocid* or bactericid* or biocid* or microbicid*) adj6 topical*).ti,ab,kf. (8550)
37	((bacteria* or microb* or mycobacteria*) adj3 bind* adj6 topical*).ti,ab,kf. (3)
38	or/29-37 (81957)
39	Chlorhexidine/ (9769)
40	chlorhex*.ti,ab,kf,rn,nm,ot. (15418)
41	(chlorohex* or clohex* or clorhex* or mk 412a or mk412a).ti,ab,kf,rn,nm,ot. (426)
42	(chg or chx).ti,ab,kf,rn,nm,ot. (6495)
43	(18472-51-0 or 200-238-7 or 242-354-0 or 36466-50-9 or 3697-42-5 or 55-56-1 or 56-95-1 or 5908zuf22y or 74194-72-2 or e64xl9u38k or mor84mud8e or r4ko0dy52l).ti,ab,kf,rn,nm,ot. (9793)
44	or/39-43 (18789)
45	Copper/ (80638)
46	copper*.ti,ab,kf,rn,nm,ot. (165296)
47	(cuprum metallicum or nanocopper*).ti,ab,kf,rn,nm,ot. (77)
48	(cu or cuo or cuonp or cuonps or nanocuo or nanocuos).ti,ab,kf,rn,nm,ot. (140230)
49	(1344-70-3 or 15158-11-9 or 231-159-6 or 7440-50-8 or 789u1901c5).ti,ab,kf,rn,nm,ot. (80575)
50	medcu*.ti,ab,kf,rn,nm,ot. (3)
51	or/45-50 (245538)
52	(dialkylcarb* or dialkyl carb*).ti,ab,kf,rn,nm,ot. (184)
53	dacc.ti,ab,kf. (1087)
54	sorbact*.ti,ab,kf,rn,nm,ot. (37)
55	or/52-54 (1263)
56	Honey/ (5265)
57	(honey or honeys).ti,ab,kf,rn,nm,ot. (16553)
58	(hy1 or hy 1).ti,ab,kf,rn,nm,ot. (418)
59	(y9h1v576fh or 8028-66-8).ti,ab,kf,rn,nm,ot. (0)
60	Apitherapy/ (203)
61	apitherap*.ti,ab,kf,rn,nm,ot. (148)
62	(actibalm* or actilite* or activon* or algivon* or l-mesitran* or lmesitran* or manuka* or medihoney* or melladerm* or melloxy* or revamil* or surgihoney*).ti,ab,kf,rn,nm,ot. (968)
63	or/56-62 (17744)
64	exp Iodine/ or exp Iodine Compounds/ (103321)
65	iodin*.ti,ab,kf,rn,nm,ot. (136091)
66	(cadexomeriodine* or iodate* or iodide* or iodium* or iodophor* or iodopovidone* or iosal* or jodium* or povidoneiodine* or pvp-i or pvp iodine*).ti,ab,kf,rn,nm,ot. (59250)

67 (25655-41-8 or 85h0hzu99m or 9679tc07x4 or 7553-56-2 or 94820-09-4).ti,ab,kf,rn,nm,ot. (30796)
68 (inadine* or iodoflex* or iodosorb* or povitulle*).ti,ab,kf,rn,nm,ot. (35)
69 or/64-68 (186377)
70 Biguanides/ (3435)
71 (polyhexamethylene* or poly hexamethylene*).ti,ab,kf,rn,nm,ot. (955)
72 (polihexamethylene* or poli hexamethylene*).ti,ab,kf,rn,nm,ot. (0)
73 (polyhexanide* or poly hexanide* or polihexanide* or poli hexanide*).ti,ab,kf,rn,nm,ot. (706)
74 phmb*.ti,ab,kf,rn,nm,ot. (656)
75 (28757-47-3 or 32289-58-0 or 322u039gmf or 4xi6112496).ti,ab,kf,rn,nm,ot. (554)
76 (activheal* or celludress* or kendall* amd* or prontosan* or suprasorb*).ti,ab,kf,rn,nm,ot. (83)
77 or/70-76 (4431)
78 Silver/ or exp Silver Compounds/ or Silver Sulfadiazine/ or Silver Proteins/ (38304)
79 silver*.ti,ab,kf,rn,nm,ot. (99453)
80 ag.ti,ab,kf,rn,nm,ot. (103323)
81 (agnp or agnps or argenti or argentum or nanosilver* or ssd or ssds).ti,ab,kf,rn,nm,ot. (16885)
82 (22199-08-2 or 231-131-3 or 24342-30-1 or 3m4g523w1g or 41034-18-8 or 7440-22-4 or 7761-88-8 or 7783-90-6 or 95it3w8jze or w46jy43ejr).ti,ab,kf,rn,nm,ot. (36016)
83 (acticoat* or actisorb* or algicell* or algisite* or allevyn* or aquacel* or askina* calgitrol* or atrauman* or biatain* or durafiber* or exufiber* or granufoam* or kerracel* or kerracontact* or melgisorb* or mepilex* or polymem* or sorbsan* or tegaderm* alginate* or urgoclean* or urgosorb* or urgotul*).ti,ab,kf,rn,nm,ot. (761)
84 or/78-83 (185158)
85 Alginates/ and Hydrogels/ (2567)
86 Alginates/ and (Lactoperoxidase/ or Glucose Oxidase/) (57)
87 (alginogel* or algino gel*).ti,ab,kf,rn,nm,ot. (11)
88 ((biocatalyst* or catalyst* or enzym*) and (algin or alginic or alginat* or polymannur* or poly mannur*)).ti,ab,kf,rn,nm,ot. (3192)
89 (((glucose adj2 oxidase*) or glucose aerodehydrogenase or glucose oxygen oxidoreductase or glucose oxyhydrase or glucosoxidase or god or gox or microcid or notatin*) and alginat*).ti,ab,kf,rn,nm,ot. (104)
90 ((lactoperoxidase* or lactoperoxydase*) and alginat*).ti,ab,kf,rn,nm,ot. (11)
91 ((algin or alginic or alginat* or polymannur* or poly mannur*) and (gel* or hydrogel*)).ti,ab,kf,rn,nm,ot. (11341)
92 flaminal*.ti,ab,kf,rn,nm,ot. (18)
93 or/85-92 (13574)
94 Chitosan/ (31184)
95 chitosan*.ti,ab,kf,rn,nm,ot. (48221)
96 (deacetylchitin* or deacetylated chitin* or nanochitosan* or poliglusam*).ti,ab,kf,rn,nm,ot. (281)
97 (9012-76-4 or 42617-20-9 or 87582-10-3 or 82lks4qv2y).ti,ab,kf,rn,nm,ot. (31121)
98 maxiocel*.ti,ab,kf,rn,nm,ot. (2)
99 or/94-98 (48312)
100 octenidine*.ti,ab,kf,rn,nm,ot. (484)
101 (las189962 or las-189962).ti,ab,kf,rn,nm,ot. (0)
102 (71251-02-0 or 70775-75-6 or 274-861-8 or 86767-75-1 or oze0372s5a or u84956nu4b or r337868tdw).ti,ab,kf,rn,nm,ot. (278)
103 octenilin*.ti,ab,kf,rn,nm,ot. (24)
104 or/100-103 (487)
105 44 or 51 or 55 or 63 or 69 or 77 or 84 or 93 or 99 or 104 (693750)
106 28 and 38 (608)
107 28 and 105 (664)
108 106 or 107 (1076)
109 exp animals/ not humans/ (5242260)
110 (news or editorial or case reports).pt. or case report.ti. (3391126)
111 108 not (109 or 110) (839)
112 limit 111 to english language (678)

Key to Ovid symbols and commands:

* Unlimited right-hand truncation symbol

ti,ab,kf,rn,nm,ot	Searches are restricted to the Title (ti), Abstract (ab), Keyword Heading Word (kf), Registry Number/Name of Substance (rn) and Name of Substance Word (nm) fields
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/1-15	Combines sets 1 to 15 using OR

Saved in Ovid as: temp-mtac310-lsa-med-protocol-240724

Appendix C – Protocol Amendments

The following protocol amendments (PA) were made subsequent to agreement of the draft protocol. The final protocol was agreed by email on 9th August 2024.

Date of amendment	Protocol Section	PA number	Description of change
07 August 2024	Table 2.1 and Section 2.4	PA#1	**Evidence relating to diabetic foot ulcers** Diabetic foot ulcers will not be included in the economic model. However, should the review fail to identify evidence for any of the listed agents, records retrieved by the searches and relating to infected diabetic foot ulcers will be re-assessed to include those with data relating to agents with no or insufficient evidence.
07 August 2024	Table 2.1 and Section 2.4	PA#2	**Evidence from in-vitro studies** Should the review fail to identify evidence for any of the listed agents, key in-vitro studies for that agent will be identified from the company RFIs and (if necessary) a pragmatic screen of the search results. Any identified studies will be assessed for outcomes suitable as surrogates for the clinical outcomes listed in the decision problem. Any such studies will be incorporated into the evidence base. The suitability of outcomes for use as surrogates will be assessed in accordance with the NICE health technology evaluations manual [21].
07 August 2024	Table 2.1	PA#3	**Screening of conference abstracts** To expedite the screening process, conference abstracts and posters were deprioritised until the end of the screening process. At this point abstracts reporting on agents for which evidence is limited will be prioritised for screening and potential inclusion, if required.
07 August 2024	Section 2.3	PA#4	**Prioritisation of unobtainable papers** After starting record screening, it became apparent that some full text papers would not available via the EAG's normal access routes. Such papers will be grouped and revisited at the end of the screening process, at which point papers reporting on agents for which evidence is limited will be prioritised for access.

PA: Protocol Amendment