National Institute for Health and Care Excellence

Draft for consultation

Joint replacement (primary): hip, knee and shoulder

[H] Evidence review for wound lavage

NICE guideline

Intervention evidence review

October 2019

Draft for Consultation

This evidence review was developed by the National Guideline Centre, hosted by the Royal College of Physicians

Disclaimer

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1.1 Review question: In adults having primary elective joint replacement, what is the clinical and cost effectiveness of antibiotic or antiseptic wound lavage during the procedure?

1.2 Introduction

Wound lavage or irrigation is a washout process routinely used during surgery when performing hip, knee and shoulder replacements. It is used to remove contamination and debris from the site of an operation during the procedure. It is seen as a key part of joint replacement surgery.

In so doing this enables:

1) the clinician to have a clear view of the site.

2) the exposure and preparation of bone surfaces - allowing the adhesive cement, used in the procedure, to penetrate the bone enabling a solid and lasting fix (of the implant).

3) the removal of debris that, potentially, might pass into the blood stream and so to another site in the body.

4) a reduction in microbial contamination of the operative site, potentially reducing infection.

The solution used to washout the area of surgery during joint replacement surgery varies; usually influenced by the surgeon's preference: normal saline, an antiseptic solution or a solution containing antibiotics can be used. However, what is not known is whether the addition of antibiotics and/or antiseptic solutions to the wound lavage fluid help to reduce the risk of infection more effectively than using wound lavage with normal saline solution, alone.

This review focuses on whether antiseptic and/or antibiotic components, when added to the irrigation fluid, are clinically and cost effective when compared to irrigation with saline alone.

1.3 PICO table

For full details, see the review protocol in appendix A.

Table 1: PICO characteristics of review question

Population	Adults having primary elective joint replacement.
Interventions	• Wound lavage with saline and antiseptic agent(s) • Wound lavage with saline and antibiotic agent(s) • Wound lavage with saline and antiseptic and antibiotic agents
Comparisons	• Wound lavage with saline
Outcomes	Critical • Mortality at 30 days • Quality of life • Superficial Surgical site infection • Deep surgical site infection

	Important • Return to theatre • Allergic reaction • Adverse antibiotic reactions • Hospital readmission • Pain • Length of stay
Study design	Randomised controlled trials If no well-conducted RCTs are available, then observational studies with multivariate analysis will be investigated.

1.4 Clinical evidence

1.4.1 Included studies

No relevant clinical studies were identified comparing saline wound lavage with an additional antiseptic and/or antibiotic agent to saline wound lavage without additional agent in adults having primary elective joint replacement. The searches looked for both RCTs and also non-randomised studies.

See also the study selection flow chart in appendix C, study evidence tables in appendix D, forest plots in appendix E and GRADE tables in appendix H.

1.4.2 Excluded studies

See the excluded studies list in appendix I.

1.5 Economic evidence

1.5.1 Included studies

No relevant health economic studies were identified.

1.5.2 Excluded studies

No health economic studies that were relevant to this question were excluded due to assessment of limited applicability or methodological limitations.

1.5.3 Unit costs

Relevant unit costs are provided below to aid consideration of cost effectiveness.

Table 2: UK costs for irrigation solution composition

Active Ingredient	Size	Unit Cost	Cost (per litre)
Sodium chloride 9 mg per 1 ml[(a)]	1000ml	£1.09	£1.09
Chlorhexidine gluconate 5 mg per 1 ml	600ml	£4.72	£7.87
Chlorhexidine gluconate 40 mg per 1 ml	500ml	£5.25	£10.50
Povidone-Iodine 75 mg per 1 ml	500ml	£7.67	£15.34
Vancomycin (as Vancomycin hydrochloride)	500mg	£6.25	£13.59[(b)]

Source: Joint Formulary Committee[9]

(a) Costs only available for 1L bags when 3L more commonly used
(b) When used as a concentration of 1g/L, cost includes 1L saline solution as listed above

Table 3: UK costs for irrigation delivery method

Site of surgery	Brand	Model description	Unit Cost
Hip or Knee	Fannin	Clean disposable pulse lavage system	£21.03
	Tava	Single use pulse lavage system	£21.65
	Morgan Steer	Microaire fan kit including fully-disposable pulse lavage component kit and fan spray tip with splash shield	£34.77
	Ortho Dynamics	Knee or hip kit including fully disposable pulse lavage component kit and shower spray tip with splash shield	£38.40
	MDM Medical ltd	Single use pulse lavage system with knee tip only	£48.87
	No brand listed	Eco hip arthroplasty brush pump lavage kit with suction 702	£50.54

Site of surgery	Brand	Model description	Unit Cost
Shoulder	Rocialle	Sterile 1 litre jug	£0.49
	BD Plastipak	50ml catheter syringe	£0.35

Source: NHS Supply Catalogue 2018[16]

1.6 Evidence statements

1.6.1 Clinical evidence statements

No relevant clinical studies were identified.

1.6.2 Health economic evidence statements

No relevant economic evaluations were identified.

1.7 The committee's discussion of the evidence

1.7.1 Interpreting the evidence

1.7.1.1 The outcomes that matter most

The critical outcomes were agreed to be mortality at 30 days, quality of life (QOL), and superficial and deep surgical site infection. Ultimately this review sought to discover whether wound lavage with antiseptic or antibiotics reduces infections (superficial and deep surgical site) and therefore these were the critical outcomes. Mortality at 30 days and quality of life (QOL) considered were surrogates for infection.

The important outcomes were return to theatre, allergic reaction, adverse antibiotic reactions, hospital readmission, pain and length of stay.

1.7.1.2 The quality of the evidence

No clinical studies relevant to the review question were identified.

1.7.1.3 Benefits and harms

Infections after joint replacement surgery are rare, but when they occur, the cost to the person can be very high, and the financial cost to the NHS is significant. Surgical site infection can lead to catastrophic outcomes, in extreme cases it can result in systemic infection and sepsis resulting in death or it can lead to severe local infection that may necessitate amputation of the affected limb.

The committee discussed how wound lavage/irrigation might reduce surgical site infection. It is thought that a vector of infection is bacteria settling on the wound during surgery and that irrigation of the wound might remove these bacteria and consequently reduces infections. The addition of antibiotics or antiseptics to the irrigation solution has been postulated to increase the anti-infection effect.

The committee accepted that no evidence was found for this evidence review and there was no consensus amongst the committee that the addition of antibiotics or antiseptics to irrigation solution reduces infections. The committee were also concerned this uncertainly of effectiveness would be combined with the potential negative effect of the agents leading to increase antimicrobial resistance.

The committee spoke about the role of irrigation in joint replacement surgery outside of formal infection control. It is used to remove debris generated during the preparation of the joint surfaces so that the surgeon can properly see the operative field and can accurately undertake the surgery. For cemented implants, it is doubly important as it helps to prepare the joint surfaces for cementation as well as helping to reduce the risk of cement embolisation syndrome. Thus, irrigation is an established practice that is currently utilised for more purposes than simply reduction of surgical site infections.

The committee were aware of the wound irrigation and intracavity lavage recommendations in Surgical site infections: prevention and treatment NICE guideline (NG125).[15] The guideline recommends not using wound irrigation or intracavity lavage to reduce the risk of surgical site infection. The committee agreed that current practice for prevention infection includes giving all people having joint replacement surgery prophylactic antibiotics and doing the surgery in ultra clean-air theatres. With this in mind and because of the lack of evidence the committee agreed to recommend not using antibiotic or antiseptic agents in wound lavage for elective joint replacement.

1.7.2 Cost effectiveness and resource use

No economic evaluations were found that matched the protocol. It was discussed that the use of wound lavage is an established part of current practice in joint replacement. The committee noted that saline solution is also used as an irrigation fluid for purposes other than reducing surgical site infection (SSI). Therefore, its use for reducing SSI does not represent an additional cost to a joint replacement operation.

The addition of antiseptics or antibiotics to the wound lavage would represent an additional cost to wound lavage given that their unit costs are greater. However, the additional cost could be unnecessary given that there was no evidence that the addition of antiseptics or antibiotics reduced SSI.

The committee decided against modelling in this area given the lack of clinical evidence.

1.7.3 Other factors the committee took into account

It was acknowledged during the discussions that there would be economic considerations for the methods of lavage. For example, pulsed lavage may cost significantly more than using a jug or syringe due to the equipment and batteries required. However, there was no comparison of the methods of lavage in this evidence review; therefore, no recommendations have been made on this.

NJR data would have been used had the data been analysed and adjusted for confounding factors. No such data were identified.

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Appendices

Appendix A: Review protocols

Table 4: Review protocol: Wound lavage

ID	Field	Content
0.	PROSPERO registration number	Not registered
1.	Review title	Wound lavage during joint replacement
2.	Review question	In adults having primary elective joint replacement, what is the clinical and cost effectiveness of antibiotic or antiseptic wound lavage during the procedure?
3.	Objective	The burden of deep hardware infections continues to rise in orthopaedics; there is increasing interest in strategies for more effective debridement of colonised tissues and biofilm. One method of surgically reducing the bacterial load is irrigation with saline and antiseptic or antibiotic agents, or a combination of the two. It is currently uncertain if use of these agents for wound lavage reduce infections in people undergoing joint replacement surgery. The objective of this review is to assess whether wound lavage reduces infections in people undergoing joint replacement surgery.
4.	Searches	The following databases will be searched: Cochrane Central Register of Controlled Trials (CENTRAL) Cochrane Database of Systematic Reviews (CDSR) Embase MEDLINE Searches will be restricted by: English language Human studies Letters and comments are excluded. Other searches: Inclusion lists of relevant systematic reviews will be checked by the reviewer. The searches may be re-run 6 weeks before final committee meeting and further studies retrieved for inclusion if relevant.

ID	Field	Content
		The full search strategies will be published in the final review.
5.	Condition or domain being studied	Wound lavage during joint replacement
6.	Population	Inclusion: Adults having primary elective joint replacement. Exclusion: Adults having joint replacement as immediate treatment following fracture. Adults having revision joint replacement. Adults having joint replacement as treatment for primary or secondary cancer affecting the bones.
7.	Intervention/Exposure/Test	Wound lavage with saline and antiseptic agent(s) Wound lavage with saline and antibiotic agent(s) Wound lavage with saline and antiseptic and antibiotic agents
8.	Comparator/Reference standard/Confounding factors	Placebo Wound lavage with saline
9.	Types of study to be included	Randomised controlled trials If no well-conducted RCTs are available, then observational studies with multivariate analysis will be investigated.
10.	Other exclusion criteria	Non-English language studies. Abstracts will be excluded as it is expected there will be sufficient full text published studies available.
11.	Context	N/A
12.	Primary outcomes (critical outcomes)	Mortality 30 day (dichotomous) Quality of life (continuous) Superficial surgical site infection (dichotomous) Deep surgical site infection (dichotomous)

ID	Field	Content
13.	Secondary outcomes (important outcomes)	Return to theatre (dichotomous) Allergic reaction (dichotomous) Adverse antibiotic reactions Hospital readmission (dichotomous) Pain (continuous) Length of stay (continuous)
14.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. Titles and/or abstracts of studies retrieved using the search strategy and those from additional sources will be screened for inclusion. The full text of potentially eligible studies will be retrieved and will be assessed for eligibility in line with the criteria outlined above. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. An in-house developed database; EviBase, will be used for data extraction. A standardised form is followed to extract data from studies (see Developing NICE guidelines: the manual section 6.4) and for undertaking assessment of study quality. Summary evidence tables will be produced including information on: study setting; study population and participant demographics and baseline characteristics; details of the intervention and control interventions; study methodology' recruitment and missing data rates; outcomes and times of measurement; critical appraisal ratings. A second reviewer will quality assure the extracted data. Discrepancies will be identified and resolved through discussion (with a third reviewer where necessary).
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. For Intervention reviews the following checklist will be used according to study design being assessed: Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) Randomised Controlled Trial: Cochrane RoB (2.0) Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
16.	Strategy for data synthesis	Where possible, data will be meta-analysed. Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5) to combine the data given in all studies for each of the outcomes stated above. A fixed effect meta-analysis, with weighted mean differences for continuous outcomes and risk ratios for binary outcomes will be used, and 95% confidence intervals will be calculated for each outcome.

ID	Field	Content
		Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. We will consider an I^2 value greater than 50% indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented using random-effects. GRADE pro will be used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. If the population included in an individual study includes children aged under 12, it will be included if the majority of the population is aged over 12, and downgraded for indirectness if the overlap into those aged less than 12 is greater than 20%. Publication bias is tested for when there are more than 5 studies for an outcome. Other bias will only be taken into consideration in the quality assessment if it is apparent. Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. If sufficient data is available to make a network of treatments, WinBUGS will be used for network meta-analysis.
17.	Analysis of sub-groups	Site of joint replacement: knee shoulder hip Lavage type power assisted manual lavage Specific antibiotics utilised, for example vancomycin, gentamycin. Joint Prostheses Cemented

ID	Field	Content			
		non cemented Specific antiseptics utilised, for example (Chlorhexidine, iodine, hydrogen peroxide)			
18.	Type and method of review	☒	Intervention		
		☐	Diagnostic		
		☐	Prognostic		
		☐	Qualitative		
		☐	Epidemiologic		
		☐	Service Delivery		
		☐	Other (please specify)		
19.	Language	English			
20.	Country	England			
21.	Anticipated or actual start date	31/08/18			
22.	Anticipated completion date	20/03/20			
23.	Stage of review at time of this submission	Review stage		Started	Completed
		Preliminary searches		☐	☑
		Piloting of the study selection process		☐	☑
		Formal screening of search results against eligibility criteria		☐	☑
		Data extraction		☐	☑
		Risk of bias (quality) assessment		☐	☑
		Data analysis		☐	☑
24.	Named contact	5a. Named contact National Guideline Centre			

ID	Field	Content
		5b Named contact e-mail 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and the National Guideline Centre
25.	Review team members	From the National Guideline Centre: Mr Carlos Sharpin [Guideline lead] Mr Alex Allen [Senior Systematic Reviewer] Ms Rafina Yarde [Systematic reviewer] Mr Robert King [Health economist] Ms Agnès Cuyàs [Information specialist] Ms Eleanor Priestnall [Project Manager]
26.	Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: [NICE guideline webpage].
29.	Other registration details	
30.	Reference/URL for published protocol	
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: notifying registered stakeholders of publication

ID	Field	Content	
		publicising the guideline through NICE's newsletter and alerts issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
32.	Keywords	Wound lavage, joint replacement, antiseptic agents, antibiotic agents, saline	
33.	Details of existing review of same topic by same authors	N/A	
34.	Current review status	☐	Ongoing
		☒	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
35..	Additional information	N/A	
36.	Details of final publication	www.nice.org.uk	

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Table 5: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2003, abstract-only studies and studies from low or middle-income countries (e.g. most non-OECD countries) or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[14] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example,

	Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2003 or later but that depend on unit costs and resource data entirely or predominantly from before 2003 will be rated as 'Not applicable'. • Studies published before 2003 will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

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Appendix B: Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[14]

For more detailed information, please see the Methodology Review.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the searches where appropriate.

Table 6: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 01 May 2019	Exclusions Randomised controlled trials Systematic review studies Observational studies
Embase (OVID)	1974 – 01 May 2019	Exclusions Randomised controlled trials Systematic review studies Observational studies
The Cochrane Library (Wiley)	Cochrane Reviews to 2019 Issue 5 of 12 CENTRAL to 2019 Issue 5 of 12 DARE, and NHSEED to 2015 Issue 2 of 4 HTA to 2016 Issue 4 of 4	None

Medline (Ovid) search terms

1.	arthroplasty/ or arthroplasty, replacement/ or arthroplasty, replacement, hip/ or arthroplasty, replacement, knee/ or arthroplasty, replacement, shoulder/ or hemiarthroplasty/
2.	joint prosthesis/ or hip prosthesis/ or knee prosthesis/ or shoulder prosthesis/
3.	((joint* or knee* or shoulder* or hip*) adj5 (surger* or replace* or prosthe* or endoprosthe* or implant* or artificial or arthroplast* or hemiarthroplast*)).ti,ab.
4.	or/1-3
5.	letter/
6.	editorial/
7.	news/
8.	exp historical article/
9.	Anecdotes as Topic/
10.	comment/
11.	case report/
12.	(letter or comment*).ti.
13.	or/5-12
14.	randomized controlled trial/ or random*.ti,ab.

15.	13 not 14
16.	animals/ not humans/
17.	exp Animals, Laboratory/
18.	exp Animal Experimentation/
19.	exp Models, Animal/
20.	exp Rodentia/
21.	(rat or rats or mouse or mice).ti.
22.	or/15-21
23.	4 not 22
24.	limit 23 to English language
25.	Therapeutic Irrigation/
26.	(irrigat* or lavage or douch*).ti,ab.
27.	(wound* adj5 (clean* or decontaminat* or soak* or rins* or wash*)).ti,ab.
28.	(water or H2O or saline or solution* or soap* or detergent*).ti,ab.
29.	((Intraoperative or intra-operative or operative or surg*) adj3 (clean* or decontaminat* or soak* or rins* or wash*)).ti,ab.
30.	((medicat* or pump* or power-puls* or puls* or power assist* or assist* or pressure* or manual) adj3 (wash* or clean*)).ti,ab.
31.	Saline Solution, Hypertonic/
32.	Detergents/
33.	Soaps/
34.	Water/
35.	Solutions/
36.	or/25-35
37.	Anti-bacterial agents/
38.	Cephalosporins/
39.	Vancomycin/
40.	Gentamicins/
41.	Bacitracin/
42.	(antibiotic* or anti-biotic* or antibacteri* or anti-bacteri* or cephalosporin* or vancomycin or gentamicin* or bacitracin).ti,ab.
43.	or/37-42
44.	Anti-Infective Agents, Local/
45.	Chlorhexidine/
46.	Hydrogen Peroxide/
47.	Povidone-Iodine/
48.	Iodine/
49.	Hypochlorous Acid/
50.	(antiseptic* or antimicrobi* or anti-microbi* or anti-infecti* or antiinfective or chlorhexidine* or peroxide* or povidone* or iodine or betadine or hypochlor*).ti,ab.
51.	or/44-50
52.	24 and (36 or 43 or 51)
53.	randomized controlled trial.pt.
54.	controlled clinical trial.pt.
55.	randomi#ed.ti,ab.
56.	placebo.ab.

57.	randomly.ti,ab.
58.	Clinical Trials as topic.sh.
59.	trial.ti.
60.	or/53-59
61.	Meta-Analysis/
62.	exp Meta-Analysis as Topic/
63.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
64.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
65.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
66.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
67.	(search* adj4 literature).ab.
68.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
69.	cochrane.jw.
70.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
71.	or/61-70
72.	Epidemiologic studies/
73.	Observational study/
74.	exp Cohort studies/
75.	(cohort adj (study or studies or analys* or data)).ti,ab.
76.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
77.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
78.	Controlled Before-After Studies/
79.	Historically Controlled Study/
80.	Interrupted Time Series Analysis/
81.	(before adj2 after adj2 (study or studies or data)).ti,ab.
82.	or/73-82
83.	exp case control study/
84.	case control*.ti,ab.
85.	or/84-85
86.	83 or 86
87.	Cross-sectional studies/
88.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
89.	or/88-89
90.	83 or 90
91.	83 or 86 or 90
92.	52 and (60 or 71 or 91)

1 Embase (Ovid) search terms

1.	*arthroplasty/ or *replacement arthroplasty/ or *hip replacement/ or *knee replacement/ or *shoulder replacement/ or *hemiarthroplasty/
2.	*joint prosthesis/ or *hip prosthesis/ or *knee prosthesis/ or *shoulder prosthesis/
3.	((joint* or knee* or shoulder* or hip*) adj5 (surger* or replace* or prosthe* or endoprosthe* or implant* or artificial or arthroplast* or hemiarthroplast*)).ti,ab.

4.	or/1-3
5.	letter.pt. or letter/
6.	note.pt.
7.	editorial.pt.
8.	case report/ or case study/
9.	(letter or comment*).ti.
10.	or/5-9
11.	randomized controlled trial/ or random*.ti,ab.
12.	10 not 11
13.	animal/ not human/
14.	nonhuman/
15.	exp Animal Experiment/
16.	exp Experimental Animal/
17.	animal model/
18.	exp Rodent/
19.	(rat or rats or mouse or mice).ti.
20.	or/12-19
21.	4 not 20
22.	limit 21 to English language
23.	lavage/
24.	(irrigat* or lavage or douch*).ti,ab.
25.	(wound* adj5 (clean* or decontaminat* or soak* or rins* or wash*)).ti,ab.
26.	(water or H2O or saline or solution* or soap* or detergent*).ti,ab.
27.	((Intraoperative or intra-operative or operative or surg*) adj3 (clean* or decontaminat* or soak* or rins* or wash*)).ti,ab.
28.	((medicat* or pump* or power-puls* or puls* or power assist* or assist* or pressure* or manual) adj3 (wash* or clean*)).ti,ab.
29.	hypertonic solution/
30.	detergent/
31.	soap/
32.	water/
33.	"solution and solubility"/
34.	or/23-33
35.	antibiotic agent/
36.	cephalosporin derivative/
37.	vancomycin/
38.	gentamicin/
39.	bacitracin/
40.	(antibiotic* or anti-biotic* or antibacteri* or anti-bacteri* or cephalosporin* or vancomycin or gentamicin* or bacitracin).ti,ab.
41.	or/35-40
42.	antiinfective agent/
43.	chlorhexidine/
44.	hydrogen peroxide/
45.	povidone iodine/
46.	iodine/

47.	hypochlorous acid/
48.	(antiseptic* or antimicrobi* or anti-microbi* or anti-infecti* or antiinfective or chlorhexidine* or peroxide* or povidone* or iodine or betadine or hypochlor*).ti,ab.
49.	or/42-48
50.	22 and (34 or 41 or 49)
51.	random*.ti,ab.
52.	factorial*.ti,ab.
53.	(crossover* or cross over*).ti,ab.
54.	((doubl* or singl*) adj blind*).ti,ab.
55.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
56.	crossover procedure/
57.	single blind procedure/
58.	randomized controlled trial/
59.	double blind procedure/
60.	or/51-59
61.	systematic review/
62.	meta-analysis/
63.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
64.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
65.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
66.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
67.	(search* adj4 literature).ab.
68.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
69.	cochrane.jw.
70.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
71.	or/61-70
72.	Clinical study/
73.	Observational study/
74.	family study/
75.	longitudinal study/
76.	retrospective study/
77.	prospective study/
78.	cohort analysis/
79.	follow-up/
80.	cohort*.ti,ab.
81.	80 and 81
82.	(cohort adj (study or studies or analys* or data)).ti,ab.
83.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
84.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
85.	(before adj2 after adj2 (study or studies or data)).ti,ab.
86.	or/73-79,82-86
87.	exp case control study/

88.	case control*.ti,ab.
89.	or/88-89
90.	87 or 90
91.	cross-sectional study/
92.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
93.	or/92-93
94.	87 or 94
95.	87 or 90 or 94
96.	50 and (60 or 71 or 95)

1 **Cochrane Library (Wiley) search terms**

#1.	MeSH descriptor: [Arthroplasty] this term only
#2.	MeSH descriptor: [Arthroplasty, Replacement] this term only
#3.	MeSH descriptor: [Arthroplasty, Replacement, Hip] this term only
#4.	MeSH descriptor: [Arthroplasty, Replacement, Knee] this term only
#5.	MeSH descriptor: [Arthroplasty, Replacement, Shoulder] this term only
#6.	MeSH descriptor: [Hemiarthroplasty] this term only
#7.	(or #1-#6)
#8.	MeSH descriptor: [Joint Prosthesis] this term only
#9.	MeSH descriptor: [Hip Prosthesis] this term only
#10.	MeSH descriptor: [Knee Prosthesis] this term only
#11.	MeSH descriptor: [Shoulder Prosthesis] this term only
#12.	(or #8-#11)
#13.	((joint* or knee* or shoulder* or hip*) near/5 (surger* or replace* or prosthe* or endoprosthe* or implant* or artificial or arthroplast* or hemiarthroplast*)):ti,ab
#14.	(or #7, #12-#13)
#15.	MeSH descriptor: [Therapeutic Irrigation] this term only
#16.	(irrigat* or lavage or douch*):ti,ab
#17.	(wound* near/5 (clean* or decontaminat* or soak* or rins* or wash*)):ti,ab
#18.	(water or H2O or saline or solution* or soap* or detergent*):ti,ab
#19.	((Intraoperative or intra-operative or operative or surg*) near/3 (clean* or decontaminat* or soak* or rins* or wash*)):ti,ab
#20.	((medicat* or pump* or power-puls* or puls* or power assist* or assist* or pressure* or manual) near/3 (wash* or clean*)):ti,ab
#21.	MeSH descriptor: [Saline Solution, Hypertonic] this term only
#22.	MeSH descriptor: [Detergents] this term only
#23.	MeSH descriptor: [Soaps] this term only
#24.	MeSH descriptor: [Water] this term only
#25.	MeSH descriptor: [Solutions] this term only
#26.	(or #15-#25)
#27.	MeSH descriptor: [Anti-Bacterial Agents] this term only
#28.	MeSH descriptor: [Cephalosporins] this term only
#29.	MeSH descriptor: [Vancomycin] this term only
#30.	MeSH descriptor: [Gentamicins] this term only
#31.	MeSH descriptor: [Bacitracin] this term only
#32.	(antibiotic* or anti-biotic* or antibacteri* or anti-bacteri* or cephalosporin* or vancomycin or gentamicin* or bacitracin):ti,ab

#33.	(or #27-#32)
#34.	MeSH descriptor: [Anti-Infective Agents, Local] this term only
#35.	MeSH descriptor: [Chlorhexidine] this term only
#36.	MeSH descriptor: [Hydrogen Peroxide] this term only
#37.	MeSH descriptor: [Povidone-Iodine] this term only
#38.	MeSH descriptor: [Iodine] this term only
#39.	MeSH descriptor: [Hypochlorous Acid] this term only
#40.	(antiseptic* or antimicrobi* or anti-microbi* or anti-infecti* or antiinfective or chlorhexidine* or peroxide* or povidone* or iodine or betadine or hypochlor*):ti,ab
#41.	(or #34-#40)
#42.	#14 and (or #26, #33, #41)

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to the joint replacement population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional health economics searches were run in Medline and Embase.

Table 7: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	2014 – 01 May 2019	Exclusions Health economics studies
Embase	2014 – 01 May 2019	Exclusions Health economics studies
Centre for Research and Dissemination (CRD)	HTA - Inception – 01 May 2019 NHSEED - Inception to March 2015	None

Medline (Ovid) search terms

1.	arthroplasty/ or arthroplasty, replacement/ or arthroplasty, replacement, hip/ or arthroplasty, replacement, knee/ or arthroplasty, replacement, shoulder/ or hemiarthroplasty/
2.	joint prosthesis/ or hip prosthesis/ or knee prosthesis/ or shoulder prosthesis/
3.	((joint* or knee* or shoulder* or hip*) adj5 (surger* or replace* or prosthe* or endoprosthe* or implant* or artificial or arthroplast* or hemiarthroplast*)).ti,ab.
4.	or/1-3
5.	letter/
6.	editorial/
7.	news/
8.	exp historical article/
9.	Anecdotes as Topic/
10.	comment/
11.	case report/
12.	(letter or comment*).ti.
13.	or/5-12

14.	randomized controlled trial/ or random*.ti,ab.
15.	13 not 14
16.	animals/ not humans/
17.	exp Animals, Laboratory/
18.	exp Animal Experimentation/
19.	exp Models, Animal/
20.	exp Rodentia/
21.	(rat or rats or mouse or mice).ti.
22.	or/15-21
23.	4 not 22
24.	limit 23 to English language
25.	Economics/
26.	Value of life/
27.	exp "Costs and Cost Analysis"/
28.	exp Economics, Hospital/
29.	exp Economics, Medical/
30.	Economics, Nursing/
31.	Economics, Pharmaceutical/
32.	exp "Fees and Charges"/
33.	exp Budgets/
34.	budget*.ti,ab.
35.	cost*.ti.
36.	(economic* or pharmaco?economic*).ti.
37.	(price* or pricing*).ti,ab.
38.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
39.	(financ* or fee or fees).ti,ab.
40.	(value adj2 (money or monetary)).ti,ab.
41.	or/25-40
42.	24 and 41

1 Embase (Ovid) search terms

1.	*arthroplasty/ or *replacement arthroplasty/ or *hip replacement/ or *knee replacement/ or *shoulder replacement/ or *hemiarthroplasty/
2.	*joint prosthesis/ or *hip prosthesis/ or *knee prosthesis/ or *shoulder prosthesis/
3.	((joint* or knee* or shoulder* or hip*) adj5 (surger* or replace* or prosthe* or endoprosthe* or implant* or artificial or arthroplast* or hemiarthroplast*)).ti,ab.
4.	or/1-3
5.	letter.pt. or letter/
6.	note.pt.
7.	editorial.pt.
8.	case report/ or case study/
9.	(letter or comment*).ti.
10.	or/5-9
11.	randomized controlled trial/ or random*.ti,ab.

12.	10 not 11
13.	animal/ not human/
14.	nonhuman/
15.	exp Animal Experiment/
16.	exp Experimental Animal/
17.	animal model/
18.	exp Rodent/
19.	(rat or rats or mouse or mice).ti.
20.	or/12-19
21.	4 not 20
22.	limit 21 to English language
23.	health economics/
24.	exp economic evaluation/
25.	exp health care cost/
26.	exp fee/
27.	budget/
28.	funding/
29.	budget*.ti,ab.
30.	cost*.ti.
31.	(economic* or pharmaco?economic*).ti.
32.	(price* or pricing*).ti,ab.
33.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
34.	(financ* or fee or fees).ti,ab.
35.	(value adj2 (money or monetary)).ti,ab.
36.	or/23-35
37.	22 and 36

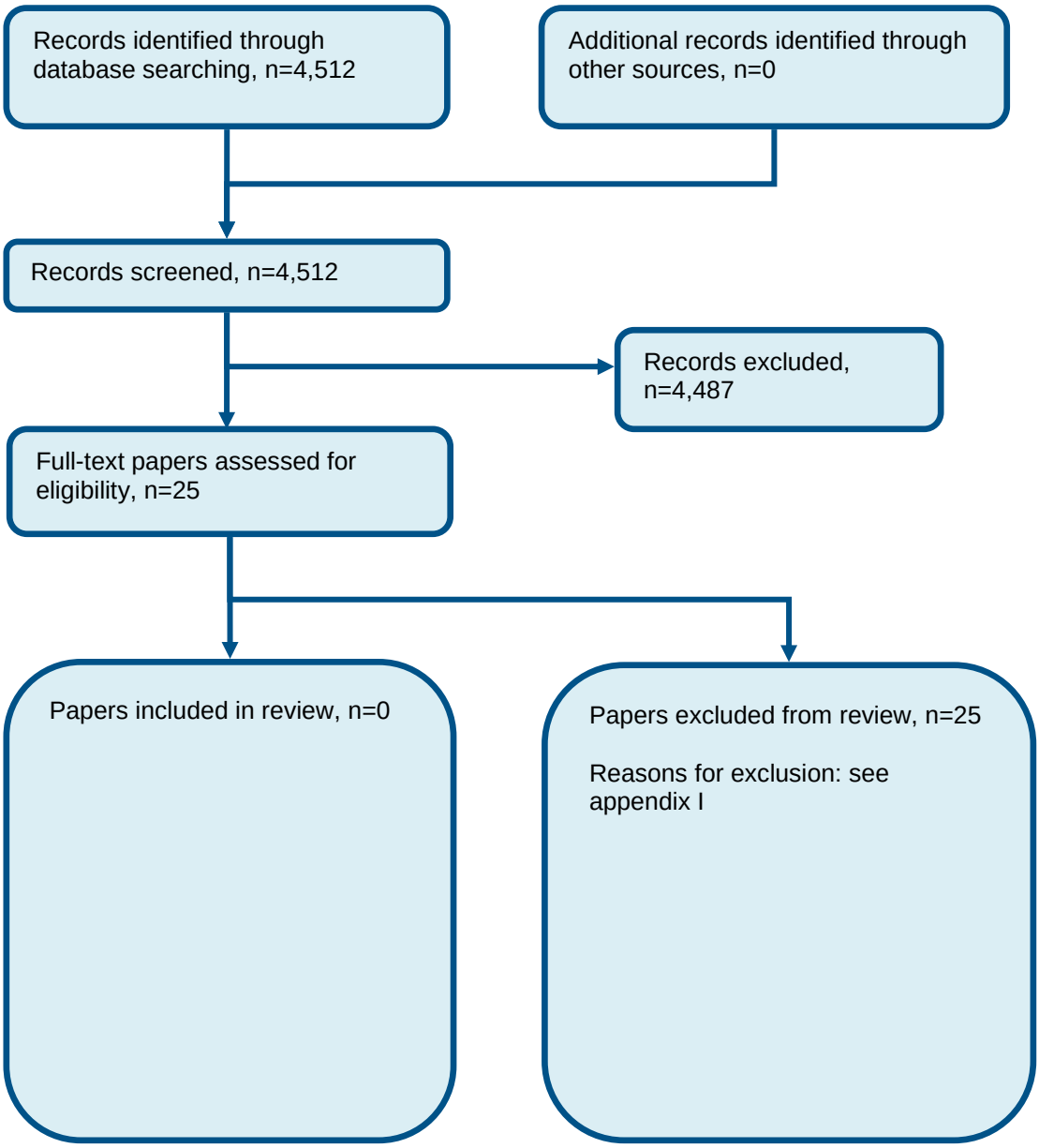
1 NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR arthroplasty
#2.	MeSH DESCRIPTOR arthroplasty, replacement
#3.	MeSH DESCRIPTOR arthroplasty, replacement, hip
#4.	MeSH DESCRIPTOR arthroplasty, replacement, knee
#5.	MeSH DESCRIPTOR arthroplasty, replacement, shoulder
#6.	MeSH DESCRIPTOR hemiarthroplasty
#7.	MeSH DESCRIPTOR joint prosthesis
#8.	MeSH DESCRIPTOR hip prosthesis
#9.	MeSH DESCRIPTOR knee prosthesis
#10.	MeSH DESCRIPTOR shoulder prosthesis
#11.	(((joint* or knee* or shoulder* or hip*) adj5 (surger* or replace* or prosthe* or endoprosthe* or implant* or artificial or arthroplast* or hemiarthroplast*)))

#12.	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11) IN NHSEED
#13.	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11) IN HTA

Appendix C: Clinical evidence selection

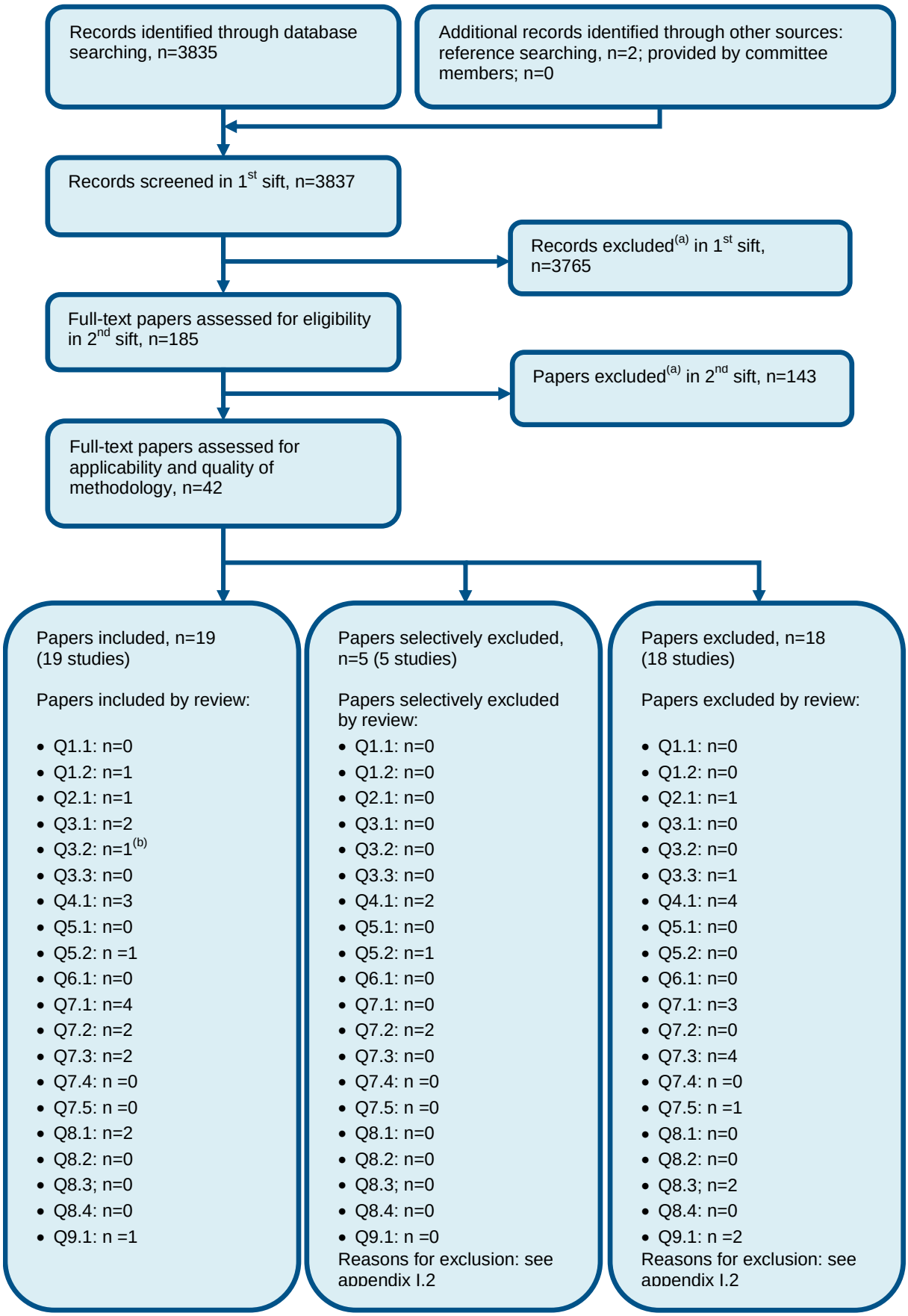
Figure 1: Flow chart of clinical study selection for the review of wound lavage



1

Appendix D: Health economic evidence selection

Figure 2: Flow chart of health economic study selection for the guideline



a) Non-relevant population, intervention, comparison, design or setting; non-English language
b) One study was applicable to both Q3.1 and Q3.2

Appendix E: Excluded studies

E.1 Excluded clinical studies

Table 8: Studies excluded from the clinical review

Abdeldayem 2018[1]	Incorrect comparisons
Anglen 2005[2]	Incorrect population
Brown, 2012[3]	Incorrect analysis for observational studies, not suitably adjusted for confounders
Capito 2017[4]	Incorrect interventions, incorrect population
Ennin 2012[5]	Literature review
Fei 2011[6]	Incorrect comparisons
Frisch, 2017[7]	Multivariate analysis not used
Gupta 2016[8]	Incorrect interventions
Kantak 2017[10]	Incorrect comparisons
Memon 2018[11]	Incorrect interventions
Mont 2000[12]	Incorrect interventions
Moseley 1996[13]	Incorrect population
Norman 2017[17]	Incorrect population
Riesgo 2018[18]	Incorrect population, incorrect intervention
Sneath 2001[19]	Incorrect interventions
Teeny 1990[20]	Incorrect population
Timperley 2009[21]	Literature review
Triantafyllopoulos 2015[22]	Incorrect population
Weenders 2016[23]	Incorrect interventions
Wintzell 1999[24]	Incorrect population, incorrect comparisons
Yazdi 2014[25]	Incorrect population
Zhao 2015[26]	Incorrect comparisons

1