



Intracavity lavage and wound irrigation for prevention of surgical site infection (Protocol)

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[Intervention Protocol]

Intracavity lavage and wound irrigation for prevention of surgical site infection

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the effects of wound irrigation and intracavity lavage on the prevention of surgical site infection (SSI).

BACKGROUND

Description of the condition

Surgical site infections (SSIs) encompass a range of superficial to deep wound infections which can occur after an invasive operative procedure. SSIs are a preventable complication, responsible for substantial financial burden to health services that can result in poorer patient outcomes, increased mortality, morbidity and reoperation rates. A 2006 prevalence survey in the UK National Health Service (NHS) indicated that approximately 8% of all patients (5743/75,694 patients over a four-month period) admitted to hospital suffer healthcare-associated infections, with 15% of these infections being SSIs (Smyth 2008). A US study found that in over 750,000 episodes of surgical hospitalisation, 1% resulted in a SSI, and similar estimates have been found in France (Astagneau 2009; de Lissovoy 2009). However, such values are known to underestimate the levels of SSI by not considering those that de-

velop outside hospitals (Bruce 2001; Gibbons 2011), as most SSIs present within the first 30 days following a procedure, although commonly between the fifth and tenth postoperative day (NICE 2008). Patients who develop SSIs have longer hospital stays and incur higher treatment costs than other patients; in some types of surgery they also have higher mortality rates (Coello 2005; Jenks 2014). Diagnosis with a SSI after hospital discharge is associated with a greater number of healthcare visits, higher resource use, and more readmissions (Perencevich 2003). While more data are available for Western healthcare settings, SSI was the leading cause of hospital-acquired infection in a systematic review of studies in low- and middle-income countries (Allegranzi 2010). While the cause of SSIs is multifactorial, recognised risk factors include: length of hospital stay, obesity, patient co morbidities, duration and complexity of surgery, and degree of wound contamination (Anderson 2008; Chemaly 2010; Edwards 2008; Korol 2013; Omran 2007). Using the classification system adopted by the Centres for Disease Control and Prevention (CDC; HICPAC

1999), wounds can be classified by their level of contamination as follows.

- Clean (Class 1): Noninfective operative wounds in which no inflammation is encountered, with no involvement of respiratory, gastrointestinal, genitourinary tract, and oropharyngeal cavity.
- Clean-contaminated (Class 2): Operative wounds in which either the respiratory, gastrointestinal, or genitourinary tract is entered under controlled conditions and with only minor contamination. This category specifically includes wounds as a result of operations involving the biliary tract, appendix, and oropharynx, provided no evidence of infection or a major break in sterile technique is encountered.
- Contaminated (Class 3): Fresh, accidental wounds, resulting from operations with major breaks in sterile technique or gross spillage from the gastrointestinal tract, and incisions in which acute, nonpurulent (free from pus) inflammation is encountered. This category includes traumatic lacerations.
- Dirty (Class 4): Old traumatic wounds with retained devitalised tissue and those that involve existing clinical infection or perforated viscera. Organisms causing postoperative infection are likely to be present in the operative field before the operation.

The risk of developing a SSI is related to the level of contamination of the wound. Higher classifications of contamination are associated with higher risks of a SSI, as demonstrated in a recent surveillance of surgical infections in NHS hospitals in England which showed that gastrointestinal procedures, especially large bowel surgery, carry the highest risk of bacterial contamination (10.2%) (Public Health England 2014). Conversely, hip and knee prosthesis surgeries were shown to carry the lowest risk of infection, with an occurrence rate of 0.7% and 0.6%, respectively (Public Health England 2014).

Standard definitions of SSIs exist, as described by the CDC, the Surgical Site Infection Surveillance Service, the Southampton wound scoring system, and the ASEPSIS scores (Bailey 1992; Horan 1992; Ridgeway 2005; Wilson 1986). The most commonly applied definition by the CDC describes three levels of SSI (Horan 1992). The lowest level of SSI can be defined as *superficial incisional* infections. These are limited to the skin and subcutaneous tissue. Such infections are identified by localised clinical (Celsian) signs such as redness, pain, heat, swelling, or the drainage of pus. *Deep incisional* infections affect the fascial and muscular layers and are identified by the presence of pus, abscess, fever, localised tenderness, or the separation of incision edges. Finally, *cavity space* infection is considered the most severe level of SSI. Such infections can be identified by the drainage of pus, formation of an abscess or histological, radiological, or visual signs during reoperation. These involve anatomical parts of the body which have been manipulated during a surgical procedure, for example, a joint cavity or the peritoneum. Visceral infection is not included within the scope of the CDC guidelines.

SSIs are not restricted to these definitions and are often accompanied by microbiological evidence from microscopy and culture of infection tissue and fluid. However, it is important to note that normal flora may colonise superficial skin sites, and therefore positive microbiological growth in the absence of clinical signs is rarely indicative of SSIs.

Description of the intervention

Surgical wound irrigation is an intraoperative surgical technique, which may reduce the rate of SSIs by the removal of debris (dead or damaged tissue), metabolic waste, and wound exudate. It aims to create the optimal environment for wound healing, and is used with variable uptake among surgical practitioners (Barnes 2014). The theoretical advantage of surgical wound irrigation is to reduce the bacterial load in a surgical or traumatic wound by a combination of water pressure, dilution, or the application of antimicrobial agents. Usually, this is undertaken at the end of an operative procedure, prior to wound closure, however postoperative wound irrigation may also be applied.

Intracavity lavage is another intraoperative surgical technique which utilises similar principles to surgical wound irrigation, and may reduce the rate of SSIs. It can be adopted during any operation that exposes a bodily cavity, but is most commonly used for procedures on the abdominal (peritoneal) cavity and during joint replacement surgery. Both wound irrigation and intracavity lavage can be altered by three basic variables: volume of irrigation fluid; mechanism/timing of delivery; or solution composition. The terms *irrigation* and *lavage* are used separately in this review, however they do not necessarily describe distinctly separate surgical techniques, and may often refer to similar methods of washout for a cavity or a wound.

How the intervention might work

The aim of wound irrigation is to reduce the bacterial load in a surgical or traumatic wound by a combination of water pressure, dilution, or the application of antimicrobial agents. Usually, this is undertaken at the end of an operative procedure, prior to wound closure, to reduce the likelihood of the introduction of bacteria. Both wound irrigation and intracavity lavage can be achieved using various solutions. Normal saline is commonly used along with antimicrobial agents for intracavity lavage. However, there is concern that antimicrobial agents may damage tissue and prevent normal healing. The theoretical disadvantage of intracavity lavage is the removal of wound exudate, containing growth factors and chemokines (signalling proteins), which may render a patient more susceptible to infection by disrupting normal healing processes. Furthermore, it is thought that the introduction of large volumes of fluid into a cavity or wound could wash away inflammatory cells vital to the host defence (Schultz 2011).

Why it is important to do this review

National Institute for Care and Health Excellence (NICE) guidelines reviewed evidence from 20 randomised controlled trials (RCTs) and concluded that the use of surgical wound irrigation or intracavity lavage could not be recommended to reduce the risk of SSIs (NICE 2008). The search used to inform this guideline is now almost 10 years old, making it likely that a number of additional trials will be available. In some areas of surgical practice this is likely to lead to changes in conclusions; we are aware of a recent systematic review which found a benefit to intraoperative irrigation over no irrigation (Mueller 2015). A recent expert consensus paper also identified the need for more evidence on several of the questions in this review (Barnes 2014). This review aims to update this evidence base.

OBJECTIVES

To assess the effects of wound irrigation and intracavity lavage on the prevention of surgical site infection (SSI).

METHODS

Criteria for considering studies for this review

Types of studies

We will include published and unpublished randomised controlled trials (RCTs), including cluster-RCTs, irrespective of language of report. We will exclude studies using quasi-randomisation (i.e. a method of allocating participants to different forms of care that is not truly random, for example, allocation by date of birth, day of the week, medical record number, month of the year, or the order in which participants are included in the study (alternation)).

Types of participants

All patients undergoing elective or emergency surgery, where surgery is defined as a procedure involving: (1) an incision being made into the skin forming an open wound; or (2) an operative procedure to treat an existing traumatic wound/injury. We will include studies including either, or both adults and children. Only studies focusing on wounds intended to heal by primary intention (i.e. where wound edges are held together after surgery) are included in this review. This would also include interventions for open fractures or operated traumatic wounds if the aim of the procedure was to heal the wound by primary intention. We will exclude wounds healing by secondary intention (i.e. left open to heal

through the formation of new tissues) or wounds healing by delayed primary/tertiary intention (these are both terms for wounds which are intentionally initially left open for a period of time, but then have the edges brought together for the rest of the healing process).

Types of interventions

We will include studies where the type or schedule of intraoperative washout (either wound irrigation or intracavity lavage) is the only systematic difference between study arms.

Surgical wound irrigation may occur as a singular event during wound closure, or involve the irrigation of a wound continuously/repeatedly during surgery, or in the postoperative period. Types of surgical wound irrigation may vary by volume of irrigation fluid, mechanism of delivery, or solution composition.

Intracavity lavage may occur as a singular event during surgery, which exposes a body cavity, or involve the irrigation of a cavity continuously/repeatedly during surgery, or in the postoperative period. Types of intracavity lavage may vary by volume of irrigation fluid, mechanism of delivery, or solution composition.

We anticipate that likely comparisons in this review may include:

- comparison of wound irrigation/intracavity lavage with no washout;
- comparison of different solutions used for wound irrigation or intracavity lavage;
- comparison of different volumes of fluid used for wound irrigation or intracavity lavage;
- comparison of different mechanisms of delivery used for wound irrigation or intracavity lavage; and
- comparison of different schedules/timings of wound irrigation or intracavity lavage.

Types of outcome measures

We list primary and secondary outcome measures below. If a trial is otherwise eligible (correct study design, population, and intervention/comparator) but does not report a listed outcome, then we will contact the study authors, where possible, in order to establish whether a relevant outcome was measured but not reported. However, we do not plan to exclude otherwise eligible studies solely on the basis of reported outcomes.

Where possible, we anticipate grouping outcomes by the following time points; the review authors' judgement will be used as to whether statistical pooling within these time categories is appropriate.

- Short-term: 30 days.
- Medium-term: > 30 days to 12 months.
- Long-term: > 12 months.

Primary outcomes

1. Surgical site infection measured as: occurrence of postoperative surgical site infection (SSI) as defined by the CDC criteria (Horan 2008), or the authors' definition of SSI. We will not differentiate between superficial and deep incisional infection. We will document septicemia or septic shock under this outcome.

2. Wound dehiscence within 30 days of operation. This includes both superficial dehiscence (involving skin and subcutaneous tissues) or deep dehiscence (burst abdomen or dehiscence of fascia). Postoperative wound dehiscence refers to wound disruption resulting from poor wound healing. This may be caused by various factors, including infection, as well as the type of incision and patient characteristics, such as diabetes or smoking (Sandy-Hodgetts 2015).

Secondary outcomes

- 30-day mortality/in-hospital mortality
- Proportion of participants with postoperative SSI using systemic antibiotics within 30 days of surgery
 - Occurrence of infections which show antibiotic resistance
 - Adverse events including postoperative abscess formation; these will be included where reported as total number of individuals with an adverse event in each intervention group
 - Surgical re-intervention rates (including the placement of radiologically-guided drains and joint revision surgery)
 - Mean length of hospital stay
 - Number of hospital readmissions.

Search methods for identification of studies

Electronic searches

We will search the following electronic databases for randomised controlled trials:

- The Cochrane Wounds Specialised Register (to present).
- The Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library) (latest issue).
 - Ovid MEDLINE (1946 to present).
 - Ovid MEDLINE (In-Process & Other Non-Indexed Citations) (latest issue).
 - Ovid EMBASE (1974 to present).
 - EBSCO CINAHL Plus (1937 to present).

The draft search strategy for CENTRAL is presented in [Appendix 1](#). We will adapt this strategy to search Ovid MEDLINE, Ovid EMBASE, and EBSCO CINAHL.

We will combine the Ovid MEDLINE search with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision) (Lefebvre 2011). We will combine the EMBASE

search with the Ovid EMBASE randomised trials filter terms developed by the UK Cochrane Centre (Lefebvre 2011). We will combine the CINAHL searches with the randomised trials filter terms developed by the Scottish Intercollegiate Guidelines Network (SIGN 2015). We will not impose any restrictions with respect to language, date of publication, or study setting.

We will also search the following clinical trials registries for ongoing studies:

- ClinicalTrials.gov (<http://www.clinicaltrials.gov/>).
- The World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (<http://apps.who.int/trialsearch/Default.aspx>).
- The European Union (EU) Clinical Trials Register (<https://www.clinicaltrialsregister.eu/>).

Searching other resources

We will try to identify other potentially eligible trials or ancillary publications by searching the reference lists of retrieved included trials as well as relevant systematic reviews, meta-analyses, and health-technology assessment reports.

Data collection and analysis

Selection of studies

Two review authors (CR and either TS or GN) will independently assess the titles and abstracts of the citations retrieved by the searches for relevance. After this initial assessment, we will obtain full-text copies of all studies considered to be potentially relevant. Two review authors (CR and TS) will independently check the full papers for eligibility; disagreements will be resolved by discussion and, where required, the input of a third review author (GN). Where required and possible, we will contact study authors where the eligibility of a study is unclear. We will record all reasons for exclusion of studies for which we had obtained full copies. We will complete a PRISMA flowchart to summarise this process (Liberati 2009).

Where studies have been reported in multiple publications/reports, we will obtain all publications. Whilst we will include the study only once in the review, we will extract data from all reports to ensure maximal relevant data is obtained.

Data extraction and management

We will extract and summarise details of the eligible studies using a data extraction sheet. Two review authors (CR and TS) will extract data independently and will resolve disagreements by discussion, drawing on a third review author (GN or JD) where required. Where data are missing from reports, we will attempt to contact the study authors to obtain this information. Where a study with

more than two intervention arms is included, we will only extract data from intervention and control groups that meet the eligibility criteria.

We will extract the following data, where possible, by treatment group for the prespecified interventions and outcomes in this review. We will collect outcome data for relevant time points, as described in [Types of outcome measures](#).

- Country of origin.
- Type of wound and surgery.
- Unit of randomisation (e.g. patient or wound).
- Unit of analysis (e.g. patient or wound).
- Trial design e.g. parallel; cluster.
- Number of participants/wounds randomised to each trial arm.
- Eligibility criteria and key baseline participant data.
- Details of treatment regimen received by each group.
- Duration of treatment.
- Details of any co-interventions.
- Primary and secondary outcome(s) (with definitions and time points).
 - Outcome data for primary and secondary outcomes (by group).
 - Duration of follow-up.
 - Number of withdrawals (by group).
 - Publication status of study.
 - Source of funding for trial.

Assessment of risk of bias in included studies

Two review authors (CR and TS) will independently assess included studies using the Cochrane approach for assessing risk of bias as detailed in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). Disagreements will be resolved through discussion or by consulting a third review author (GN or JD). The tool addresses specific domains: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, incomplete data, selective outcome reporting, and other issues - in this review we will record issues with unit of analysis, for example, where a cluster trial has been undertaken but analysed at the individual level in the study report (Appendix 2). We will assess blinding and completeness of outcome data for each of the review outcomes separately. In this review we anticipate that blinding of participants and personnel may not be possible. For this reason the assessment of the risk of detection bias will focus on whether blinded outcome assessment was reported (because assessment of wound outcomes, such as breakdown and healing, can be subjective and at high risk of detection bias when outcome assessment is not blinded). We will use blinding of outcome assessment to determine risk of bias from blinding in these instances. We will present our assessment of risk of bias using two 'Risk of bias' summary figures; one which is a summary of bias for each item across all studies, and a second

which shows a cross-tabulation of each trial by all of the risk of bias items.

For trials using cluster-randomisation, we will also consider the risk of bias considering: recruitment bias, baseline imbalance, loss of clusters, incorrect analysis, and comparability with individually randomised trials (Higgins 2011b; Appendix 3).

Measures of treatment effect

For dichotomous outcomes, we will calculate the risk ratio (RR) with 95% confidence intervals (CIs). For continuous outcomes we will use the mean difference (MD) with 95% CIs, if all trials use the same or similar assessment scale. If trials use different assessment scales, we will use the standardised mean difference (SMD) with 95% CIs.

Unit of analysis issues

Where studies randomise at the participant level and measure outcomes at the wound level we will treat the participant as the unit of analysis when the number of wounds assessed appears equal to the number of participants (e.g. one wound per person).

Particular unit of analysis issues in wound care trials can occur when: (1) studies randomise at the participant level, use the allocated treatment on multiple wounds per participant, and then analyse outcomes per wound; or (2) studies undertake multiple assessments of an outcome over time per participant. These approaches should be treated as cluster trials, alongside more standard cluster designs - such as delivery of interventions at an organisational level.

Where a cluster trial has been conducted and correctly analysed, effect estimates and their standard errors may be meta-analysed using the generic inverse-variance method in Review Manager 5 (RevMan 2014).

We will record where a cluster-randomised trial has been conducted, but incorrectly analysed. We will record this as part of the 'Risk of bias' assessment. If possible, we will approximate the correct analyses based on guidance from the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b), using information on:

- the number of clusters (or groups) randomised to each intervention group; or the average (mean) size of each cluster;
- the outcome data ignoring the cluster design for the total number of individuals (for example, number or proportion of individuals with events, or means and standard deviations); and
- an estimate of the intra cluster (or intra class) correlation coefficient (ICC).

If we cannot analyse the study data correctly, we will extract and present outcome data but not analyse it further.

Dealing with missing data

It is common to have data missing from trial reports. Excluding participants post-randomisation from the analysis, or ignoring those participants who are lost to follow-up compromises the randomisation, and potentially introduces bias into the trial. Where there are missing data that we think should be included in the analyses, we will contact relevant study authors to request whether these data are available.

Where data remain missing for the proportion of participants with dehisced wounds or participants with SSI, we will assume that if randomised participants were not included in the results section of the paper, that their wound did not show dehiscence or that they did not have an SSI (i.e. in the analysis, missing participants would be considered in the denominator but not the numerator). If appropriate, we will conduct a completed case analysis as a sensitivity analysis and will also explore alternative scenarios using different assumptions about missing cases.

For continuous variables e.g. length of hospital stay, and for all secondary outcomes, we will present available data from the study reports/study authors, but we do not plan to impute missing data. Where measures of variance are missing, we will calculate these wherever possible. If calculation is not possible, we will contact study authors. Where these measures of variation are not available, we will exclude the study from any relevant meta-analyses that we conduct.

Assessment of heterogeneity

Assessment of heterogeneity can be a complex, multifaceted process. Firstly, we will consider clinical and methodological heterogeneity: that is, the degree to which the included studies vary in terms of participant, intervention, outcome, and characteristics such as duration of follow-up. We will supplement this assessment of clinical and methodological heterogeneity by information regarding statistical heterogeneity - assessed using the Chi^2 test (we will consider a significance level of $P < 0.10$ to indicate statistically significant heterogeneity) in conjunction with the I^2 measure (Higgins 2003). I^2 examines the percentage of total variation across RCTs that is due to heterogeneity rather than chance (Higgins 2003). In general, I^2 values of 25%, or less, can be interpreted as a low level of heterogeneity (Higgins 2003), and values of 75% or more, indicate very high heterogeneity (Deeks 2011). However, these figures are only a guide, and it has been recognised that statistical tests and metrics may miss important heterogeneity - thus, whilst these will be assessed, the overall assessment of heterogeneity will assess these measures in combination with the methodological and clinical assessment of heterogeneity: see [Data synthesis](#) for further information about how we will deal with potential heterogeneity in the data analyses.

Assessment of reporting biases

Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results. Publication bias is one of a number of possible causes of 'small study effects', that is, a tendency for estimates of the intervention effect to be more beneficial in smaller RCTs. Funnel plots allow a visual assessment of whether small study effects may be present in a meta-analysis. A funnel plot is a simple scatter plot of the intervention effect estimates from individual RCTs against some measure of each trial's size or precision (Sterne 2011). We plan to present funnel plots for meta-analyses comprising 10 RCTs or more using Review Manager 5 (RevMan 2014).

Data synthesis

We will combine details of included studies in narrative review according to type of comparator, possibly by location of/type of wound, and then by outcomes by time period. We will consider clinical and methodological heterogeneity, and undertake pooling when studies appear appropriately similar in terms of wound type, intervention type, duration of follow-up, and outcome type.

In terms of meta-analytical approach, our default approach will be to use the random-effects model. We will only use a fixed-effect approach when clinical heterogeneity is thought to be minimal and statistical heterogeneity is not statistically significant for the Chi^2 value and 0% for the I^2 assessment (Kontopantelis 2013). We will adopt this approach as it is recognised that statistical assessments can miss potentially important between-study heterogeneity in small samples, hence the preference for the more conservative random-effects model (Kontopantelis 2012). Where clinical heterogeneity is thought to be acceptable, or of interest, we may meta-analyse even when statistical heterogeneity is high, but we will attempt to interpret the causes behind this heterogeneity, and will consider using meta-regression for that purpose, if possible (Thompson 1999).

We will present data using forest plots, where possible. For dichotomous outcomes, we will present the summary estimate as a RR with 95% CI. Where continuous outcomes are measured in the same way across studies, we plan to present a pooled MD with 95% CI; we plan to pool SMD estimates where studies measure the same outcome, but use different methods. For time to event data, we plan to plot (and, if appropriate, pool) estimates of hazard ratios and 95% CIs, as presented in the study reports, using the generic inverse variance method in Review Manager 5 (RevMan 2014). Where time to healing is analysed as a continuous measure but it is not clear if all wounds healed, we will document use of the outcome in the study, but we will not summarise or use data in any meta-analysis.

We will obtain pooled estimates of treatment effect using Cochrane Review Manager 5 software (RevMan 2014).

'Summary of findings' tables

We will present the main results of the review in 'Summary of findings' tables. These tables present key information concerning the quality of the evidence, the magnitude of the effects of the interventions examined, and the sum of the available data for the main outcomes (Schunemann 2011a). The 'Summary of findings' tables also include an overall grading of the evidence related to each of the main outcomes using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach. The GRADE approach defines the quality of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the true quantity of specific interest. The quality of a body of evidence involves consideration of within-trial risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates, and risk of publication bias (Schunemann 2011b). We plan to present the following primary outcomes in the 'Summary of findings' tables.

- Surgical site infection (SSI).
- Wound dehiscence within 30 days of operation.

Subgroup analysis and investigation of heterogeneity

Where feasible, we will explore the effects of interventions in children (aged under 18) and adults separately. If possible, we will additionally explore the effects of interventions according to classification of wound contamination (clean, clean-contaminated, contaminated, dirty).

Where possible, we plan to perform sensitivity analyses to explore the effect of the following criteria.

- Studies at high risk of bias for any domain compared with other studies with no domain classed at high risk of bias.
- Studies at high risk of detection bias compared with other studies.

Elements of this Methods section are based on the standard Cochrane Wounds Protocol Template.

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* Indicates the major publication for the study

APPENDICES

Appendix I. The Cochrane Central Register of Controlled Trials (CENTRAL) provisional search strategy

- #1 MeSH descriptor: [Surgical Wound Infection] explode all trees
- #2 MeSH descriptor: [Surgical Wound Dehiscence] explode all trees
- #3 (surg* near/5 infect*):ti,ab,kw
- #4 (surg* near/5 wound*):ti,ab,kw
- #5 (surg* near/5 site*):ti,ab,kw
- #6 (surg* near/5 incision*):ti,ab,kw
- #7 (surg* near/5 dehisc*):ti,ab,kw
- #8 (wound* near/5 dehisc*):ti,ab,kw
- #9 (wound* near/5 infect*):ti,ab,kw
- #10 (wound near/5 disruption*):ti,ab,kw
- #11 (wound next complication*):ti,ab,kw
- #12 SSI:ti,ab,kw

#13 {or #1-#12}
#14 MeSH descriptor: [Therapeutic Irrigation] explode all trees
#15 (intraoperative near/3 wash*):ti,ab,kw
#16 (intra-operative near/3 wash*):ti,ab,kw
#17 irrigat*:ti,ab,kw
#18 lavage:ti,ab,kw
#19 {or #14-#18}
#20 {and #13, #19} in Trials

Appendix 2. Risk of bias assessment (individually randomised controlled trials)

1. Was the allocation sequence randomly generated?

Low risk of bias

The investigators describe a random component in the sequence generation process such as: referring to a random number table; using a computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots.

High risk of bias

The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example: sequence generated by odd or even date of birth; sequence generated by some rule based on date (or day) of admission; sequence generated by some rule based on hospital or clinic record number.

Unclear

Insufficient information about the sequence generation process to permit judgement of low or high risk of bias.

2. Was the treatment allocation adequately concealed?

Low risk of bias

Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation: central allocation (including telephone, web-based and pharmacy-controlled randomisation); sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes.

High risk of bias

Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on: use of an open random allocation schedule (e.g. a list of random numbers); assignment envelopes without appropriate safeguards (e.g. envelopes were unsealed, non-opaque, or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.

Unclear

Insufficient information to permit judgement of low or high risk of bias. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement, for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed.

3. Blinding - was knowledge of the allocated interventions adequately prevented during the study?

Low risk of bias

Any one of the following:

- No blinding, but the review authors judge that the outcome and the outcome measurement are not likely to be influenced by lack of blinding.
- Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
- Either participants or some key study personnel were not blinded, but outcome assessment was blinded and the non-blinding of others unlikely to introduce bias.

High risk of bias

Any one of the following:

- No blinding or incomplete blinding, and the outcome or outcome measurement is likely to be influenced by lack of blinding.
- Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken.
- Either participants or some key study personnel were not blinded, and the non-blinding of others likely to introduce bias.

Unclear

Either of the following:

- Insufficient information to permit judgement of low or high risk of bias.
- The study did not address this outcome.

4. Were incomplete outcome data adequately addressed?

Low risk of bias

Any one of the following:

- No missing outcome data.
- Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias).
- Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups.
- For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate.
- For continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size.
- Missing data have been imputed using appropriate methods.

High risk of bias

Any one of the following:

- Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups.
- For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate.
- For continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size.
- 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation.
- Potentially inappropriate application of simple imputation.

Unclear

Either of the following:

- Insufficient reporting of attrition/exclusions to permit judgement of low or high risk of bias (e.g. number randomised not stated, no reasons for missing data provided).
- The study did not address this outcome.

5. Are reports of the study free of suggestion of selective outcome reporting?

Low risk of bias

Either of the following:

- The study protocol is available and all of the study's prespecified (primary and secondary) outcomes that are of interest in the review have been reported in the prespecified way.
- The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were prespecified (convincing text of this nature may be uncommon).

High risk of bias

Any one of the following:

- Not all of the study's prespecified primary outcomes have been reported.
- One or more primary outcomes are reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not prespecified.
- One or more reported primary outcomes were not prespecified (unless clear justification for their reporting is provided, such as an unexpected adverse effect).
- One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis.
- The study report fails to include results for a key outcome that would be expected to have been reported for such a study.

Unclear

Insufficient information to permit judgement of low or high risk of bias. It is likely that the majority of studies will fall into this category.

6. Other sources of potential bias

Low risk of bias

The study appears to be free of other sources of bias.

High risk of bias

There is at least one important risk of bias. For example, the study:

- had a potential source of bias related to the specific study design used; or
- has been claimed to have been fraudulent; or
- had some other problem.

Unclear

There may be a risk of bias, but there is either:

- insufficient information to assess whether an important risk of bias exists; or
- insufficient rationale or evidence that an identified problem will introduce bias.

Appendix 3. Risk of bias assessment (cluster-randomised controlled trials)

In cluster-randomised trials, particular biases to consider include: (i) recruitment bias; (ii) baseline imbalance; (iii) loss of clusters; (iv) incorrect analysis; and (v) comparability with individually randomised trials.

(i) Recruitment bias can occur when individuals are recruited to the trial after the clusters have been randomised, as the knowledge of whether each cluster is an 'intervention' or 'control' cluster could affect the types of participants recruited.

(ii) Cluster-randomised trials often randomise all clusters at once, so lack of concealment of an allocation sequence should not usually be an issue. However, because small numbers of clusters are randomised, there is a possibility of chance baseline imbalance between the randomised groups, in terms of either the clusters or the individuals. Although not a form of bias as such, the risk of baseline differences can be reduced by using stratified or pair-matched randomisation of clusters. Reporting of the baseline comparability of clusters, or statistical adjustment for baseline characteristics, can help reduce concern about the effects of baseline imbalance.

(iii) Occasionally, complete clusters are lost from a trial, and have to be omitted from the analysis. Just as for missing outcome data in individually randomised trials, this may lead to bias. In addition, missing outcomes for individuals within clusters may also lead to a risk of bias in cluster-randomised trials.

(iv) Many cluster-randomised trials are analysed by incorrect statistical methods, not taking the clustering into account. Such analyses create a 'unit of analysis error' and produce over-precise results (the standard error of the estimated intervention effect is too small) and P values that are too small. They do not lead to biased estimates of effect. However, if they remain uncorrected, they will receive too much weight in a meta-analysis.

(v) In a meta-analysis including both cluster and individually randomised trials, or including cluster-randomised trials with different types of clusters, possible differences between the intervention effects being estimated need to be considered. For example, in a vaccine trial of infectious diseases, a vaccine applied to all individuals in a community would be expected to be more effective than if the vaccine was applied to only half of the people. Another example is provided by a Cochrane review of hip protectors. The cluster trials showed large positive effect, whereas individually randomised trials did not show any clear benefit. One possibility is that there was a 'herd effect' in the cluster-randomised trials (which were often performed in nursing homes, where compliance with using the protectors may have been enhanced). In general, such 'contamination' would lead to underestimates of effect. Thus, if an intervention effect is still demonstrated despite contamination in those trials that were not cluster-randomised, a confident conclusion about the presence of an effect can be drawn. However, the size of the effect is likely to be underestimated. Contamination and 'herd effects' may be different for different types of cluster.

CONTRIBUTIONS OF AUTHORS

Tanya Smith: conceived the review question, developed the protocol, contributed to writing and editing the protocol, and approved the final version of the protocol prior to submission.

Ceri Rowlands: conceived the review question, developed the protocol, contributed to writing and editing the protocol, and approved the final version of the protocol prior to submission.

Jo Dumville: conceived the review question, developed the protocol, secured funding, contributed to writing and editing the protocol and advised on the protocol.

Gill Norman: developed the protocol, contributed to writing and editing the protocol, advised on the protocol, approved the final version of the protocol prior to submission and is guarantor of the protocol.

Contributions of the editorial base

Nicky Cullum (Editor): edited the protocol; advised on methodology interpretation and protocol content; approved the final protocol prior to submission.

Gill Rizzello (Managing Editor): co-ordinated the editorial process; advised on content; edited the protocol.

Reetu Child (Information Specialist) : designed the search strategy and edited the search methods section.

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Tanya Smith: Nothing to declare.

Ceri Rowlands: Nothing to declare.

Jo Dumville: Nothing to declare.

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