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Negative pressure wound therapy for traumatic wounds (Protocol)

Newton K, Wordsworth M, Allan AY, Dumville JC

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[Intervention Protocol]

Negative pressure wound therapy for traumatic wounds

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the effects of NPWT for managing traumatic wounds in any care setting.

BACKGROUND

Description of the condition

The World Health Organization estimates that 5.8 million people worldwide die from injuries (WHO 2014). These deaths account for a small proportion of the overall number of injured (Alexandrescu 2009). Traumatic wounds (wounds caused by injury) range from abrasions and minor skin incisions or lacerations (tears), to wounds with extensive tissue damage or loss, and may be associated with injury to underlying structures such as soft tissue, bone, or viscera (internal organs) (DeBoard 2007; Edlich 2010). The extent of tissue damage is influenced by the mechanism of injury. Traumatic wounds can be caused by blunt trauma, penetrating trauma, crush injury, blast injury, burns and animal bites. Surgical wounds can be classified as: clean, clean/contaminated, contaminated and dirty/infected depending on degree of infection or bodily fluid contamination (saliva, phlegm, enteric contents or faeces) (Garner 1985). Acute traumatic wounds can be described as contaminated or dirty/infected (dependent on the mechanism and area of the body injured) (Mangram 1999). Older traumatic wounds that may have retained devitalised (dead) tissue, those presenting with signs of infection or involving infected material, and those involving perforated viscera (internal organs) can be described as dirty/infected (Mangram 1999). Early management of traumatic wounds is frequently dictated by the need for urgent assessment and management of concomitant severe, life-threatening injuries (Hollander 1995). Ongoing management of traumatic injuries is governed by the degree of damage to underlying or associated structures and aims to preserve, or restore, both function and form thus minimising disability and disfigurement.

Description of the intervention

Negative pressure wound therapy (NPWT) is a technology that is currently used widely in wound care and is promoted for use on complex wounds (Guy 2012). NPWT involves the application of a wound dressing through which a negative pressure is applied, often

with any wound and tissue fluid drawn away from the area being collected into a canister. The amount of pressure applied using the therapy can vary and there is no single protocol for use however, pressure being delivered ranges from 75mmHg to 150mmHg with 125mmHg being commonly used (Peinemann 2011). The intervention was developed in the 1990s, and the uptake of NPWT in the healthcare systems of developed countries has been dramatic. A US Department of Health report estimated that between 2001 and 2007, Medicare payments for NPWT pumps and associated equipment increased from USD 24 million to USD 164 million (an increase of almost 600%) (HHS 2009). No national cost data is available for the UK. Initially only one NPWT manufacturer supplied NPWT machines (the V.A.C. system: KCI, San Antonio Texas), however, as the NPWT market has grown, a number of different commercial NPWT systems have been developed with machines becoming smaller and more portable. Indeed, the most recent introduction to the market is a single use, or 'disposable', negative pressure product (e.g. PICO: Smith & Nephew, UK). Ad hoc, non-commercial , negative pressure devices are also used, especially in resource-poor settings. These devices tend to use simple wound dressings, such as gauze, or transparent occlusive (non-permeable) dressings, with negative pressure generated in hospital by vacuum suction pumps.

A number of different healthcare professionals prescribe and apply NPWT, and it is now used both in secondary and primary (community) care, particularly following the introduction of ambulatory systems. Whilst the NPWT systems outlined above differ in a number of respects - such as type of pressure (constant or cyclical) applied to the wound, the material in contact with the surface of the wound and also the type of dressing used - the principle of applying a negative pressure to the wound in a closed environment is the same for all products.

How the intervention might work

NPWT ostensibly facilitates wound healing via several different mechanisms. The negative pressure exerted by the dressing causes deformation of the wound, drawing the skin edges closer together therefore reducing the volume of tissue and skin needed to heal the wound (KCI Medical 2012). The pressure effects also cause strain or tension across the tissue, which is thought to increase capillary flow, ultimately stimulating granulation tissue formation and growth of new blood vessels (Saxena 2004). Removal of high volumes of wound exudate, containing enzymes and other proteins involved in inflammation, may prevent further tissue damage. Removal of this fluid also reduces the frequency of dressing changes by keeping the surrounding skin dry, particularly around anatomically-challenging wounds (for example around joints or skin creases). Manufacturers have also suggested that NPWT removes infected material, which may reduce the bacterial burden that can delay healing and reconstructive surgery (KCI Medical 2012). The molecular effects of negative pressure on the wound bed are still being investigated (Glass 2014). NPWT can be used on traumatic wounds (with or without fasciotomy; opening of fascial compartment) with the aim of reducing compartment syndrome. Compartment syndrome occurs when there is increased pressure within an enclosed muscle compartment (muscle surrounded by fascial connective tissue) due to injury, reduced arterial blood flow or reduced venous drainage. The increased pressure can cause irreversible damage to muscles and nerves.

There are some potentially negative aspects associated with NPWT; these include wound maceration (softening due to prolonged exposure to liquid), retention of dressings, and wound infection as well as other injuries (FDA 2011). NPWT devices are usually worn continually by patients during treatment, they can interfere with mobility, and, anecdotally, are often noisy, which prevents some patients from sleeping. However there have been some recent technological advances of smaller, more portable machines which may reduce these issues, and may also be more cost-effective.

Why it is important to do this review

It is important to assess current evidence regarding the clinical- and cost-effectiveness of NPWT given its widespread use. There is no national guidance on the use of NPWT in traumatic wounds. The production of a robust and current systematic review can contribute to this aim by identifying, appraising and synthesising the current evidence base to inform decision makers and possibly guide future research.

OBJECTIVES

To assess the effects of NPWT for managing traumatic wounds in any care setting.

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 cross-over trials, as they are not an appropriate design in this context. We will also exclude studies using quasi-randomisation.

Types of participants

We will consider RCTs recruiting people (adults and children) described in the primary report as having traumatic wounds involving either soft tissue wounds (including for example blunt degloving injuries (where skin is completely torn off underlying tissue) and gunshot wounds), or open fractures, managed in any care setting, to be eligible for inclusion. RCTs recruiting people with traumatic wounds due to burns will be excluded (including exclusion of blast-related injuries that are likely to be burns). As the method of defining soft tissue traumatic wounds may vary, we will accept definitions as used by the study authors. We will exclude studies recruiting participants with traumatic wounds alongside people with other types of wounds unless wound type was stratified for in the randomisation and data for traumatic wounds are presented separately.

Types of interventions

The primary intervention of interest is NPWT (both commercial and non-commercial treatments). We will include any RCT in which use of a specific NPWT intervention during the treatment period is the only systematic difference between treatment groups. We anticipate that likely comparisons will include use of NPWT during the care pathway compared with no use of NPWT or comparison of different types/brands of NPWT used during the care pathway.

Types of outcome measures

We list primary and secondary outcomes below. If a study is otherwise eligible (i.e. correct study design, population and intervention/comparator) but does not report a listed outcome, then we will contact the study authors where possible to establish whether an outcome of interest here was measured but not reported.
We will report outcome measures at the latest time point available (assumed to be length of follow-up if not specified) and the time point specified in the methods as being of primary interest (if this is different from latest time point available). For all outcomes we will class assessment of outcome measures from:

- one week or less to eight weeks as short term;
- eight weeks to 16 weeks as medium term; and
- more than 16 weeks as long term.

Primary outcomes

The primary outcomes for this review are complete wound healing and adverse events.

Complete wound healing

For this review we will regard the following as providing the most relevant and rigorous measures of outcome:

- time to complete wound healing (we will record if this has been correctly analysed using censored data and with adjustment for prognostic covariates such as baseline size);
- the proportion of wounds healed (frequency of complete healing).

Where both the outcomes above are reported we will present all data in a summary outcome table for reference, but will focus on reporting time to healing. We will accept study authors' definitions of what constituted a healed wound.

Adverse events

We will extract reported data on adverse events that are classed as 'serious adverse events' and 'non-serious adverse events' where the study provides a clear methodology for the collection of adverse event data. This methodology should make it clear whether events were reported at the participant level or, where multiple events per person were reported, that an appropriate adjustment was made for data clustering. We will not extract individual types of adverse events such as pain or infection, which require specific assessment, under this outcome, rather we will use the assessment of any event classed as adverse by the participant or health professional, or both, during the trial.

Secondary outcomes

- Proportion of wounds closed with surgery: complete wound closure (including skin grafting) that was specified as the result of surgical closure rather than healing.
- Time to surgery: NPWT is often not used until complete wound healing but until a point where the wound is ready for further treatment such as closure surgery.
- Participant health-related quality of life/health status (measured using a standardised generic questionnaire such as EQ-5D, SF-36, SF-12 or SF-6 or wound-specific questionnaires such as the Cardiff wound impact schedule). We will not include ad hoc measures of quality of life that are not likely to be validated and would not be common to multiple trials.
- Wound recurrence: we will accept study author definitions of wound recurrence unless it is clear that the term has not been used to describe the return of a wound that was previously healed.
- Incidence of compartment syndrome. As defined by study authors.
- Mean pain scores: (including pain at dressing change) will be included only where it is reported as either a presence or absence of pain or as a continuous outcome using a validated scale such as a visual analogue scale (VAS).

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 (including In-Process & Other Non-Indexed Citations, MEDLINE Daily and Epub Ahead of Print) (1946 to present);
- Ovid Embase (1974 to present);
- EBSCO CINAHL Plus (1937 to present).

The Cochrane Central Register of Controlled Trials (CENTRAL) search strategy is available in Appendix 1 and this will be adapted to search MEDLINE, Embase and 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 filter developed by the UK Cochrane Centre (Lefebvre 2011). We will combine the CINAHL searches with the trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN 2015). There will be no restrictions with respect to language, date of publication or study setting.

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

- ClinicalTrials.gov (www.clinicaltrials.gov/);
- WHO International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en/).

Searching other resources

We will contact corresponding study authors and the manufacturers and distributors of NPWT. 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 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 will independently check the full papers for eligibility; we will resolve any disagreements by discussion and, where required, the input of a third review author. 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 the study will be included only once in the review, we will extract data from all reports to ensure maximal relevant data are obtained.

Data extraction and management

We will extract and summarise details of the eligible studies using a data extraction sheet. Two review authors will extract data independently and will resolve disagreements by discussion, drawing on a third review author 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 extract only data from intervention and control groups that meet the eligibility criteria. In the case of a three-arm trial with two NPWT groups and a control group, we will extract all data and report comparisons narratively. Review authors will make a decision as to how to analyse data further but ensure that multiple analyses, which pose a risk of spurious findings, are avoided. Options include grouping NPWT groups together or the inclusion of comparisons in different meta-analyses depending on treatments being evaluated.

We will extract the following data where possible by treatment group for the pre-specified interventions and outcomes in this review. We will collect outcome data for relevant time points as described in Types of outcome measures. Where details are unclear, we will aim to contact study authors for clarification where possible:

- country of origin;
- type of wound;
- unit of randomisation (per participant) - single wound or multiple wounds on the same participant;
- unit of analysis;
- trial design, for example, parallel, cluster;
- care setting;
- number of participants 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);
- outcome data for primary and secondary outcomes (by group);
- duration of follow-up;
- number of withdrawals (by group);
- publication status of study; and
- source of funding for trial.

Assessment of risk of bias in included studies

Two review authors will independently assess included studies using the Cochrane tool for assessing risk of bias (Higgins 2011a). This tool addresses six specific domains: sequence generation, allocation concealment, blinding, 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. We note that, since wound healing is a subjective outcome, it can be at high risk of measurement bias when outcome assessment is not blinded. 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. We will class studies with an assessment of high risk of bias for the randomisation sequence domain and/or the allocation concealment domain and/or the blinded outcome assessment domain (for specified outcome) as being at overall high risk of bias (for specified outcome). 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 (CI). For continuously distributed outcome data 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. We will only consider mean or median time to healing without survival analysis as a valid outcome if reports specify that all wounds healed (i.e. if the trial authors regarded time-to-healing as a continuous measure as there is no censoring). We will report time-to-event data (e.g. time-to-complete wound healing) as hazard ratios (HR), where possible in accordance with the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011). If studies reporting time to event data (e.g. time to healing) do not report a hazard ratio, then, where feasible, we plan to estimate this using other reported outcomes, such as the numbers of events, through the application of available statistical methods (Parmar 1998).

Unit of analysis issues

Where studies randomise at the participant level and measure outcomes at the wound level, for example, wound healing, 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, we plan to use the generic inverse-variance method in Review Manager (RevMan) (RevMan 2014) to meta-analyse effect estimates and their standard errors.

We will record where a cluster-randomised trial has been conducted but incorrectly analysed. This will be recorded as part of the risk of bias assessment. If possible we will approximate the correct analyses based on guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011c) 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 intracluster (or intraclass) correlation coefficient (ICC).

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

We will also note when randomisation has been undertaken at the wound level; that is a split-site or split-body design. We will assess whether the correct paired analysis has been undertaken in the study. Again, we will record issues in the 'Risk of bias' section. If an incorrect analysis has been undertaken we will try and approximate a correct analysis if the required data are available from the study report or the study authors. If this is not possible we will extract and present the relevant outcome data but not analyse them 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 the review authors think should be included in the analyses, we will contact the relevant study authors to request whether these data are available.

Where data remain missing for proportion of wounds healed data, for analysis we will assume that if randomised participants were not included in an analysis, their wound did not heal (i.e. they would be considered in the denominator but not the numerator). In a time-to-healing analysis using survival analysis methods, drop-outs should be accounted for as censored data so we will not take any action regarding missing data.

For all secondary outcomes we will present available data from the study reports/study authors and 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 the study will be excluded from any relevant meta-analyses that are conducted.

Assessment of heterogeneity

Assessment of heterogeneity can be a complex, multi-faceted 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 length of follow-up. This assessment of clinical and methodological heterogeneity will be supplemented by information regarding statistical heterogeneity, assessed using the Chi² test (a significance level of $P < 0.10$ will be considered to indicate statistically significant heterogeneity) in conjunction with the I^2 statistic (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 40%, or less, may not be important (Higgins 2003), and values of more than 75%, or more, indicate considerable 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. Where there is evidence of high heterogeneity we will attempt to explore this further: see Data synthesis for further information about how potential heterogeneity be will handled 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 RevMan 5 (RevMan 2014).

Data synthesis

We will combine details of included studies in a narrative review according to type of comparator, possibly by location or type of wound (also cause of trauma) 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, thus synthesis is considered viable.

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 estimated as non-statistically significant for the Chi^2 value and 0% for the I^2 assessment (Kontopantelis 2012a). 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 2012b). 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 risk ratio (RR) with 95% CI. Where continuous outcomes are measured in the same way across studies, we plan to present a pooled mean difference (MD) with 95% CI; we plan to pool standardised mean difference (SMD) estimates where studies measure the same outcome using 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 RevMan 5.3 (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 data will not be summarised or used in any meta-analysis.

We will obtain pooled estimates of treatment effect using Cochrane RevMan software (version 5.3) (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 (Schünemann 2011a). The 'Summary of findings' tables also include an overall grading of the evidence related to each of the main outcomes using the GRADE approach, which 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 (Schünemann 2011b). We plan to present the following outcomes in the 'Summary of findings' tables:

- time to complete wound healing where analysed using appropriate survival analysis methods

- time to reconstructive surgery or surgical wound closure
- proportion of wounds completely healed during the trial period (with or without surgery)
- adverse events
- mean pain scores.

Subgroup analysis and investigation of heterogeneity

If there is heterogeneity in the primary outcome of complete healing, we will investigate it using the following pre-specified subgroup analyses, provided there are at least two studies per subgroup:

- type of traumatic wound
- grade of wound injury
- contamination level of wounds.

Sensitivity analysis

Where possible we plan to perform sensitivity analyses to explore the effect of the following:

- removal of studies classed at high risk of bias for any domain.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Cochrane Central Register of Controlled Trials (CENTRAL) provisional search strategy

#1 MeSH descriptor: [Wounds, Penetrating] explode all trees
#2 MeSH descriptor: [Lacerations] explode all trees
#3 MeSH descriptor: [Fractures, Open] explode all trees
#4 (laceration* or gunshot or "gun shot" or "stab" or stabbing or stabbed):ti,ab,kw
#5 (traumatic next wound* or acute next wound*):ti,ab,kw
#6 ("mechanical trauma" or polytrauma):ti,ab,kw
#7 ((blast or crush or avulsion) next injur*):ti,ab,kw
#8 {or #1-#7}
#9 MeSH descriptor: [Negative-Pressure Wound Therapy] explode all trees
#10 MeSH descriptor: [Suction] explode all trees
#11 MeSH descriptor: [Vacuum] explode all trees
#12 ("negative pressure" or negative-pressure or TNP or NPWT):ti,ab,kw
#13 (sub-atmospheric or subatmospheric):ti,ab,kw
#14 ((seal* next surface*) or (seal* next aspirat*)):ti,ab,kw
#15 (wound near/3 suction*):ti,ab,kw
#16 (wound near/3 drainage):ti,ab,kw
#17 ((foam near suction) or (suction near dressing*)):ti,ab,kw
#18 ("vacuum assisted closure" or VAC):ti,ab,kw
#19 ((vacuum near therap*) or (vacuum near dressing*) or (vacuum near seal*) or (vacuum near closure) or (vacuum near compression) or (vacuum near pack*) or (vacuum near drainage) or (suction* near drainage)):ti,ab,kw
#20 {or #9-#19}
#21 {and #8, #20} in Trials

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

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

High risk of bias

Any one of the following.

- Not all of the study's pre-specified 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 pre-specified.
- One or more reported primary outcomes were not pre-specified (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 (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-randomized 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

Katy Newton: conceived the review question; developed the protocol; coordinated the protocol development; produced the first draft of the protocol; contributed to writing and editing the protocol; approved the final version of the protocol prior to submission; and is a guarantor of the protocol.

Matthew Wordsworth: contributed to writing and editing the protocol; made an intellectual contribution to the protocol; advised on the protocol; and approved the final version of the protocol prior to submission.

Anna Allan: contributed to writing and editing the protocol; made an intellectual contribution to the protocol; advised on the protocol; and approved the final version of the protocol prior to submission.

Jo Dumville: conceived the review question; developed the protocol; produced the first draft of the protocol; contributed to writing and editing the protocol; approved the final version of the protocol prior to submission; and is a guarantor of the protocol.

Contributions of the editorial base

Kurinchi Gurusamy (Editor): edited the protocol; advised on methodology, interpretation and 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, ran the search and edited the search methods section.

DECLARATIONS OF INTEREST

Katy Newton: none known.

Matthew Wordsworth: none known.

Anna Y Allan; none known.

Jo Dumville: I receive research funding from the NIHR for the production of systematic reviews focusing on high priority Cochrane reviews in the prevention and treatment of wounds.

Abraham D Janis (peer reviewer) has worked in industry on medical device technology development since 2002. However none of the companies he has worked for market NWPT technologies.

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