



Reconstructive surgery for treating pressure ulcers

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[Intervention Review]

Reconstructive surgery for treating pressure ulcers

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ABSTRACT

Background

The management of pressure ulcers involves several interventions ranging from pressure-relieving measures such as repositioning, to treatments that can include reconstructive surgery. Such surgery may be considered for recalcitrant wounds when full thickness skin loss arises and deeper structures such as muscle fascia and even bone are exposed. The surgery commonly involves wound debridement followed by the addition of new tissue into the wound. Whilst reconstructive surgery is an accepted means of ulcer management, the benefits and harms of surgery compared with non-surgical treatments, or alternative surgical approaches are not clear.

Objectives

To assess the effects of reconstructive surgery for healing pressure ulcers (stage II or above), comparing surgery with no surgery or comparing alternative forms of surgery in any care setting.

Search methods

We searched the following electronic databases to identify reports of relevant randomised clinical trials (searched 26 September 2016): the Cochrane Wounds Specialised Register, CENTRAL, MEDLINE, Embase, and CINAHL. We also searched three clinical trials registers and reference lists of relevant systematic reviews, meta-analyses and health technology assessment reports.

Selection criteria

Published or unpublished randomised controlled trials that assessed reconstructive surgery in the treatment of pressure ulcers.

Data collection and analysis

Two review authors independently performed study selection. We planned that two review authors would also assess the risk of bias and extract study data.

Main results

We did not identify any studies that met the review eligibility criteria nor any registered studies investigating the role of reconstructive surgery in the management of pressure ulcers.

Authors' conclusions

Currently there is no randomised evidence that supports or refutes the role of reconstructive surgery in pressure ulcer management. This is a priority area and there is a need to explore this intervention with more rigorous and robust research.

PLAIN LANGUAGE SUMMARY

Reconstructive surgery for treating pressure ulcers

Review question

We aimed to review the evidence as to whether reconstructive surgery is an effective treatment for healing pressure ulcers. We were unable to find any randomised controlled trials investigating this question.

Background

Pressure ulcers are areas of skin and tissue damage that result largely from people remaining in the same position for long periods of time. When parts of the body, especially those that have less fat such as the lower back and heel, have constant external pressure applied (for example sitting on the same area of the body without changing position) this restricts blood flow to the skin and underlying tissues which can lead them to break down. People at risk of developing pressure ulcers include the elderly and those with mobility problems such as wheelchair users and long-term hospital patients. Pressure ulcers can be classified using a staging system where stage I ulcers still have intact skin, stage II ulcers involve partial skin and tissue loss and are often shallow wounds and stage III and IV ulcers are open wounds with deeper tissue damage. Pressure ulcers are serious wounds that are costly to treat, so care is focused on their prevention. When ulcers do occur, treatment options include wound dressings, and antibiotics and antiseptics. Reconstructive surgery is often reserved for deep or hard to heal pressure ulcers, or both. There are different types of surgeries that can be conducted: most involve removal of dead tissue from the wound and then use of fat, muscle and/or skin from other parts of the patient's body to fill the wound cavity.

Study Characteristics

In September 2016 we searched for randomised controlled trials studying the use of surgery for treating pressure ulcers. However, whilst reconstructive surgery for pressure ulcers is practised widely, we found no randomised controlled trials that investigated the potential benefits and harms associated with surgery or that could guide the optimal choice of surgical technique. Many studies excluded from this review reported data from groups of people undergoing reconstructive surgery without a comparison of outcomes for similar groups of people who did not have surgery, or who had different types of surgery. This means that it is not possible to weigh up the benefits and harms of surgery, or different surgical techniques.

Key results

We found no randomised controlled trials investigating reconstructive surgery for pressure ulcers.

Certainty of the evidence

The benefits and harms of reconstructive surgery for the treatment of pressure ulcers are uncertain and more rigorous research in this area is needed, especially as this question has been prioritised by patients, carers and health professionals.

This plain language summary is up to date as of September 2016.

Description of the condition

Pressure ulcers, also known as bedsores, decubitus ulcers and pressure injuries, are localised areas of ischaemic injury to the skin and

BACKGROUND

underlying tissue. They are caused by prolonged external mechanical forces such as pressure or shear beyond the normal physiological constraints (EPUAP-NPUAP-PPPIA 2014). These forces are higher in the presence of an underlying bony prominence such as the sacrum, ischium, trochanter and heel (Vanderwee 2007), which is where pressure sores tend to occur.

Populations at greatest risk include those with spinal cord injuries (Gefen 2014), and non-ambulatory individuals. People with prolonged impaired consciousness can be affected, like those having long surgery (Chen 2012; Primiano 2011) people in intensive care (Ranzani 2016) and people found incapacitated through intoxication (Yanagawa 2011). Furthermore, acute and chronic comorbidities that limit mobility or tactile sensation increase risk, with the elderly population most vulnerable (Allman 1997; Bergstrom 1998; Berlowitz 1990; Berlowitz 1997; Brandeis 1994). It is not uncommon for these pressure ulcers to occur with systemic disease such as diabetes (Brem 2003). Incontinence can increase the risk of ulceration by producing a moist, contaminated environment for the skin injury (Brandeis 1994). Poor nutritional status also impairs the ability of some individuals to heal these complex wounds (Allman 1997; Donini 2005). However, there is currently limited evidence for the effectiveness of nutritional intake interventions for preventing or treating pressure ulcers (Langer 2014; Smith 2013).

Pressure ulcers vary in severity. One of the most widely recognised systems for categorising pressure ulcers is that of the National Pressure Ulcer Advisory Panel, which is summarised below (NPUAP 2016).

Category/Stage I - non-blanchable erythema: “Intact skin with non-blanchable redness of a localised area usually over a bony prominence. Darkly pigmented skin may not have visible blanching; its colour may differ from the surrounding area. The area may be painful, firm, soft, warmer or cooler as compared to adjacent tissue. Category I may be difficult to detect in individuals with dark skin tones. May indicate “at risk” persons.”

Category/Stage II - partial thickness: “Partial thickness loss of dermis presenting as a shallow open ulcer with a red pink wound bed, without slough. May also present as an intact or open/ruptured serum-filled or sero-sanguinous filled blister. Presents as a shiny or dry shallow ulcer without slough or bruising (bruising indicates deep tissue injury). This category should not be used to describe skin tears, tape burns, incontinence associated dermatitis, maceration or excoriation.”

Category/Stage III - full thickness skin loss: “Full thickness tissue loss. Subcutaneous fat may be visible but bone, tendon or muscle are not exposed. Slough may be present but does not obscure the depth of tissue loss. May include undermining and tunnelling. The depth of a Category/Stage III pressure ulcer varies by anatomical location. The bridge of the nose, ear, occiput and malleolus where there is little subcutaneous tissue (adipose) can form Category/Stage III ulcers that are shallow. In contrast, areas of significant adiposity can develop extremely deep Category/Stage III

pressure ulcers. Bone/tendon is not visible or directly palpable.”

Category/Stage IV - full thickness tissue loss: “Full thickness tissue loss with exposed bone, tendon or muscle. Slough or eschar may be present. Often includes undermining and tunnelling. The depth of a Category/Stage IV pressure ulcer varies by anatomical location. The bridge of the nose, ear, occiput and malleolus which have little subcutaneous tissue (adipose), can form ulcers that are shallow. Category/Stage IV ulcers can extend into muscle and/or supporting structures (e.g. fascia, tendon or joint capsule) making osteomyelitis or osteitis likely to occur. Exposed bone/muscle is visible or directly palpable.”

Prevalence estimates vary according to the population being assessed, the data collection methods used and decisions about whether or not stage I pressure ulcers should be included (since there is no active wound at this stage, but patients are ‘at risk’). A large survey of hospital patients undertaken in several European countries returned a pressure ulcer prevalence (stage II and above) of 10.5% (Vanderwee 2007). In 2009, a US estimate for pressure ulcer prevalence (stage II and above) across acute care, long-term care and rehabilitation settings was 9% with prevalence highest in long-term acute care settings (26%) (VanGilder 2009). In the UK, national pressure ulcer data are collected across community and acute settings - although data collection is not yet universal - as part of the National Health Service (NHS) Safety Thermometer initiative (Power 2012). Five per cent of patients across these settings were estimated to have a pressure ulcer in January 2014 (National Safety Thermometer 2014).

We note that all the prevalence figures quoted above are for populations currently receiving medical care. The point prevalence of pressure ulceration in the total adult population was recently estimated using a cross-sectional survey undertaken in Leeds, UK. Of the total adult population of 751,485, the point prevalence of pressure ulceration per 1000 was 0.31 (Hall 2014). UK pressure ulcer prevalence estimates specifically for community settings have reported rates of 0.77 per 1000 adults in a UK urban area (Stevenson 2013).

Pressure ulcers have a large impact on those affected and can be painful, and become infected or malodorous. After adjustment for age, sex and co-morbidities, people with pressure ulcers have a lower health-related quality of life than those without pressure ulcers (Essex 2009). The financial cost of treating ulcers in the UK was recently estimated as being between GBP 1214 for a stage I ulcer, to GBP 14,108 for a stage IV ulcer (Dealey 2012). In 2004, the total annual cost of treating pressure ulcers in the UK was estimated as being GBP 1.4 to 2.1 billion, which was equivalent to 4% of the total NHS expenditure (Bennett 2004). Pressure ulcers have been shown to increase length of hospital stay, readmission and mortality rates (Lyder 2012), and add considerably to the cost of an episode of hospital care (Chan 2013). Figures from the USA suggest that half a million hospital stays in 2006 had the diagnosis of ‘pressure ulcer’; for adults, the total hospital costs of these stays was USD 11 billion (Russo 2008). Costs to the

Australian healthcare system for treating pressure ulceration have been estimated at AUD 285 million per annum (Graves 2005). Traditional approaches to managing pressure ulcers have been to utilise conservative measures such as dressings that are often associated with a protracted investment of resources. Surgical intervention for pressure ulcers is reserved for the most recalcitrant of pressure sores. In theory, if the aetiology of pressure sores is removed and nutrition optimised (Bergstrom 1996; Bergstrom 1992), the majority should heal. Surgery is usually indicated after failure of conservative measures and usually reserved for stage III and IV ulcers (Margara 2003). Debridement of unhealthy and necrotic tissue, underlying bursae (fibrotic capsule) and bone if necessary remains the cornerstone of surgical management, with or without immediate soft tissue cover (Conway 1956). Other than the choice of surgical reconstruction, quality of local tissues, aetiological factors, patient co-morbidities, education status and motivation contribute significantly to successful outcomes (Kruger 2013).

Description of the intervention

This review focuses on the evidence for the surgical reconstruction of pressure ulcers, where surgical reconstruction is defined as any surgical procedure that leads to primary epithelial closure of the wound. A diverse spectrum of surgical procedures can be performed to help heal pressure ulcers, however selection must be based on a number of participant and wound level factors. Many surgical procedures start with thorough debridement, involving excision of the fibrotic capsule or bursa that forms around the chronic wound, to healthy bleeding tissue. If the residual tissue is badly scarred, skin is subject to further breakdown. If there is underlying dead or infected tissue or heterotrophic ossification (formation of ectopic bone) this should be debrided.

Once surgical debridement has been performed, reconstructive surgical methods conducted include the following (Maslauskas 2009):

Primary wound closure: involves direct advancement of the wound edges either directly or in layers to close the wound (Simman 2009).

Skin grafts: involve harvesting a thin piece of skin that is surgically removed from a donor area to replace skin in the defect or denuded area. Skin grafts are occasionally used to treat pressure ulceration when all precipitating factors for pressure sore formation have been removed. They are used to facilitate quick wound cover and subsequently to accelerate wound healing (Srivastava 2009).

Local random pattern flaps: this reconstructive method involves surgically moving the local tissues around the wound, based on a random pattern of blood supply, into the wound defect (Nesbit 2015).

Regional flaps including:

- muscle or musculocutaneous flaps; this surgical approach involves moving whole or part of a named muscle based on a

defined blood supply with or without a skin island to provide cover to the wound (Liu 2013);

- fascial or fasciocutaneous flaps; this surgical approach involves moving a surgically defined fascial based island of tissue with its intact blood supply with or without skin to cover the wound (Robertson 2015);

- perforator flaps; this is a refinement of the previous musculocutaneous or fasciocutaneous flaps approach whereby the specific perforating blood vessels are identified in the flap and dissected to allow either greater movement or less muscle sacrifice as well as separation of components to each flap (Koshima 1993).

Free flaps: this surgical approach involves raising a defined island of tissue with an artery and vein that is surgically detached and moved to the site of the wound where other local arteries or veins of similar size are identified and then the vessels are surgically anastomosed to re-establish blood flow to the island of tissue (Lemaire 2008).

Tissue expansion: this surgical approach involves a gradual increment and recruitment of tissue surrounding a pressure ulcer. It is performed by expanding the skin with a tissue expander, which is inserted into a subcutaneous pocket near the ulcer and slowly expanded at a defined rate with saline. Once the skin and soft tissues are expanded to a volume capable of covering the pressure ulcer, the expander is removed and the tissues are inset to cover the wound. Another method is to apply slow skin traction over the wound with an incremental traction dressing, which works on the same principle of gradual mechanical traction on skin, promoting tissue creep (Johnson 1993). Eventually the extra skin recruited can be used to close the wound (Wagh 2013).

All of the above approaches can be performed as a one-stage procedure, or part of a multistage procedure to increase the likelihood of the tissue surviving manipulation, reduce the overall surgical impact on the patient and ensure that all infected or aggravating factors are minimised. This is particularly important as the skin quality around pressure ulcers is usually sub-optimal (Maslauskas 2009).

How the intervention might work

Surgery is indicated when conservative measures have failed to accelerate the healing process in pressure ulceration, but only when all other parameters are optimised. Thus, surgical closure is often reserved for more complex pressure ulcers (most often stage III or IV but occasionally stage II), with strong consideration of the probability of ulcer recurrence in each individual. The underpinning rationale for reconstructive surgery is that following the removal of devitalised tissue, the wound defect is filled with vascularised healthy tissue with adequate skin cover, which then forms a healed wound.

Why it is important to do this review

In general, much of the current literature around the treatment of pressure ulcers focuses on their non-surgical management. It is also important to assess current evidence regarding the clinical effectiveness of surgery to assess its potential for use in suitable patient populations. Surgical options have increased with the advent of more novel approaches such as perforator flaps and free tissue transfer, although it is difficult to find any figures regarding the number of people with pressure ulcers treated using reconstructive surgery in any country. The published UK National Institute for Health and Clinical Excellence (NICE) guidelines on the prevention and management of pressure ulcers (NICE 2014), does not make any specific recommendations or suggestions regarding reconstructive surgery for people with these wounds. A recent review of the evidence for all treatments for pressure ulcers included four studies investigating the role of reconstructive surgery, but it did not identify randomised controlled trials, and as a result, could only draw very limited conclusions (Smith 2013). The role of surgery in closing pressure ulcers was prioritised highly by patients, carers and health professionals in a James Lind Alliance priority setting partnership (Cullum 2016).

The production of a current and robust Cochrane systematic review is required to present an overview of the current evidence base to help inform decision-making in the treatment of pressure ulcers as well as to guide possible future research.

OBJECTIVES

To assess the effects of reconstructive surgery for healing pressure ulcers (category/stage II or above), comparing surgery with no surgery or comparing alternative forms of reconstructive surgery in any care setting.

METHODS

Criteria for considering studies for this review

Types of studies

We planned to include published and unpublished randomised controlled trials (RCTs), including cluster-RCTs, irrespective of language of report. We intended to exclude cross-over trials and exclude studies using quasi-randomisation.

Types of participants

We planned to include studies that recruited adults with a diagnosis of a pressure ulcer (category/stage II or above) managed in any care setting. We excluded studies involving participants with category/stage I ulcers. We accepted study authors' definitions of stage II or above, unless it was clear that they included wounds with unbroken skin. We planned to exclude studies with mixed wound populations; that is studies that did not restrict inclusion to pressure ulcers only and which may have included participants with other types of wounds such as venous leg or diabetic foot ulcers, although we did not find any such studies.

Types of interventions

The primary intervention was reconstructive surgery for pressure ulceration (where reconstructive surgery is defined as any surgical procedure that leads to epithelial closure of the wound). We planned to include any RCT in which the use of a specific surgical closure technique was the only systematic difference between treatment groups and anticipated that likely comparisons would include surgery compared with no surgery and different types of surgery compared with each other. We anticipated that reconstructive surgery would often include a stage of surgical wound debridement. We would have included this as a co-intervention, extracted data and discussed it in the presentation of results. We did not plan to treat surgical debridement alone as a type of reconstructive surgery. Other co-intervention details would have included postoperative protocols. Where there was evidence of a difference in use of co-interventions between groups, we would not have considered the type of reconstructive surgery to be the only systematic difference between groups and we would have excluded these studies.

Types of outcome measures

We listed primary and secondary outcomes below. If a study was otherwise eligible (i.e. correct study design, population and intervention/comparator) but did not report a listed outcome then we planned to contact the study authors where possible to establish whether an outcome of interest here was measured but not reported, however this was not required in this review.

We planned to report outcome measures at the latest time point available for a study (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 was different from latest time point available). For all outcomes we planned to class outcome measures from:

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

Primary outcomes

The primary outcomes for this review were complete wound healing and wound breakdown.

Complete wound healing

We accepted study authors' definitions of wound healing. We planned to record whether healing was defined immediately following surgery or whether healing was not confirmed until some defined period following surgery when the surgery was deemed to be successful.

For this review we regarded the following as providing the most relevant and rigorous measures of outcome;

- Time to complete wound healing. We planned to record whether this had been correctly analysed using techniques that account for data censoring and with adjustment for prognostic covariates such as baseline size;
- The proportion of ulcers healed (frequency of complete healing).

Where both the outcomes above were reported we planned to present the data in a summary outcome table for reference and report time to healing.

Wound breakdown

We planned to present data on wound breakdown using the following two outcomes that would be presented separately:

Wound dehiscence

We planned to assess this as the proportion of wounds that dehisce along the wound edges that have been apposed and held together with sutures, staples, etc. in the reconstructive surgery. We intended to record study authors' definitions of wound dehiscence.

Wound recurrence

This was defined as occurrence of a new pressure ulcer on the same site as a previous ulcer.

Secondary outcomes

Secondary outcomes were as follows:

- **Resource use:** resource use (including measurements of resource use such as number of dressing changes, nurse visits, length of hospital stay, re-admission and re-operation/intervention);
- **Health-related quality of life:** we planned to include quality of life where it was reported using a validated scale such as the SF-36 or EQ-5D or a validated disease-specific

questionnaire such as the Cardiff Wound Impact Schedule. We did not plan to include ad hoc measures of quality of life that were unvalidated or were not common to multiple trials;

- **Wound infection:** we planned to accept study authors' definitions of wound infection;
- **Costs:** any costs applied to resource use;
- **Incidence of secondary ulceration:** this would have applied to a second pressure ulcer that formed in a different area during the follow-up period.

Search methods for identification of studies

Electronic searches

We searched the following electronic databases:

- the Cochrane Wounds Specialised Register (searched 26 September 2016);
- the Cochrane Central Register of Controlled Trials (CENTRAL; The Cochrane Library, 2016, Issue 2);
- Ovid MEDLINE (1946 to 26 September 2016);
- Ovid MEDLINE (In-Process & Other Non-Indexed Citations) (searched 26 September 2016);
- Ovid Embase (1974 to 26 September 2016);
- EBSCO CINAHL Plus (1937 to 26 September 2016).

The search strategies used for CENTRAL, Ovid MEDLINE, Ovid Embase and EBSCO CINAHL can be found in [Appendix 1](#). We combined 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 combined the Embase search with the Ovid Embase filter developed by the UK Cochrane Centre ([Lefebvre 2011](#)). We combined the CINAHL searches with the trial filters developed by the Scottish Intercollegiate Guidelines Network ([SIGN 2015](#)). There were no restrictions with respect to language, date of publication or study setting. Citations were de-duplicated as part of the search process so identical records included more than once would be removed prior to screening. We also searched the following registers:

- WHO International Clinical Trials Registry Platform (ICTRP) apps.who.int/trialsearch/Default.aspx
- ClinicalTrials.gov www.clinicaltrials.gov/
- EU Clinical Trials Register www.clinicaltrialsregister.eu/ctr-search/search.

Searching other resources

We aimed 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 independently assessed the titles and abstracts of the citations retrieved by the searches for relevance. After the initial assessment, we obtained full-text copies of all studies considered to be potentially relevant. Two review authors independently checked the full papers for eligibility. We resolved disagreements by discussion and, where required, we sourced the input of a third review author. We did not need to contact study authors to query any study details with regard to eligibility. We recorded all reasons for exclusion of studies for which we had obtained full copies. We completed a PRISMA flowchart to summarise this process (Liberati 2009).

Where studies had been reported in multiple publications/reports we obtained all the available publications. Whilst a study would only be included once in the review, we planned to extract data from all reports to ensure maximal relevant data were obtained.

Data extraction and management

We planned to extract and summarise details of the eligible studies using a data extraction sheet. Two review authors would have extracted data independently and resolved disagreements by discussion, drawing on a third review author where required. Where data was missing from reports, we planned to contact the study authors to obtain this information. Where a study with more than two intervention arms was included, we anticipated only extracting data from intervention and control groups that met the eligibility criteria.

We planned to extract the following data where possible by treatment group for the pre-specified interventions and outcomes in this review. We planned to 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 (per participant) - single wound or multiple wounds on the same participant
- Unit of analysis
- Trial design (e.g. 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
- Source of funding for trial.

Assessment of risk of bias in included studies

We planned that two review authors would 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). This tool addresses six specific domains: sequence generation, allocation concealment, blinding, incomplete data, selective outcome reporting and other issues. In this review we planned to record issues with unit of analysis, for example where a cluster trial had been undertaken but analysed at the individual level in the study report (Appendix 2). We planned to assess blinding and completeness of outcome data for each of the review outcomes separately. If comparisons had been included we anticipated that blinding of participants and personnel would not have been possible. For this reason, the assessment of the risk of detection bias would have focused 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 planned to present our assessment of risk of bias using two 'Risk of bias' summary figures; one that is a summary of bias for each item across all studies, and a second that shows a cross-tabulation of each trial by all of the risk of bias items.

For trials using cluster randomisation, we also planned to 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 planned to calculate the risk ratio (RR) with 95% confidence intervals (CI). For continuously distributed outcome data we planned to use the mean difference (MD) with 95% CIs, where trials used the same or a similar assessment scale. If trials used different assessment scales, we planned to use the standardised mean difference (SMD) with 95% CIs. We planned to only consider mean or median time to healing without survival analysis as a valid outcome if reports specified that all wounds had healed (i.e. if the trial authors regarded time to healing as a continuous measure as there was no censoring). We planned to 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) did not report a hazard ratio, then, where feasible, we planned to estimate this using other reported outcomes, such as the numbers of events, through the application of available statistical methods (Parmar 1998), however this was not required.

Unit of analysis issues

Where studies randomised at the participant level and measured outcomes at the wound level, (e.g. wound healing), we planned to treat the participant as the unit of analysis when the number of wounds assessed appeared 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 would have been treated as cluster trials, alongside more standard cluster designs - such as delivery of interventions at an organisational level.

Where a cluster trial had been conducted and correctly analysed, effect estimates and their standard errors would have been meta-analysed using the generic inverse-variance method in RevMan. We planned to record where a cluster-randomised trial had been conducted but incorrectly analysed. This would have been recorded as part of the 'Risk of bias' assessment. If possible we planned to approximate the correct analyses based on *Cochrane Handbook for Systematic Reviews of Interventions* guidance (Higgins 2011c). We would have used 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 could not be analysed correctly, we planned to extract and present outcome data but not analyse the data 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 were lost to follow-up, compromises the randomisation and potentially introduces bias into the trial. Where there was missing data we planned to contact the relevant study authors to ask whether these data were available.

Where data remained missing for a proportion of the wounds healed, we planned to assume that if randomised participants were not included in the results section of the paper, their wound did not heal (i.e. in the analysis, missing participants would be considered in the denominator but not the numerator).

For continuous variables (e.g. length of hospital stay and for all secondary outcomes) we would have presented available data from the study reports/study authors and we did not plan to impute missing data. Where measures of variance were missing we planned to calculate these wherever possible. If calculation was not possible we planned to contact study authors. Where these measures of

variation were not available we planned to exclude the study from any relevant meta-analyses that we conducted.

Assessment of heterogeneity

Assessment of heterogeneity is a complex, multi-faceted process. We planned to consider clinical and methodological heterogeneity: that is the degree to which the included studies varied in terms of participants, interventions, outcomes and characteristics such as length of follow-up. We planned to supplement this assessment of clinical and methodological heterogeneity with information regarding statistical heterogeneity, assessed using the Chi² test (we would have considered a significance level of $P < 0.10$ to indicate statistically significant heterogeneity) in conjunction with the I² statistic (Higgins 2003). The I² statistic examines the percentage of total variation across RCTs that is due to heterogeneity rather than chance (Higgins 2003). In general I² values of 25%, or less, may mean 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 is recognised that statistical tests and metrics may miss important heterogeneity - thus whilst we planned to assess these, the overall assessment of heterogeneity would have looked at these measures in combination with the methodological and clinical assessment of heterogeneity. See [Data synthesis](#) for further information about how potential heterogeneity would have been 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 planned to present funnel plots for meta-analyses comprising 10 RCTs or more using Review Manager 5.3 (RevMan) (RevMan 2014).

Data synthesis

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

In terms of meta-analysis, our default approach would have been to use the random-effects model. We planned to only use a fixed-effect approach when we considered clinical heterogeneity to be

minimal and estimated statistical heterogeneity as non-statistically significant for the Chi^2 value and 0% for the I^2 assessment (Kontopantelis 2012a). We planned to 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 was thought to be acceptable or of interest we planned to consider meta-analysis even when statistical heterogeneity was high but we would have attempted to interpret the causes behind this heterogeneity, possibly using meta-regression for this purpose (Thompson 1999). However we did not undertake this in this review.

We planned to present data using forest plots where possible. For dichotomous outcomes we planned to present the summary estimate as a risk ratio (RR) with 95% CI. Where continuous outcomes were measured in the same way across studies, we planned to present a pooled mean difference (MD) with 95% CI. We planned to pool standardised mean difference (SMD) estimates where studies measured the same outcome using different methods. For time-to-event data, we planned 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 (RevMan 2014).

We planned to obtain pooled estimates of treatment effect using Cochrane RevMan software (version 5) (RevMan 2014).

'Summary of findings' tables

We planned to 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 certainty 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 certainty of a body of evidence involves consideration of within-trial risk of bias (methodological quality), directness of evidence, hetero-

geneity, precision of effect estimates and risk of publication bias (Schünemann 2011b). We plan to present the following outcomes in the 'Summary of findings' tables.

- Complete wound healing
- Wound dehiscence
- Wound recurrence

Subgroup analysis and investigation of heterogeneity

Where feasible we planned to explore the findings based on the following groups (not undertaken):

- Ulcer stage
- Type of surgery.

Sensitivity analysis

Where possible we planned to perform sensitivity analyses to explore the effect of the following criterion on any pooled analysis (not undertaken):

- Removal of studies at high risk of bias for any domain.

Elements of this methods section are based on the standard Cochrane Wounds protocol template.

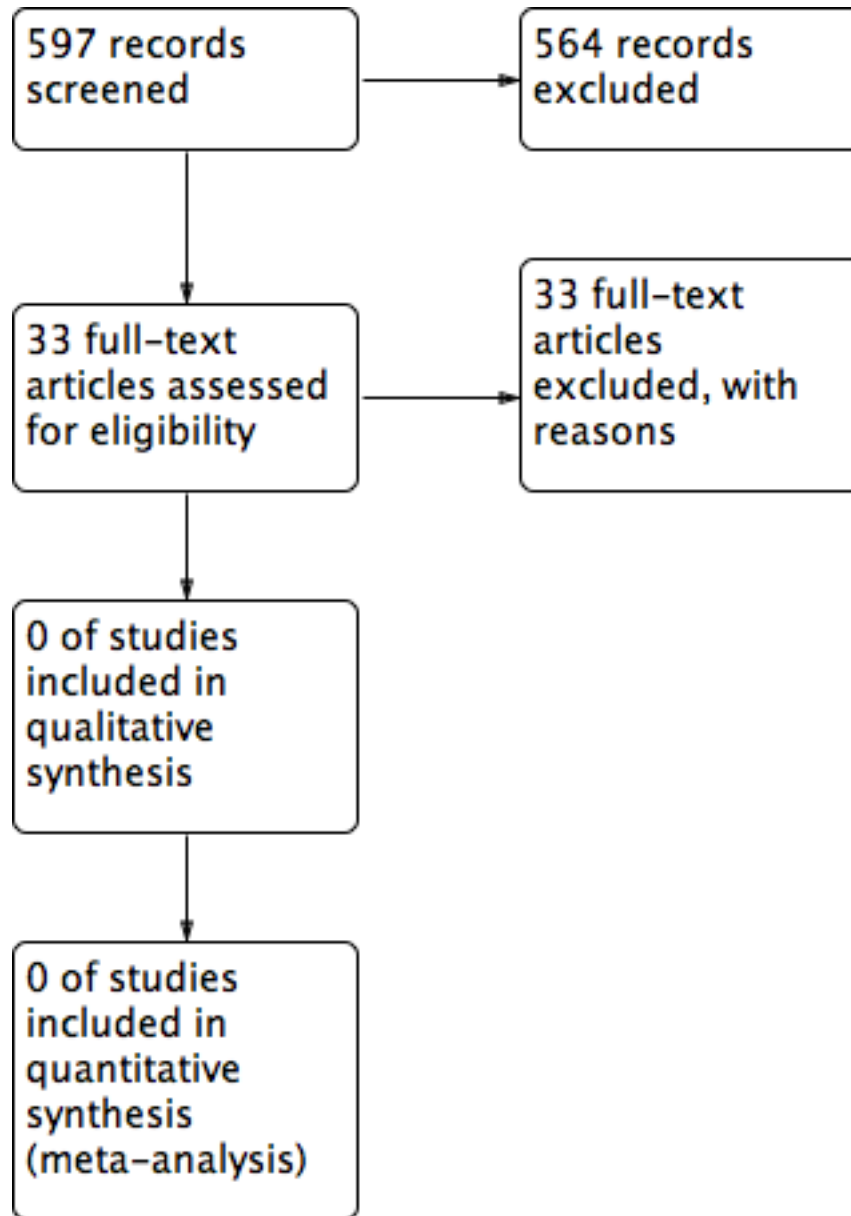
RESULTS

Description of studies

Results of the search

The search retrieved 597 unique records. We obtained 33 full texts as potentially relevant to this review. We took a comprehensive approach to checking other reviews and guidelines in the field of reconstructive surgery as well as trials registers and did not identify any additional records. No studies met the inclusion criteria for this review (Figure 1).

Figure 1. Study flow diagram



Included studies

We did not include any studies for analysis in this review and there were no pending studies awaiting assessment. No relevant ongoing studies were located.

Excluded studies

We excluded 33 studies ([Characteristics of excluded studies](#)). Of these 19 were excluded because they did not assess reconstructive surgery as an intervention. A further seven were excluded because they were not randomised controlled trials. Five were excluded because they were neither accessing reconstructive surgery nor randomised controlled trials and two were excluded as they were systematic reviews.

Risk of bias in included studies

It was not possible to undertake a risk of bias assessment because no studies met the inclusion criteria.

Effects of interventions

Meta-analysis or a narrative synthesis was not possible in this study as no studies met the inclusion criteria.

DISCUSSION

Summary of main results

Despite an extensive search of numerous electronic databases, reviews, guidelines and clinical trials registers we did not identify any studies that met the inclusion criteria for this review. We excluded studies because they were not RCTs or because they did not evaluate reconstructive surgery for the management of pressure ulcers. We did not identify any relevant randomised controlled trials as being in progress.

Overall completeness and applicability of evidence

There is no randomised, controlled trial evidence regarding the effects of reconstructive surgical techniques on the management of pressure ulcers, thus this area is lacking a robust evidence base.

Potential biases in the review process

This review employed a robust search strategy to locate as much relevant evidence as possible relevant to the objectives of this review. We located all potentially relevant papers and translated them where required. There were no restrictions on the language of studies assessed. We also searched trials registers and did not find any relevant on-going or previously conducted but unpublished studies. It is possible, however, that there may be additional unpublished data that we have not been able to access.

We did consider the use of a broader inclusion criteria in order to avoid an “empty” review ([Yaffe 2012](#)). However broadening the eligibility criteria to include quasi-randomised or controlled clinical studies would have yielded no further studies. The studies we did identify were largely retrospective cohort studies or case series.

Agreements and disagreements with other studies or reviews

There is a lack of rigorous evidence regarding the benefits and harms of reconstructive surgery for people with pressure ulcers ([Levine 2013](#)). Some systematic reviews have regarded surgical reconstruction for pressure ulcers favourably but these have included non-randomised case series and/or retrospective studies, hence their usefulness in decision making is limited. NICE guidelines on the prevention and management of pressure ulcer ([NICE 2014](#)) do not refer to reconstructive surgery in their recommendations, also reflecting the lack of robust evidence in this area.

AUTHORS' CONCLUSIONS

Implications for practice

There is no randomised controlled trial (RCT) evidence on the relative effectiveness of reconstructive surgery for treating pressure ulcers. Despite this lack of evidence, surgery is used to treat recalcitrant ulcers, as evidenced by the reporting of retrospective cohorts in the field ([Sameem 2012](#)) although figures on the frequency of this type of surgery are not available. Given the uncertainty on the clinical and cost effectiveness of this approach, current decisions on the use of reconstructive surgery are likely based on local care pathways, local surgical expertise, patient and health professional preferences and cost.

Implications for research

Reconstructive surgery is currently used in the treatment of pressure ulcers where other treatments have little or no impact. Re-

search, in the form of RCTs of reconstructive surgery, should be assessed for feasibility. A rigorous RCT evaluating the clinical and cost effectiveness and patient-reported experiences would likely be in the interests of patients and carers affected by pressure ulcers and clinicians managing these wounds. Indeed resolving uncertainty about the effectiveness of surgery for pressure ulcers was highlighted as a priority within a James Lind Alliance research prioritisation exercise (Cullum 2016).

Further efforts should be made to engage patients and surgeons in discussions about such a trial. Early feasibility work will be required to assess the acceptability of the trial to potential participants as well as surgeons; likely recruitment rates and other methodological

and logistical considerations. A future trial in this area could have a major impact on decision making and potentially benefit patients in terms of improved quality of life.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ashby 2012	Reconstructive surgery not the intervention evaluated
Azimian 2015	Reconstructive surgery not the intervention evaluated
Brem 2000	Not a RCT
Erba 2010	Reconstructive surgery not the intervention evaluated
Fulco 2015	Reconstructive surgery not the intervention evaluated
Garber 2002	Reconstructive surgery not the intervention evaluated
Gargano 2013	Not a RCT
Granick 1998	Not a RCT or an evaluation of reconstructive surgery
Guihan 2007	Reconstructive surgery not the intervention evaluated
Hallock 2013	Not a RCT
Halter 2003	Reconstructive surgery not the intervention evaluated
Hosseini 2014	Reconstructive surgery not the intervention evaluated
Kallianinen 2000	Reconstructive surgery not the intervention evaluated
Knops 2011	Reconstructive surgery not the intervention evaluated
Landi 2003	Reconstructive surgery not the intervention evaluated
Margara A 2008	Not a RCT
Mo 2015	Reconstructive surgery not the intervention evaluated
Moues 2005	Reconstructive surgery not the intervention evaluated
Mulder 1991	Reconstructive surgery not the intervention evaluated
Nussbaum 1994	Not a RCT or an evaluation of reconstructive surgery
Payne 2001	Reconstructive surgery not the intervention evaluated

(Continued)

Payne 2004	Reconstructive surgery not the intervention evaluated
Robson 2000	Reconstructive surgery not the intervention evaluated
Satoh 1989	Not a RCT
Scevola 2010	Reconstructive surgery not the intervention evaluated
Sipponen 2008	Reconstructive surgery not the intervention evaluated
Smith 2013	A systematic review, not an evaluation of reconstructive surgery
Stamate 2005	Not a RCT
Suissa 2011	A systematic review, not an evaluation of reconstructive surgery
Vink 2011	Not a RCT or an evaluation of reconstructive surgery
Wagstaff 2014	Reconstructive surgery not the intervention evaluated
Zuloff-Shani 2004	Not a RCT or an evaluation of reconstructive surgery
Zuloff-Shani 2010	Not a RCT or an evaluation of reconstructive surgery

RCT - Randomised controlled trial

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix I. Search strategies

The Cochrane Central Register of Controlled Trials (CENTRAL)

ID Search

#1 MeSH descriptor: [Surgical Procedures, Operative] explode all trees

#2 MeSH descriptor: [Surgical Flaps] explode all trees

#3 (surger* or surgical*) .ti

#4 (primary near/3 closure*):ti,ab,kw

#5 (skin near/3 (graft* or transplant*)):ti,ab,kw

#6 ((surg* or random or region* or muscle or musculocutaneous or fascial* or fasciocutaneous* or perforat* or free) near/2 flap*):
ti,ab,kw

#7 "tissue expansion":ti,ab,kw

#8 {or #1-#7}

#9 MeSH descriptor: [Pressure Ulcer] explode all trees

#10 (pressure next (ulcer* or sore* or injur*)):ti,ab,kw

#11 (decubitus next (ulcer* or sore*)):ti,ab,kw

#12 ((bed next sore*) or bedsore*):ti,ab,kw

#13 {or #9-#12}

#14 {and #8, #13} in Trials

Ovid MEDLINE

1 exp surgical procedures, operative/

2 exp Surgical Flaps/

3 (surger* or surgical*).ti.

4 (primary adj3 closure*).ti,ab.

5 (skin adj3 (graft* or transplant*)).ti,ab.

6 ((surg* or reconstruct* or random or region* or muscle or musculocutaneous or fascial* or fasciocutaneous* or perforat* or free) adj2
flap*).ti,ab.

7 tissue expansion.ti,ab.

8 or/1-7

9 exp Pressure Ulcer/

10 (pressure adj (ulcer* or sore* or injur*)).tw.

11 (decubitus adj (ulcer* or sore*)).tw.

12 (bedsore* or bed sore*).tw.

13 or/9-12

14 and/8,13

15 randomized controlled trial.pt.

16 controlled clinical trial.pt.

17 randomi?ed.ab.

18 placebo.ab.

19 clinical trials as topic.sh.

20 randomly.ab.

21 trial.ti.

22 or/15-21

23 exp animals/ not humans.sh.

24 22 not 23

25 and/14,24

26 limit 25 to ed=20160301-20160926

Ovid Embase

1 exp surgical technique/

2 exp skin graft/

3 exp tissue flap/

4 exp tissue expansion/

5 (surger* or surgical*).ti.

6 (primary adj3 closure*).ti,ab.

7 (skin adj3 (graft* or transplant*)).ti,ab.

8 ((surg* or reconstruct* or random or region* or muscle or musculocutaneous or fascial* or fasciocutaneous* or perforat* or free) adj2 flap*).ti,ab. (26038)

9 tissue expansion.ti,ab.

10 or/1-9

11 exp decubitus/

12 (pressure adj (ulcer* or sore* or injur*)).tw.

13 (decubitus adj (ulcer* or sore*)).tw.

14 (bedsore* or bed sore*).tw.

15 or/11-14

16 10 and 15

17 Randomized controlled trials/

18 Single-Blind Method/

19 Double-Blind Method/

20 Crossover Procedure/

21 (random* or factorial* or crossover* or cross over* or cross-over* or placebo* or assign* or allocat* or volunteer*).ti,ab. (1563193)

22 (doubl* adj blind*).ti,ab.

23 (singl* adj blind*).ti,ab.

24 or/17-23

25 exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/ (22565994)

26 human/ or human cell/

27 and/25-26

28 25 not 27

29 24 not 28

30 and/16, 29

EBSCO CINAHL

S27S13 AND S26

S26S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25

S25TI allocat* random* or AB allocat* random*

S24MH "Quantitative Studies"

S23TI placebo* or AB placebo*

S22MH "Placebos"

S21TI random* allocat* or AB random* allocat*

S20MH "Random Assignment"

S19TI randomi?ed control* trial* or AB randomi?ed control* trial*

S18AB (singl* or doubl* or trebl* or tripl*) and AB (blind* or mask*)

S17TI (singl* or doubl* or trebl* or tripl*) and TI (blind* or mask*)

S16TI clinic* N1 trial* or AB clinic* N1 trial*

S15PT Clinical trial

S14MH "Clinical Trials+"

S13S7 AND S12

S12S8 OR S9 OR S10 OR S11

S11TI decubitus or AB decubitus
S10TI (bed sore* or bedsore*) or AB (bed sore* or bedsore*)
S9TI (pressure ulcer* or pressure sore*) or AB (pressure ulcer* or pressure sore*)
S8(MH “Pressure Ulcer+”)
S7S1 OR S2 OR S3 OR S4 OR S5 OR S6
S6TI tissue expansion OR AB tissue expansion
S5TI ((surg* or reconstruct* or random or region* or muscle or musculocutaneous or fascial* or fasciocutaneous* or perforat* or free) N2 flap*) OR AB ((surg* or random or region* or muscle or musculocutaneous or fascial* or fasciocutaneous* or perforat* or free) N2 flap*)
S4TI (skin N3 (graft* or transplant*)) or AB (skin N3 (graft* or transplant*))
S3TI (primary N3 closure*) OR AB (primary N3 closure*)
S2TI surger* or surgical*
S1(MH “Surgery, Operative+”)

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

Any one 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

Any one 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

Any 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' 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

Jason Wong: conceived the review question; developed and co-ordinated the review; completed the first draft of the review; approved the final draft of the review; and is the guarantor of the review.

Kavit Amin: conceived the review question; developed the review; completed the first draft of the review; and approved the final draft of the review.

Jo Dumville: conceived the review question; secured funding; developed and co-ordinated the review; completed the first draft of the review; and approved the final draft of the review.

Contribution of the editorial base

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

Gill Rizzello/Sally Bell-Syer (Managing Editors): co-ordinated the editorial process; advised on content; edited the protocol and the review.

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

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