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Alginate dressings for donor sites of split-thickness skin grafts

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ABSTRACT

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

To assess the effects of alginate dressings on donor site wound healing following split-thickness skin grafts.

BACKGROUND

Description of the condition

A split-thickness skin graft is the most common method used by surgeons to achieve skin coverage over large areas of de-epithelialised tissue (Kanapathy 2017). De-epithelialised tissue refers to an area of the body where the integrity of skin has been lost, often measured as a percentage of total body surface area (%TBSA). Re-epithelialisation occurs by division and migration of skin elements from deeper layers (CADTH 2013). For superficial or small wounds this will occur rapidly, with little or no scarring. If the area of skin loss is large or deep then it will take correspondingly longer to re-epithelialise. During this time the wound is at risk of infection, and there will inevitably be more scarring once the wound has healed. Split-thickness skin grafting permits rapid coverage of these areas. Most commonly used in burns surgery, split-thickness skin grafting necessitates the deliberate creation of a second injury, the donor site wound. The expectation is that the cre-

ated donor site wound will heal more rapidly than the primary area of skin loss. Much attention has been devoted to the burn injury, but rather less so to the donor site wound itself. Following split-thickness skin graft harvest, dermal cells remain in the bed of the donor site wound. This wound can therefore heal on its own over time ('healing by secondary intention'). Split-thickness skin grafts are not confined to burns surgery. They are also used to cover large areas of skin loss resulting from other causes, such as non-burn trauma. It is generally accepted that specific wound care is required to support donor site wound healing without complication (CADTH 2013).

Description of the intervention

Donor site wound dressings are designed to minimise the harm of a deliberately created injury; promoting wound healing. As an iatrogenic injury (i.e. caused by medical treatment), there is an imperative to minimise the risk of wound infection, pain, delayed healing, and scarring. It is perhaps surprising that little attention

has been directed at these wounds, particularly when compared with the attention directed at the primary wounds that subsequently necessitate the use of a split-thickness skin graft in an individual patient.

There is no universally agreed classification system for wound dressings, and no unifying rationale behind grouping systems in use. The British National Formulary classification system for wound management products lists products from simple to complex. It attempts to group products, but does so partly by mode of action and partly by construction of the dressing itself. For example, absorbent dressings are not all listed together, nor are dressings with antimicrobial properties. Alginates are listed as a class of their own under advanced wound dressings (BNF 2017, see Appendix 1). Dressings can be classified as moist or dry, depending on their state at application. Dressings can also be classified as antimicrobial or not, medicated or not and simple or complex, although the definitions of these terms with respect to dressings are not universally agreed.

There are many different types of dressing used to cover donor site wounds, based on both moist and non-moist wound healing techniques (Appendix 1). The concept of moist wound healing is generally attributed to Winter (Winter 1962). It involves the application of a dressing designed to maintain a moist wound environment as opposed to one that allows wound dessication. Moist wound healing has been demonstrated to lead to more rapid healing with less pain compared with dry healing methods (Winter 1962). Despite this there are variations in practice and donor site wounds are dressed with both dry and moist dressings (Voineskos 2009).

There is some consistency of opinion amongst clinicians regarding the properties of an ideal donor dressing, with analgesia and ease of removal amongst the most desirable qualities (Lars 2013). The majority of clinicians would prefer a single dressing until the donor site wound has healed (Lars 2013). While there is some agreement regarding the properties of an ideal donor site wound dressing, there is no consensus regarding which of the multitude of available dressings is optimal, as evidenced by the variety of dressings used by clinicians (Lyll 2000; Geary 2012).

Alginates are the most common donor site wound dressing used for split-thickness skin grafts in the United Kingdom and in Australasia (Lyll 2000; Geary 2012). They are produced as ribbons, ropes, and sheets, with the sheet form being the most commonly used form for donor site wound dressings. Alginates are the first choice dressing for split-thickness skin grafts for 48% of surgeons in Australasia (Lyll 2000). They are the first choice dressing in the United Kingdom on between 56% and 64% of occasions, depending on whether the patient is an adult or a child, and on whether the donor site wound is large or small (Geary 2012).

Alginates are predominantly derived from 3 of the 265 reported genera of the marine brown algae *Phaeophyceae* (Thomas 2000). Most alginates are harvested from the genus *Macrocystis* (e.g. the giant kelp *Macrocystis pyrifera*), but they are also extracted from

horsetail kelp (*Laminaria digitata*) and sugar kelp (*L. saccharina*) (Thomas 2000). Alginates are polysaccharides, carbohydrates (e.g. starch, cellulose, or glycogen) whose molecules consist of a number of sugar molecules bonded together. Alginates have varying ratios of D-mannuronic (M) and L-glucuronic (G) acids. The proportions of M, G, and mixed MG blocks within the alginate confer different chemical and physical properties. High-M alginates have increased fluid uptake and faster gel formation, whereas high-G alginates form harder and more resistant gels (Thomas 2000). Variations in the algae from which they are derived, the ratio of M and G blocks, and even the season in which the algae are harvested, all confer different properties to the resulting alginate (Johnson 1997). The general assumption has been that these differences are of negligible clinical relevance, but this assumption is largely untested. There are research data in animal models demonstrating statistically significant differences in handling characteristics across different alginates, but without significant differences in re-epithelialisation rates (Agren 1996). Other outcomes have not been tested, so it is possible these identified differences in alginate biology may lead to differences in performance in humans.

How the intervention might work

Alginate dressings can be shelf-stored as a dry dressing, and are easy to apply to a wound. They maintain a moist wound environment, forming a hydrophilic gel by interaction between serum sodium ions in the wound and calcium ions in the dressing (Thomas 2000; Sood 2014).

Alginate dressings may help to stem bleeding more rapidly than gauze, making them useful on newly created and bleeding donor site wounds (Steenfos 1998). This haemostatic property is thought to be due to the effects of calcium ions released from alginates interacting with coagulation pathways (Steenfos 1998). Dermal calcification in healed donor site wounds has been reported as a rare complication of alginates, supporting a calcium-release theory (Davey 2000). Alginates do not appear to have significant inherent antibacterial properties, which potentially puts donor site wounds at risk of infection and therefore delayed healing. Laboratory studies suggest alginates have effects on fibroblast proliferation and motility, perhaps in response to calcium release from cells (Doyle 1996). Fibroblasts are tissue cells critical for healing, so increasing their number and movement might be expected to improve healing.

Alginate dressings have absorptive properties which can wick away wound exudate, and they can absorb up to 20 times their weight (Sood 2014). Alginate dressings can be left in situ for some days, minimising damage to healing epithelial cells from repeated dressing removal and reapplication.

Why it is important to do this review

There is no current consensus regarding the best dressing for donor site wounds (Rakel 1998; Wiechula 2003; Voineskos 2009). It would appear donor site wound dressing selection is currently determined by local practice rather than by sound evidence, with much variation between clinicians regarding their choice of dressing (Lyll 2000; Geary 2012). There is more unanimity of opinion regarding the properties of an ideal dressing than there is regarding choice of dressing (Lars 2013). Clinicians seek dressings that do not adhere to the wound bed, are pain-free at dressing change, absorbent, and easy to remove (Lars 2013). The majority of clinicians would prefer a dressing that stays in place until donor site wound re-epithelialisation (Lars 2013). They also agree that such an 'ideal' dressing does not currently exist.

Desirable properties of donor site wound dressings are not mutually inclusive and ease of use, speed of healing, cost, and analgesic properties may not coincide in the same dressing. Clinicians may have to decide which of these properties are most advantageous. For example, more rapid donor site wound healing in larger burns allows earlier graft reharvesting, as well as limiting the problems associated with large areas of skin loss. Pain at the donor site following split-thickness skin graft is often higher than at the recipient site (Feldman 1991; Persson 2000). Published studies suggest decreased pain may be associated with faster healing (Miller 2011; Brown 2014). In resource-limited countries, cost is an important issue in deciding which dressings to stock.

A systematic review of available randomised controlled trials (RCTs) will support evidence-based decision-making regarding donor site wound dressings. Dressing technology is changing continually, and previous reviews now predate newer dressing options (Rakel 1998; Wiechula 2003; Voineskos 2009). It is important to compare alginates, which are the most commonly used dressing for donor sites, with other options currently available, with the aim of updating the evidence base.

This review is part of a suite of reviews currently being conducted investigating different classes of donor site wound dressing.

OBJECTIVES

To assess the effects of alginate dressings on donor site wound healing following split-thickness skin grafts.

METHODS

Criteria for considering studies for this review

Types of studies

We will include all randomised controlled trials (RCTs), irrespective of language and publication status. We will exclude quasi-randomised studies (studies where the allocation of participants to interventions is not truly random e.g., alternate allocation, allocation by date of birth, or allocation by medical record number).

Types of participants

We will include people of any age in any setting who have a donor site wound created as a result of harvesting a split-thickness skin graft. The donor site wound may be created as an elective or an emergency procedure. Only studies involving human participants will be considered. Split-thickness skin grafts harvested for any cause will be considered (e.g. burns, trauma, pressure ulcers). We will exclude full thickness skin grafts donor site wounds, since these require alternative closure methods.

Types of interventions

We will include studies in which any alginate dressing is applied to donor site wounds with a view to promoting healing.

We anticipate that likely comparisons in this systematic review may include:

- comparisons of alginate dressings as a primary dressing with other dressings, or topical agents
- different types of alginate dressings compared with each other.

Types of outcome measures

If a trial is eligible for inclusion (i.e. has the correct design, population and intervention/s) but does not report a listed outcome we will contact the study authors, if possible, to determine if a listed outcome was recorded but not reported.

Some of the outcomes listed below may be recorded at multiple time points. An example of this might be itch or pain and during and after healing of the donor site wound. Another example is scar appearance at 3, 6, and 12 months. We anticipate grouping outcomes by the following time points:

- short-term: from donor site wound creation to 30 days;
- medium-term: > 30 days after donor site wound creation to 6 months;
- long-term: > 6 months after donor site wound creation.

Primary outcomes

1. Wound re-epithelialisation

We will use time to re-epithelialisation, correctly analysed using censored data and preferably adjusted for prognostic covariates such as baseline size.

2. Donor site pain

Donor site pain is a second primary outcome and the pain may occur at dressing changes or with dressing in situ (Mauck 2017).

Studies with pain scores that do not distinguish donor site pain from generic pain will be excluded. Pain may be measured using validated scales, or other objective measures. Patient self-reports of pain only, rather than observer reports, will be analysed.

Secondary outcomes

1. Scar appearance

Scar appearance may be measured using scales such as the Vancouver Scar Scale (VSS), the Patient and Observer Scar Assessment Scale (POSAS), or by objective measures such as ultrasound assessment of scar thickness (Draaijers 2004; Tyack 2012). Since scarring is known to alter with time, we will also record the timing of scar assessments from graft harvest and/or healing. Scar appearance by observers will be assessed separately from patient scar appearance scores, since these may differ significantly.

2. Donor site wound infection

Infection and biofilms are known to delay burn wound healing (Metcalf 2013). Authors' definition of SSI will be used: however use of the Centers for Disease Control (CDC) Surgical Site Infection (SSI) definition will be regarded as more valid (Horan 1997; NHSN 2017).

3. Donor site itch

Itch is a distressing phenomenon for patients, and is known to occur with wound healing (Mauck 2017). It may persist post-healing (Mauck 2017). As with pain, patient reports of itch only will be accepted, and only in those studies where itch is specific to the donor site (rather than the grafted wound). Visual analogue scales, numeric rating scales, or validated scales such as the Itch Man Scale (Morris 2012) will be accepted. As with pain, itch may be recorded at dressing change or with the dressing in situ.

4. Quality of life

We will assess patient quality of life, with donor site wound dressings. This review will ultimately impact on patient care. It is the patients who have to live with the consequences of these injuries, so we believe it appropriate to review patient-assessed outcomes, such as quality of life. We will measure this using validated scales, where reported, such as the Short Form (36) health survey (SF-36) or the EuroQol Five Dimensions questionnaire (EQ-5D).

Search methods for identification of studies

Electronic searches

We will search the following databases to retrieve reports of relevant trials:

- the Cochrane Wounds Specialised Register;
- the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (latest issue);
- Ovid MEDLINE (from 1946 onwards);

- Ovid MEDLINE (In-Process & Other Non-Indexed Citations);
- Ovid Embase (from 1974 onwards);
- EBSCO CINAHL Plus (from 1946 onwards).

We have devised a draft search strategy for CENTRAL which is displayed in Appendix 2. We will adapt this strategy to search Ovid MEDLINE, Ovid Embase and EBSCO CINAHL Plus. 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 terms developed by the UK Cochrane Centre (Lefebvre 2011). We will combine the CINAHL Plus searches with the randomised trial filter developed by the Scottish Intercollegiate Guidelines Network (SIGN 2017). There will be no restrictions of the searches with respect to language, date of publication or study setting.

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

- ClinicalTrials.gov (www.clinicaltrials.gov);
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/trialsearch);
- EU Clinical Trials Register (www.clinicaltrialsregister.eu/ctr-search/search).

We will also search the following databases to identify reports of relevant trials published in conference abstracts and theses:

- ProQuest COS Conference Papers Index (from 1982 onwards);
- ProQuest Dissertations & Theses Global (from 1861 onwards).

Searching other resources

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

When necessary, we will contact experts in wound care and pharmaceutical companies to enquire about unpublished, ongoing and recently published trials.

We will not perform a separate search for adverse effects of alginate dressings for donor sites of split-thickness skin grafts. We will consider adverse effects described in included studies only.

Data collection and analysis

Selection of studies

Two review authors (CM and BP) will independently screen titles, abstracts, and keyword or descriptor terms of the retrieved

articles for potential relevance. We will obtain full-text copies of studies if initial assessment suggests potential inclusion. We will retrieve full articles in ambiguous cases, and in cases where a single author has identified a study for potential inclusion. Two review authors will then independently further assess the retrieved articles for final selection. Discrepancies will be resolved by discussion and consensus. If no consensus is reached we will use a third author to make a casting decision. Depending on the number of potentially relevant articles retrieved, this task may be shared amongst the entire review authorship. In all cases at least two authors will independently check studies for final selection. All authors have clinical experience in burns, and/or experience in prior systematic reviews. We will record reasons for exclusion of those studies where full-text was retrieved. We will complete a PRISMA flowchart to summarise this selection (Liberati 2009).

Data extraction and management

Each author will be assigned a share of the included studies, such that each study has two review authors extracting data. We will use a data extraction sheet to summarise each study. Duplicated studies will have their data recorded once only, but all study reports will be used to maximise data extraction. Where there are missing data from reports, we will contact the study authors to request this information. Discrepancies will be resolved by discussion and consensus amongst all authors. If there is no consensus the majority opinion will apply. Where studies have intervention arms that are not eligible, we will only extract data from intervention and control arms that meet eligibility criteria.

We will extract the following data, by treatment group and for relevant time points where appropriate:

- year of publication, or publication status if unpublished;
- country of origin and care setting;
- trial design (e.g. parallel, cluster);
- study registration;
- pre published protocol;
- randomisation method, and unit of randomisation (patient or wound);
- allocation method;
- blinding of allocation and/or outcome assessment;
- duration of follow-up;
- funding source/s;
- declarations of potential conflicts of interest;
- number of participants or wounds randomised to each trial arm;
- unit of analysis (patient or wound);
- type of wound being grafted (e.g. burn, venous ulcer);
- primary and secondary outcome/s, with definitions and time points;
- outcome data for primary and secondary outcomes (by group);

- measurement scales used for outcomes, and rationale for use;
- number of withdrawals (by group);
- intervention received by each group;
- duration of treatment; and
- concurrent interventions.

These data will be used to populate results tables for individual studies, and to facilitate risk-of-bias assessments for each study. Separate searches will be performed for pre-published protocols. In addition, the text of published articles will be searched for mention or citation of a pre-published protocol and/or trial registration. Any available published version of a protocol will be considered for data extraction regarding trial design.

Assessment of risk of bias in included studies

Two review authors will independently apply the Cochrane tool for assessing risk of bias to the included studies (Higgins 2011a; see Appendix 3). This tool assesses six domains: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, other issues (e.g. source of funding). Blinding and the completeness of outcome data will be assessed for each outcome separately. It is difficult to blind participants and personnel to particular dressings, as many are uniquely recognisable. Therefore this domain of the 'Risk of bias' assessment will be weighted 'low' accordingly. We will focus instead on blinding for outcome assessment, and use this for assessment of risk of bias from blinding for these studies. We will construct and present a 'Risk of bias' table from the available data for each eligible study. Any disagreement will be discussed until a consensus is reached. If there is no consensus we will involve a third author as a casting vote. We will present the data as two tables. The first will be a summary of risk of bias for each domain across all studies, and a second which will cross-tabulate each study across all 'Risk of bias' items.

It is possible trials may have been conducted by industry or agents that produce or have close ties to the products under investigation. This creates a duality of interest at least, and conflicts of interest are possible in such cases. Declarations of such dualities or conflicts become important, as they contribute to judgements on whether methodological decisions may have been influenced by possible vested interests. Studies funded by industry are more likely to have outcomes favouring the funder, when compared against studies with other sponsors (Lundh 2012). Studies authored by principal investigators with ties to industry are similarly more likely to have favourable outcomes (Ahn 2017). Declarations within the published manuscript will be used to determine author/industry affiliations and will be extracted into the 'Characteristics of included studies' table.

The presence of a pre-published protocol allows assessment of outcome switching once data become available within the trial (Category 5 - selective outcome reporting).

If there are trials using cluster randomisation we will apply further 'Risk of bias' considerations: recruitment bias, baseline imbalance, loss of clusters, incorrect analysis, and comparability with individually randomised trials ([Higgins 2011b](#); see [Appendix 4](#)). If cluster randomised trials have been analysed incorrectly, we will extract and present data but perform no further analyses.

Measures of treatment effect

We will calculate treatment effects for dichotomous outcomes using relative risk (RR) and risk difference (RD) with 95% confidence intervals (CI). The numbers needed to treat for an additional beneficial or harmful outcome (NNTB or NNTH, respectively) will be estimated if RD is statistically significant.

For wound healing data we will record 'time to event (wound healing)' as the time (in days) from donor site wound creation until re-epithelialisation, as defined by each study's authors. Time to healing will be expressed as a Hazard Ratio.

For continuous outcomes, we will use the mean difference (MD) with 95% CI to describe the data if all trials use the same or similar assessment scales, and final scores will be chosen over change scores. Where trials use different assessment scales, we will use standardised mean difference (SMD) with 95% CIs. We may back-transform SMD data into a common scale (e.g. Patient Observer Scar Assessment Scale/POSAS) for the purposes of presentation. Where this is done we will present a justification for our choice of scale, and will use the pooled baseline SD of studies using that scale. For multiple studies using that scale, we will present a range from lowest to highest SD.

Unit of analysis issues

Some studies randomise by participant, but analyse outcomes by wound. Where this occurs, and the numbers of participants and wounds are equal (i.e. one wound per participant) we will treat the participant as the unit of analysis. There may be instances of clustered data, where a proportion of trial participants have outcome data collected and reported on multiple wounds. Since not all participants will have multiple wounds this is not a cluster trial per se but rather a trial that incorrectly includes a mixture of individual and clustered data. Such trials will be noted and the issue will be recorded in the risk of bias assessment. Data will be extracted and presented but not the subject of any further analyses. We will only incorporate clearly conducted fully cluster trials into meta-analyses if the trial has been analysed correctly. Where a cluster-randomised trial has been conducted but incorrectly analysed we will record this in the 'Risk of bias' assessment. If it is possible, we will approximate the correct analyses with guidance from the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011b](#)), using information on:

- the number of clusters randomised to each intervention, or the mean size of each cluster;

- outcome data ignoring cluster design for the total number of individuals; and
- an estimate of the intracluster correlation coefficient (ICC).

If we cannot analyse the study data correctly, we will extract and present the data without further analysis.

We will ensure there are no unit of analysis issues with double counting of controls when using studies with multiple intervention arms.

Where repeated observations are recorded on the same participant (e.g. pain or scar scales over time), we will define time points and analyse accordingly. Where multiple recordings are available within these time points we will incorporate all available data for an overall mean where possible.

Dealing with missing data

Missing data from trial reports potentially compromises outcome measures by introducing bias into the trial. Where data are missing we will contact authors of included studies for clarification. A partially filled data extraction form (with data from their own study) will be supplied, along with an open-ended request for more data. Where data are missing, this will be described in the Results section and also in the 'Characteristics of included studies' section. Participants with missing data will be described. Data will be analysed on an available case basis. We will substitute means for medians if a study has reported medians. If measures of variance are missing, we will calculate these where possible using standard Cochrane methodology. If we are unable to calculate these measures, then those studies will be excluded from any relevant meta-analyses.

Assessment of heterogeneity

Where appropriate, and depending on their clinical and statistical heterogeneity, we will pool data ([Higgins 2003](#)). Assessment of heterogeneity is complex and multifaceted. We will assess the clinical and methodological heterogeneity of included studies by considering them in terms of participants, dressing types, and outcome parameters. We will assess heterogeneity by visual examination of the forest plots, and assess statistical heterogeneity using the χ^2 test and I^2 measure. We will consider a χ^2 significance of $P > 0.10$ as representing statistically significant heterogeneity. I^2 examines the percentage of total variation across RCTs that is due to heterogeneity rather than chance. ([Higgins 2003](#)). Generally, I^2 values of 40% or less might not be important when assessing the level of heterogeneity. Values of 75% or more indicate considerable heterogeneity. We will use a combination of these measures to assess heterogeneity. If we judge data to be too heterogeneous (e.g. χ^2 test with $P > 0.10$, and I^2 values of 75% or greater), then results will be presented narratively only. We address how we will deal with potential heterogeneity further in [Data synthesis](#).

Assessment of reporting biases

Assymetry will be assessed by visual inspection of funnel plots. We will present funnel plots for meta-analyses comprising at least 10 RCTs using Review Manager 5 to assess publication bias ([RevMan 2014](#)). The funnel plot is essentially a scatter plot of outcome estimates from RCTs against some measure of a trial's precision or (more commonly) size ([Egger 1997](#); [Sterne 2011](#)). Smaller studies commonly over-estimate positive effects, in what is known as the 'small study effect', and can lead to biases in meta-analyses. Negative studies are less likely to be submitted, published, and cited. Assymetry in funnel plots is commonly taken to reflect publication bias, but there are other causes of such asymmetry ([Egger 1997](#)). Other possible reasons are true heterogeneity, data irregularities, artefactual, or simply chance.

Publication bias is only one form of reporting bias. Others include time lag, duplicate publication, location, citation, language and/or outcome reporting biases. Since trial registries are being searched, we will have a list of trials registered but not published at the time of this review. These will be identified for future updates of this review. Multiple publication may be identified by noting similarities in published data from the same centre or authors. In such situations we will check with the authors, and use all publications to derive a single data set such that individual patients' data are not included twice. Our strategy for searching multiple databases and languages should mitigate location, citation, and language biases. Comparison of the registered trial with its outcome data may allow us to detect any outcome reporting bias. If such bias exists we will highlight this in our results.

Data synthesis

We will provide a descriptive summary of included studies according to comparators, combining details according to primary and secondary outcomes. We will consider both clinical and methodological heterogeneity. Where studies appear appropriately similar we will pool results. Where studies are not similar enough for pooling, results will be presented narratively. Data pooling may not be possible where populations are widely dissimilar (such as the elderly versus children).

We are unable to pre-specify the amount of clinical, methodological and statistical heterogeneity in the included studies but it might be extensive. Thus, we anticipate using a random-effects approach for meta-analysis. Conducting meta-analysis with a fixed-effect model in the presence of even minor heterogeneity may provide overly narrow confidence intervals. We will only use a fixed-effect approach when clinical and methodological heterogeneity is assessed to be minimal, and the assumption that a single underlying treatment effect is being estimated holds. Chi-squared and I-squared will be used to quantify heterogeneity but will not be used to guide choice of model for meta-analysis. We will exercise caution when meta-analysed data are at risk of small study effects because a random-effects model may be unsuitable. In this case, or

where there are other reasons to question the selection of a fixed-effect or random-effects model, we will assess the impact of the approach using sensitivity analyses to compare results from alternate models. We will report any evidence that suggests that the use of a particular model might not be robust. We may meta-analyse even when there is thought to be extensive heterogeneity. We will attempt to explore the causes behind this using meta-regression, if possible ([Thompson 1999](#)).

We will use forest plots to present data. We will present summary estimates of each effect, along with 95% confidence intervals (CI). For dichotomous outcomes we will present relative risk (RR). For continuous outcomes we will present pooled MD and 95% CI where studies report the same scale or method, or pooled SMD and 95% CI where studies measure the same outcome using different methods. For time to event data (such as days to re-epithelialisation) we will plot (and pool if appropriate) estimates of hazard ratios and 95% CIs, using the generic inverse variance method in Review Manager 5 ([RevMan 2014](#)).

'Summary of findings' tables

We will present the main results of the review in 'Summary of findings' tables. These tables are designed to present key information regarding the major outcomes, illustrative comparative risks and effect estimates, numbers of participants and studies used in these determinations ([Schünemann 2011a](#)). The 'Summary of findings' table also includes an overall assessment of the quality of the evidence related to each outcome using the GRADE approach. The GRADE approach seeks to define the quality of a body of evidence as the extent to which the reader can be confident that an estimate of effect or association is close to the true quantity under interrogation. The quality of this evidence will be rated high, moderate, low, or very low depending on the directness of the evidence in addressing the study question/s, the risk of bias in the included studies (methodological quality), the precision of effect estimates, the consistency of the evidence (degree of heterogeneity), and the risk of publication bias in the body of literature available ([Schünemann 2011b](#)).

We plan to present the following outcomes in the 'Summary of findings' tables:

- time to wound re-epithelialisation;
- pain;
- donor site infection;
- itch.

Subgroup analysis and investigation of heterogeneity

If numbers and data permit, we will conduct subgroup analysis confined to paediatric patients. The definition of a paediatric patient varies, with cut-offs determined by local hospital practices somewhere in the 14 to 18 year range. This may limit our ability to determine any differences in outcomes between paediatric and

adult patients, or in varying age ranges. We will limit this subgroup analysis to patients 0-18 years of age.

Subgroup analyses for paediatric patients will be performed for each dressing type, following the British National Formulary wound dressing classification (BNF 2017). If data permit, further subgroup analyses will be performed for individual dressings.

Subgroup analyses will be performed using the same methodologies as outlined above to determine if any treatment effects observed hold true in children.

Sensitivity analysis

We will perform a sensitivity analysis to examine the sensitivity of the results to excluding high risk of bias studies; that is any study that is assessed as being high risk of bias in any of the following domains:

- generation of the randomisation sequence;
- allocation concealment;
- blinding of outcome assessment.

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

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Finally, and most importantly, we would like to thank those participants, parents and care-givers who agreed to be a part of the randomised controlled trials that will be analysed in this review. Without their consent and participation, those trials, and subsequently this review, would not have been possible.

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* Indicates the major publication for the study

APPENDICES

Appendix I. British National Formulary Wound Dressings Classification

The British National Formulary categorises dressings under the headings below (BNF 2017). Within each category there is a listing of dressings currently available.

Basic wound contact dressings

- Low adherence dressings
- Absorbent dressings

Advanced wound dressings

- Hydrogel dressings
- Sodium hyaluronate dressings
- Vapour-permeable films and membranes
- Soft polymer dressings
- Hydrocolloid dressings
- Foam dressings
- Alginate dressings
- Capillary-action dressings
- Odour-absorbent dressings

Antimicrobial dressings

- Honey
- Iodine
- Silver
- Other antimicrobials

Specialised dressings

- Protease-modulating matrix dressings
- Silicone keloid dressings

Appendix 2. The Cochrane Central Register of Controlled Trials (CENTRAL) draft search strategy

#1 MeSH descriptor: [Bandages] explode all trees

#2 MeSH descriptor: [Alginates] explode all trees

#3 (alginate* or activheal or algisite or algosteril or biatain or cutimed or curasorb or kaltostat or kendall or melgisorb or seasorb or sorbalgon or sorbsan or suprasorb or tegaderm or tegagel or urgorsorb):ti,ab,kw

#4 {or #1-#3}

#5 MeSH descriptor: [Skin Transplantation] explode all trees

#6 MeSH descriptor: [Transplantation, Autologous] explode all trees

#7 MeSH descriptor: [Transplant Donor Site] explode all trees

#8 (((split next thick*) or split-thick* or “split skin” or split-skin or “partial dermal” or partial-dermal or (partial next thick*) or partial-thick*) near/3 graft*):ti,ab,kw

#9 ((skin or derm*) next transplant*):ti,ab,kw

#10 STSG:ti,ab,kw

#11 “donor site”:ti,ab,kw

#12 {or #5-#11}

#13 {and #4, #12} in Trials

Appendix 3. The Cochrane tool for assessing risk of bias

I. 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 provided to permit a 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 provided to permit a 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 of participants/care providers/outcome assessors - 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 is 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 is likely to introduce bias.

Unclear risk of bias

Either of the following.

- Insufficient information provided 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 are unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias).
- Missing outcome data are 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 the observed event risk is not enough to have a clinically relevant impact on the intervention effect estimate.
- For continuous outcome data, a plausible effect size (difference in means or standardised difference in means) among missing outcomes is not enough to have a clinically relevant impact on the 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 are likely to be related to the true outcome, with either an imbalance in numbers or reasons for missing data across intervention groups.
- For dichotomous outcome data, the proportion of missing outcomes compared with the observed event risk is enough to induce clinically relevant bias in the intervention effect estimate.
- For continuous outcome data, a plausible effect size (difference in means or standardised difference in means) among missing outcomes is enough to induce clinically relevant bias in the observed effect size.
- 'As-treated' analysis is done with a 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 a judgement of low or high risk of bias (e.g. number randomised not stated, no reasons for missing data provided).
- The study did not address this outcome.

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

Low risk of bias

Either of the following.

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

High risk of bias

Any one of the following.

- Not all of the study's prespecified primary outcomes have been reported.
- One or more primary outcomes are reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not prespecified.
- One or more reported primary outcomes was/were not prespecified (unless clear justification for their reporting is provided, such as an unexpected adverse effect).

- One or more outcomes of interest in the review is/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 is provided to permit a 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;
- 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 4. 'Risk of bias' assessment (cluster-randomised 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 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 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 (many of which were performed in nursing home, 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

Craig McBride: conceived the review question, developed and drafted the protocol, contributed to writing and editing the protocol, approved the final version of the protocol prior to submission and is guarantor of the protocol.

Bhaveshkumar Patel: developed the protocol, contributed to writing and editing the protocol, and approved the final version of the protocol prior to submission.

Kellie Stockton: developed the protocol, contributed to writing and editing the protocol, and approved the final version of the protocol prior to submission.

Vishal Kapoor: developed the protocol, contributed to writing and editing the protocol, and approved the final version of the protocol prior to submission.

Roy Kimble: developed the protocol, contributed to writing and editing the protocol, and approved the final version of the protocol prior to submission.

Contributions of the editorial base

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

Gill Rizzello (Managing Editor): coordinated the editorial process; advised on content and edited the protocol.

Naomi Shaw and Reetu Child: designed the search strategy and edited the search methods section.

Ursula Gonthier: edited the reference section.

DECLARATIONS OF INTEREST

Craig McBride: this study forms part of my PhD in donor site wound dressings. I have performed a parallel three-arm prospective randomised controlled trial in donor site wound dressings, with alginates as one of the treatment arms. My host institution received an unrestricted research grant from Abigo Medical AB to conduct this trial, which will potentially be eligible for inclusion in this review. 'Risk of bias' assessment, decisions to include or exclude trials, and data extraction and checking will be performed by members of the review team not associated with this trial. I have received financial support for travel and accommodation in my role as an advisory board member for an intraperitoneal insulin delivery device.

Bhaveshkumar Patel: none known.

Kellie Stockton: I have performed a parallel three-arm prospective randomised controlled trial in donor site wound dressings, with alginates as one of the treatment arms. This trial will potentially be eligible for inclusion in this review. Risk of bias assessment, decision to include or exclude, and data extraction and checking will be performed by members of the review team not associated with this trial.

Vishal Kapoor: none known.

Roy Kimble: I have performed a parallel three-arm prospective randomised controlled trial in donor site wound dressings, with alginates as one of the treatment arms. This trial will potentially be eligible for inclusion in this review. Risk of bias assessment, decision to include or exclude, and data extraction and checking will be performed by members of the review team not associated with this trial.

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