Staples versus sutures for surgical wound closure in adults (Protocol)

Cirocchi R, Randolph JJ, Montedori A, Cochetti GG, Arezzo A, Mearini EE, Abraha I, Trastulli S

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[Intervention Protocol]

Staples versus sutures for surgical wound closure in adults

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ABSTRACT

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

To compare the effects of sutures and staples for the closure of surgical wounds in adults undergoing surgery in a hospital setting.

BACKGROUND

Description of the condition

Millions of surgical interventions are performed annually worldwide, and morbidity and mortality vary internationally (Pearse 2006; Weiser 2008). Wound complications are one of the most common sources of morbidity and mortality for patients undergoing surgical procedures.

Surgical site infections (SSIs) are one of the complications of surgery and they are associated with prolonged inpatient stay, increased hospital re-admission, mortality, increased costs and a detrimental effect on health-related quality of life (Anthony 2003; Kirkland 1999; Sorensen 2005).

The Centers for Disease Control and Prevention (CDC) defines three levels of severity of SSIs (Health Protection Agency 2006; Horan 1992):

1. superficial incisional, affecting the skin and subcutaneous tissue;
2. deep incisional, affecting the fascial and muscle layers;
3. organ or space infection, involving any part of the anatomy other than the incision that is opened or manipulated during the surgical procedure.

In 2006, it was estimated that healthcare-associated infections affected about 8% of hospitalised patients in the UK and that SSIs represented 14% of these infections (Smyth 2008). A recent US study on the incidence, impact and treatment costs of SSIs, which utilised data from the 2005 Healthcare Cost and Utilization Project National Inpatient Sample, found that SSI is associated with a significant economic burden in terms of extended length of stay and increased costs of treatment; it resulted in nearly one million additional inpatient days and USD 1.6 billion in excess costs (de Lissovoy 2009).

The UK National Institute for Health and Clinical Excellence (NICE) guidelines on the prevention and treatment of surgical site

infections, published in 2008, identify the following risk factors for developing a SSI, independent of the suture methods used: age, underlying illness (American Society of Anesthesiologists score of three or more, diabetes, malnutrition, low serum albumin, radiotherapy and steroid use), obesity, smoking, site, level of wound contamination and complexity of the procedure (NICE 2008). Randomised clinical trials are needed in order to evaluate the impact of these risk factors in different surgical site infections and in different types of surgery.

Wound dehiscence (rupture) is another complication of surgical procedures that may increase the inpatient stay, resulting in additional costs, and it has a 9.6% attributable mortality (Zhan 2003). Additional surgical wound complications are the formation of hypertrophic or keloid scarring, or contractures. The cosmetic appearance of the scar after healing is a relevant outcome, which affects the satisfaction of patients.

The aim of surgical wound closure is to achieve rapid wound healing and a satisfactory cosmetic result, and to reduce the risks of complications, including dehiscence and infection. Different methods and materials are used for wound closure and they are highly dependent on the length and anatomical location of the wound (Hochberg 2009). Consequently, surgeons closing wounds need to choose the best available method (Hochberg 2009).

Description of the intervention

Skin closure of surgical wounds is usually achieved with sutures. Sutures can be continuous or interrupted and the material used can be natural or synthetic, absorbable or non-absorbable, single filament or braided, depending on the length and anatomic location of the wound; their use is at the discretion of the surgeon.

Staples are an alternative option to sutures and are mainly made of stainless steel, although staples using absorbable materials are now available (Hochberg 2009). The potential advantage of staples in surgical wound closure is related to their low level of tissue reactivity (Edlich 2010). This generates a higher resistance to infection in contaminated wounds, given the non-introduction of exogenous material and consequent impairment of local immune response (Johnson 1981; Pickford 1983; Roth 1988; Stillman 1980). It is thought that the use of staples reduces the local inflammatory response, width of the wound, time to wound closure and residual cross marks (George 1985; MacGregor 1989).

How the intervention might work

A meticulous surgical technique is needed to avoid local swelling, dehiscence of the wound and a poor cosmetic result.

Staples are automatically applied directly onto the skin at the wound site using a disposable stapler. They are sometimes preferred because of their ease of use and the rapidity of application. Staples are commonly used in surgical specialties such as gastrointestinal, gynaecological, urologic, vascular, cardiothoracic, orthopaedic, head, neck and hand surgery.

The principal advantages of sutures are their flexibility, strength, non-toxicity and in vivo degradation properties.

Why it is important to do this review

There is a perception that staples are better in terms of efficacy of fixation and good cosmetic results. However, there are mixed data in the medical literature from comparisons between staples and sutures. While some studies report that there is no difference between the two methods (Clayer 1991; Eldrup 1981), others report higher rates of wound complications following the use of staples (Chughtai 2000; Smith 2010). A systematic review of randomised trials is needed to compare staples and sutures for surgical wound closure in all areas of surgery.

OBJECTIVES

To compare the effects of sutures and staples for the closure of surgical wounds in adults undergoing surgery in a hospital setting.

METHODS

Criteria for considering studies for this review

Types of studies

We will consider randomised controlled trials (RCTs) and cluster-randomised trials comparing staples with sutures in any type of surgery. We will exclude non-randomised studies.

Types of participants

Trials recruiting adults (aged 18 years or over) undergoing any type of surgical intervention in a hospital operating theatre.

Types of interventions

The interventions to be considered are staples or sutures, where these are directly compared. We will not include studies that have used any other material (e.g. steri-strips, glue, adhesives).

Types of outcome measures

Primary outcomes

- Rates of overall wound infection (including superficial, deep or space infections) (30 postoperative days). We will attempt to use the standard definitions of CDC (Horan 2008). If this is not possible, we will use the definitions given by the trial authors.
- Rates of severe wound infection (only deep or space infections) (30 postoperative days).

Secondary outcomes

- Length of hospital stay.
- Rates of readmission.
- Adverse events (e.g. rate of wound dehiscence, allergic reaction to staple or suture material) (30 postoperative days).
- Patient satisfaction (e.g. hypertrophic and keloid scarring at maximal 12-month follow-up).
- Pain, measured by a validated scale.

Search methods for identification of studies

Electronic searches

We will search the following electronic databases to identify reports of relevant randomised clinical trials::

- Cochrane Wounds Group Specialised Register;
- Cochrane Central Register of Controlled Trials (CENTRAL) (latest issue);
- The Database of Abstracts of Reviews of Effects (DARE) (latest issue);
- The NHS Economic Evaluation Database (NHS EED) (latest issue);
- Ovid MEDLINE (1946 to present);
- Ovid MEDLINE (In-Process & Other Non-Indexed Citations, to date);
- EMBASE (1974 to present);
- CINAHL (1982 to date).

The following search strategy will be used in the Cochrane Central Register of Controlled Trials (CENTRAL):
#1 MeSH descriptor: [Sutures] explode all trees
#2 MeSH descriptor: [Surgical Staplers] explode all trees
#3 MeSH descriptor: [Surgical Stapling] explode all trees
#4 #2 or #3
#5 #1 and #4
#6 ((sutur* or "hand sewn" or "hand sewing" or stitch* or hand-sewn or "manual closure" or catgut* or "cat gut") and stapl*):ti,ab
#7 #5 or #6
#8 MeSH descriptor Surgical Wound Infection explode all trees
#9 MeSH descriptor Surgical Wound Dehiscence explode all trees
#10 (surg* near/5 infect*):ti,ab,kw
#11 (surg* near/5 wound*):ti,ab,kw
#12 (surg* near/5 site*):ti,ab,kw
#13 (surg* near/5 incision*):ti,ab,kw
#14 (surg* near/5 dehisc*):ti,ab,kw
#15 (wound* near/5 dehisc*):ti,ab,kw
#16 (wound* near/5 infect*):ti,ab,kw
#17 (wound near/5 disruption*):ti,ab,kw
#18 (wound next complication*):ti,ab,kw
#19 #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18
#20 #7 and #19
We will search the following in an effort to identify published, unpublished and ongoing trials:

- ClinicalTrials.gov (clinicaltrials.gov)
- Current Controlled Trials (www.controlled-trials.com)
- Trials Central (www.trialscentral.org)

The search strategies for Ovid MEDLINE, Ovid EMBASE and EBSCO CINAHL are in found in Appendix 2; Appendix 3 and Appendix 4 respectively.
We will adapt this strategy to search Ovid MEDLINE, Ovid EMBASE and EBSCO CINAHL. We will combine the MEDLINE search with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision) (Lefebvre 2011). We will combine the EMBASE search with the Ovid EMBASE filter developed by the UK Cochrane Centre (Lefebvre 2011). We will combine the CINAHL searches with the trial filters developed by the Scottish Intercollegiate Guidelines Network (SIGN 2011).
We will check the reference lists of all relevant papers, such as systematic reviews or meta-analyses identified through the database searches. There will be no date, language or publication status restrictions.

Searching other resources

In addition, we will search the references of relevant studies. We will contact commercial companies providing sutures and staples (e.g. US Surgical Corporation Autosuture Company, Ethicon, Johnson & Johnson) to ask for references to relevant studies or unpublished data.

Data collection and analysis

Selection of studies

One review author (RC) will run all the electronic searches, download the references into bibliographic software and remove duplicates. Two review authors (RC, AR) will independently assess the

titles and abstracts first and then only assess in full text the studies that appear to be relevant. Disagreements will be resolved through discussion with the review team and the arbitrator (AM). One of the review authors (EM) will contact the corresponding author of the publications if data are missing or clarification is needed.

Data extraction and management

We will construct a data extraction sheet for the review and two review authors (RC, GC) will use this independently for data collection. These authors will be blinded to each other's data; however, they will not be blinded to the journal of publication or the trial authors.

Two review authors will independently extract the following information from each included trial:

- setting of the study;
- sample sizes
- participants
- baseline characteristics of patients
- interventions
- type of surgery
- outcomes
- follow-up points.

If information is missing from the published paper, we will contact the trial authors. We will compare results to check for inconsistencies and resolve disagreements by discussion or, if consensus cannot be reached, through adjudication by a third review author (EM).

Assessment of risk of bias in included studies

Two review authors will independently assess the included studies using The Cochrane Collaboration tool for assessing risk of bias (Higgins 2011). This tool addresses six specific domains: sequence generation, allocation concealment, blinding, incomplete data, selective outcome reporting and other issues (Appendix 5). We will assess blinding and completeness of outcome data for each outcome separately. We will complete a 'Risk of bias' table for each eligible study. We will discuss any disagreement amongst all review authors to achieve a consensus.

We will present our assessment of risk of bias using two 'Risk of bias' summary figures; one which is a summary of bias for each item across all studies, and a second which shows a cross-tabulation of each trial by all of the 'Risk of bias' items. This display of internal validity indicates the weight the reader may give the results of each study. For trials using cluster-randomisation, we will assess the risk of bias using the following domains: recruitment bias, baseline imbalance, loss of clusters, incorrect analysis and comparability with individually randomised trials (Higgins 2011).

Measures of treatment effect

We will express the treatment effects as risk ratios (RR) with 95% confidence intervals (CI) for dichotomous outcomes (e.g. rate of infection, rate of readmission).

We will be analyse continuous data (e.g. length of stay, pain) as mean differences (MD) or standardised mean differences (SMD) with standard deviations. We will report time-to-event data (e.g. time to complete wound healing) as hazard ratios (HR) where possible; where these data are incorrectly reported as continuous we will present these results narratively. We will attempt to convert outcome measures into the same metric when possible to ease interpretation and reduce heterogeneity.

Unit of analysis issues

The unit of analysis is the surgical wound subject to the type of skin closure. While we will accept the results from studies in which multiple incisions were randomised to different treatment groups, we will not analyse studies in which a part of the surgical incision is randomised to one group and the rest of the incision to another group.

Dealing with missing data

In the case of missing data, we will contact the study authors. When possible, we will perform intention-to-treat analyses including all participants according to their original allocation. Where binary data are missing, we will perform a worst-case scenario analysis of the main outcome. Such analysis in this case will assume that those patients who were lost to follow-up in the treatment group had the worse outcome, while patients lost to follow-up in the control group had the best outcome. We will compare the effects of the primary analysis with the worst-case analysis to explore whether they have the same direction and magnitude. Where continuous data are missing, we will impute the missing values with replacement data when possible. We will conduct a sensitivity analysis comparing the results with and without imputation. We will impute no more than 10% of the data.

Assessment of heterogeneity

We will assess heterogeneity both by a visual inspection of the forest plot (overlapping of horizontal lines) and through examination of the Chi^2 test and I^2 statistic. We will consider outcomes with a statistically significant Chi^2 value at the 0.10 level and I^2 values greater than 50% to be statistically heterogeneous. In the case of statistical heterogeneity, we will then ensure that the data and effect sizes are correct. If they are, we will attempt to explore heterogeneity through an analysis of the subgroups mentioned below. If there is extreme heterogeneity (e.g. if I^2 values are over 75% or if there is inconsistent direction of the effects), we will not perform pooling. If there are studies that appear to be outliers, we

will conduct an analysis with and without the outliers. If heterogeneity cannot be sufficiently explained, we will account for the heterogeneity by using a random-effects model.

Assessment of reporting biases

If there are 10 or more studies included for a particular outcome we will produce a funnel plot using RevMan (RevMan 2014), with the aim of looking for signs of asymmetry with respect to reporting bias.

Data synthesis

Two review authors will independently extract data from the included trials. We will summarise the main characteristics and results of the included studies. In terms of data synthesis, we plan to use a fixed-effect model for non-statistically heterogeneous outcomes. We will use a random-effects model for statistically heterogeneous outcomes in which the heterogeneity cannot be explained through a subgroup analysis. In the case of rare events (defined here as risks of 1 in 100 or less), we will use the Peto one-step odds ratio method. An exception to using the Peto method for rare events will occur when the risk ratio is less than 0.02 or greater than 5.00 or when the event risk is about 1% and when the N size is two or more times greater in one condition than the other. In that case, we will also report logistic regression results (Bradburn 2007).

To summarise the methods and results we will include a PRISMA (preferred reporting items for systematic reviews and meta-analyses) study selection flow chart (Liberati 2009), a 'Characteristics of included studies' table and forest plots for each synthesised outcome and other tables and figures as appropriate. In terms of interpretation, we will use the GRADE approach to assess the quality of the evidence and provide "clarification of the manner in which particular values and preferences may bear on the balance of benefits, harms, burden and costs of the intervention" (Higgins 2011; Schünemann 2011). In the discussion section, we will use the five subheadings suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (risk of bias, indirectness, inconsistency, imprecision and publication bias). We plan to create a 'Summary of findings' table that will include all the primary outcomes mentioned above.

Subgroup analysis and investigation of heterogeneity

We will conduct subgroup analyses in relation to the type of surgery (e.g. thoracic surgery, upper digestive surgery, neck surgery, breast surgery, colorectal surgery, obstetric surgery) and who conducted the closure.

To investigate heterogeneity we will use Borenstein's method for investigating heterogeneity across subgroups (Borenstein 2008). We will also examine the I^2 statistic across subgroups.

Sensitivity analysis

We will perform sensitivity analyses to explore the effect of the following methodological characteristics:

- Allocation concealment: we will re-analyse the data excluding trials at unclear or high risk of bias for allocation concealment.
- Random-effects versus fixed-effect models: we will re-analyse the data using both random-effects and fixed-effect models to see if there are substantive differences in interpretation.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Appendix 1. Search strategy Ovid MEDLINE

1 exp Sutures/ (12628)
2 Surgical Staplers/ (3677)
3 Surgical Stapling/ (2624)
4 or/2-3 (6066)
5 and/1,4 (432)
6 ((sutur* or “hand sewn” or “hand sewing” or stitch* or handsewn or “manual closure” or catgut* or “cat gut”) and stapl*).ti,ab. (2414)
7 or/5-6 (2632)
8 exp Surgical Wound Infection/ (28066)
9 exp Surgical Wound Dehiscence/ (6238)
10 (surg* adj5 infect*).tw. (18460)
11 (surg* adj5 wound*).tw. (9918)
12 (surg* adj5 site*).tw. (11248)
13 (surg* adj5 incision*).tw. (6339)
14 (surg* adj5 dehisc*).tw. (575)
15 (wound* adj5 dehisc*).tw. (2757)
16 (wound* adj5 infect*).tw. (21742)
17 (wound adj5 disrupt*).tw. (343)
18 wound complication*.tw. (2926)
19 or/8-18 (79600)
20 (intent* or second* or heal* or complic*).tw. (3120835)
21 ((open* or clos*) adj5 wound*).tw. (11369)
22 or/20-21 (3125662)
23 and/19,22 (39243)
24 and/7,23 (307)
25 randomized controlled trial.pt. (371192)
26 controlled clinical trial.pt. (88165)
27 randomi?ed.ab. (323127)
28 placebo.ab. (145194)
29 clinical trials as topic.sh. (169503)
30 randomly.ab. (191973)
31 trial.ti. (116499)

32 or/25-31 (870309)
33 exp animals/ not humans.sh. (3927741)
34 32 not 33 (800199)
35 and/24,34 (74)

Appendix 2. Appendix 2. Search strategy Ovid EMBASE

1 suture/ or absorbable suture/ or barbed suture/ or nonabsorbable suture/ or rectal suture/ or tendon suture/ or vascular suture/ (25151)
2 exp stapler/ (6377)
3 surgical stapling/ (3331)
4 or/2-3 (9174)
5 and/1,4 (1003)
6 ((sutur* or "hand sewn" or "hand sewing" or stitch* or handsewn or "manual closure" or catgut* or "cat gut") and stapl*).ti,ab. (3448)
7 or/5-6 (3756)
8 surgical infection/ (24929)
9 wound dehiscence/ (10130)
10 (surg* adj5 infect*).tw. (25956)
11 (surg* adj5 wound*).tw. (13022)
12 (surg* adj5 site*).tw. (16732)
13 (surg* adj5 incision*).tw. (9296)
14 (surg* adj5 dehisc*).tw. (806)
15 (wound* adj5 dehisc*).tw. (3823)
16 (wound* adj5 infect*).tw. (29529)
17 (wound adj5 disrupt*).tw. (489)
18 wound complication*.tw. (3942)
19 or/8-18 (102756)
20 (intent* or second* or heal* or complic*).tw. (4233059)
21 ((open* or clos*) adj5 wound*).tw. (15171)
22 or/20-21 (4239023)
23 and/19,22 (55268)
24 and/7,23 (367)
25 Randomized controlled trials/ (50830)
26 Single-Blind Method/ (18183)
27 Double-Blind Method/ (115395)
28 Crossover Procedure/ (38713)
29 (random$ or factorial$ or crossover$ or cross over$ or cross-over$ or placebo$ or assign$ or allocat$ or volunteer$).ti,ab. (1320334)
30 (doubl$ adj blind$).ti,ab. (145796)
31 (singl$ adj blind$).ti,ab. (14369)
32 or/25-31 (1386996)
33 exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/ (20185528)
34 human/ or human cell/ (14684548)
35 and/33-34 (14637872)
36 33 not 35 (5547656)
37 32 not 36 (1196742)
38 and/24,37 (94)

Appendix 3. Appendix 3. Search strategy CINAHL

S29 S16 AND S28
S28 S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27
S27 MH "Quantitative Studies"
S26 TI placebo* or AB placebo*
S25 MH "Placebos"
S24 TI random* allocat* or AB random* allocat*
S23 MH "Random Assignment"
S22 TI randomi?ed control* trial* or AB randomi?ed control* trial*
S21 AB (singl* or doubl* or trebl* or tripl*) and AB (blind* or mask*)
S20 TI (singl* or doubl* or trebl* or tripl*) and TI (blind* or mask*)
S19 TI clinic* N1 trial* or AB clinic* N1 trial*
S18 PT Clinical trial
S17 MH "Clinical Trials+"
S16 S5 AND S15
S15 (S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14)
S14 TI wound complication* or AB wound complication*
S13 TI wound* N5 dehisc* or AB wound* N5 dehisc*
S12 TI surg* N5 dehisc* or AB surg* N5 dehisc*
S11 TI surg* N5 incision* or AB surg* N5 incision*
S10 TI surg* N5 site* or AB surg* N5 site*
S9 TI surg* N5 wound* or AB surg* N5 wound*
S8 TI surg* N5 infection* or AB surg* N5 infection*
S7 (MH "Surgical Wound Dehiscence")
S6 (MH "Surgical Wound Infection")
S5 S3 OR S4
S4 TX ((sutur* or "hand sewn" or "hand sewing" or stitch* or handsewn or "manual closure" or catgut* or "cat gut") and stapl*)
S3 S1 AND S2
S2 (MH "Surgical Stapling+")
S1 (MH "Sutures")

Appendix 4. Appendix 4. Search strategy CENTRAL

#1 MeSH descriptor: [Sutures] explode all trees751
#2 MeSH descriptor: [Surgical Staplers] explode all trees176
#3 MeSH descriptor: [Surgical Stapling] explode all trees274
#4 #2 or #3 434
#5 #1 and #4 66
#6 ((sutur* or "hand sewn" or "hand sewing" or stitch* or handsewn or "manual closure" or catgut* or "cat gut") and stapl*):ti,ab 306
#7 #5 or #6 322
#8 MeSH descriptor Surgical Wound Infection explode all trees 382
#9 MeSH descriptor Surgical Wound Dehiscence explode all trees 78
#10 (surg* near/5 infect*):ti,ab,kw 4432
#11 (surg* near/5 wound*):ti,ab,kw 4776
#12 (surg* near/5 site*):ti,ab,kw 1223
#13 (surg* near/5 incision*):ti,ab,kw 1257
#14 (surg* near/5 dehisc*):ti,ab,kw 439
#15 (wound* near/5 dehisc*):ti,ab,kw 634
#16 (wound* near/5 infect*):ti,ab,kw 4790
#17 (wound near/5 disruption*):ti,ab,kw 41
#18 (wound next complication*):ti,ab,kw 479
#19 #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 9628

#20 #7 and #19 98

Appendix 5. 'Risk of bias' criteria

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: using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or 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 is 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.

CONTRIBUTIONS OF AUTHORS

Roberto Cirocchi conceived the review question and coordinated the protocol development.

Stefano Trastuli developed and completed the first draft of the protocol. Performed part of editing the protocol and advised on part of the protocol.

Alessandro Montedori made an intellectual contribution to the protocol and advised on the protocol.

Justus J Randolph developed the protocol and coordinated the development of the protocol. Edited the protocol and advised on the protocol.

Giovanni G Cochetti secured funding for the protocol.

Alberto Arezzo edited the protocol. Advised on part of the protocol. Approved the final version of the protocol prior to submission.

Ettore E Mearini secured funding for the protocol and approved the final version of the protocol prior to submission.

Iosief Abraha developed the protocol and coordinated the development of the protocol. Completed the first draft of the protocol and performed part of writing and editing the protocol. Is the guarantor of the protocol.

DECLARATIONS OF INTEREST

Roberto Cirocchi - none known

Stefano Trastuli - none known

Alessandro Montedori - none known

Justus J Randolph - none known

Giovanni G Cochetti - none known

Alberto Arezzo - none known

Ettore E Mearini - none known

Iosief Abraha - none known

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