



BMJ Open Participant recruitment and attrition in surgical randomised trials with placebo controls versus non-operative controls: a meta-epidemiological study and meta-analysis

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ABSTRACT

Objective To compare differences in recruitment and attrition between placebo control randomised trials of surgery, and trials of the same surgical interventions and conditions that used non-operative (non-placebo) controls.

Design Meta-epidemiological study.

Data sources Randomised controlled trials were identified from an electronic search of MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials from their inception date to 21 November 2018.

Study selection Placebo control trials evaluating efficacy of any surgical intervention and non-operative control trials of the same surgical intervention were included in this study. 25 730 records were retrieved from our systemic search, identifying 61 placebo control and 38 non-operative control trials for inclusion in analysis.

Outcome measures Primary outcome measures were recruitment and attrition. These were assessed in terms of recruitment rate (number of participants enrolled, as a proportion of those eligible) and overall attrition rate (composite of dropout, loss to follow-up and cross-overs, expressed as proportion of total sample size). Secondary outcome measures included participant cross-over rate, dropout and loss to follow-up.

Results Unadjusted pooled recruitment and attrition rates were similar between placebo and non-operative control trials. Study characteristics were not significantly different apart from time to primary timepoint which was shorter in studies with placebo controls (365 vs 274 days, $p=0.006$). After adjusting for covariates (follow-up duration and number of timepoints), the attrition rate of placebo control trials was almost twice as high compared with non-operative controlled-trials (incident rate ratio (IRR) (95% CI) 1.8 (1.1 to 3.0), $p=0.032$). The incorporation of one additional follow-up timepoint (regardless of follow-up duration) was associated with reduced attrition in placebo control surgical trials (IRR (95% CI) 0.64 (0.52 to 0.79), $p<0.001$).

Conclusions Placebo control trials of surgery have similar recruitment issues but higher attrition compared with non-operative (non-placebo) control trials. Study design should incorporate strategies such as increased timepoints for

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Randomised controlled trials incorporating a placebo control to evaluate effectiveness of a surgical intervention were compared with randomised trials comparing the effectiveness of the same surgical intervention with non-operative controls.
- ⇒ In addition to primary outcomes collected, secondary outcomes including participant cross-over rate, participant dropout and participant loss to follow-up were recorded and evaluated.
- ⇒ To minimise bias, data was extracted independently by pairs of investigators and arbitrated by a third investigator if necessary.
- ⇒ Findings are limited by missing data and non-reporting of recruitment ($n=42$ studies) or attrition ($n=4$ studies) data.
- ⇒ The relatively small amount of placebo-controlled surgical trials published in the literature limit the certainty of our evaluations.

given follow-up duration to mitigate losses to follow-up and dropout.

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INTRODUCTION

Placebo control trials are the gold standard for determining the true therapeutic effect of interventions.¹ However, placebo trials commonly face difficulties in participant recruitment due to a lack of willingness to participate especially in surgical placebo trials due to its inherently invasive nature and higher risks of anaesthetic adverse events and infection.^{2–4}

Invasive and lengthy procedural processes in surgical trials may also lead to participant attrition.^{5–7} Attrition refers to losses in participant information either due to dropout or missing data over the duration of

a longitudinal study.⁸ These losses can create imbalances in study groups introducing bias and reduced statistical power secondary to a smaller sample size.^{8,9}

The extent of attrition and recruitment issues in placebo control trials of surgical interventions have not been explored empirically. The aim of this study was therefore to investigate differences in participant recruitment and attrition rates between placebo and non-operative (non-placebo) control surgical trials testing the same surgical intervention to guide future planning of placebo control studies.

METHODS

Design

We performed a meta-epidemiological study and registered the protocol in the PROSPERO International Prospective Register of Systematic Reviews (CRD42019117364) (online supplemental files 1 and 2). We followed the reporting guidance of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).¹⁰

Inclusion criteria and eligible study identification

This study included randomised controlled trials incorporating a placebo control to evaluate the efficacy of any surgical intervention and randomised trials comparing the effectiveness of the same surgical intervention with non-operative controls. The latter may comprise either standard care or no treatment. Trials were excluded if they were not evaluating the same surgical effect as the corresponding placebo control trial, for example, the non-operative control group received co-interventions not provided to the surgical group.

Surgery was defined as any invasive procedure that allows access to internal anatomy for example through a skin incision. The surgical placebo is ill-defined and can vary in fidelity but was defined as any 'imitation procedure' differentiated by the patient, which lacks the key surgical element(s).¹¹

This study used the search strategy and eligibility criteria from an associated publication by Karjalainen *et al* (online supplemental appendix 1).¹² Detailed data on the search strategy and eligibility criteria (including the PRISMA diagram of included studies) are available via the supplementary files of Karjalainen *et al*.¹² Based on a full-text assessment, trials were excluded because of two main reasons: they did not meet our definition of a surgical intervention (such as the injection or heating of tissue) or they were duplicate articles. The search identified 62 placebo controlled surgical trials.

Our search included eligible placebo control trials from a published systematic review by Wartolowska *et al*¹ as well as an extension of its search until 21 November 2018. We also searched the reference lists of included studies for additional eligible studies. To identify relevant effectiveness trials (incorporating non-blinded non-operative controls), relevant Cochrane reviews assessing the index surgical procedure were identified and their

literature searches were also extended until 13 March to 15 March, 2019. Where no relevant Cochrane review was identified, a search algorithm was devised and applied to the Cochrane Central Register of Controlled Trials, MEDLINE and Embase from their inception until the same date of search. To determine eligibility, pairs of authors independently completed title/abstract screening (TK, SA) followed by full-text review (PN, SM, LH, MM, SA).

Data extraction

All data were extracted independently by pairs of investigators (PN, SM, LH, MM) and arbitrated by a third investigator (SA) if necessary. Extracted data from included trials included year of publication, participant characteristics (age, sex), sample size, condition, intervention type (open or minimally invasive/percutaneous surgery), planned length of follow-up and number of follow-up timepoints.

Primary and secondary outcome measures

Primary outcomes were participant recruitment and attrition. These outcomes were assessed in terms of *recruitment rate* (number of participants enrolled, as a proportion of those eligible) and *overall attrition rate* (composite of dropout, loss to follow-up and cross-overs, expressed as proportion of total sample size).

Secondary measures included the *participant cross-over rate*, defined as an unplanned protocol violation resulting in participants in the control group receiving the intervention and vice versa, and *participant dropout*, defined as an inability for the participant to progress further with the study. These were both reported as a proportion of total number recruited. Finally, we also included *participant loss to follow-up*, defined as the inability of investigators to obtain information at planned timepoints for reasons other than participant dropout. Where available, these components of attrition were characterised at each follow-up timepoint.

Statistical analyses

Descriptive statistics were used to summarise key aspect of the selected studies. The 'metaprop' command in Stata V.16 was used to estimate pooled recruitment and attrition rates, stratified by study type (placebo vs non-operative control). Overall recruitment and attrition rates were the primary outcomes used for this analysis. To account for between-study heterogeneity, all analyses were based on the random effect model. Random effect meta-analysis was used to summarise attrition rates (overall, dropout, loss to follow-up and cross-over) in placebo versus non-operative control trials, stratified by trial groups.

Due to the nature of the data (with varying follow-up duration), a generalised linear latent and mixed model¹³ was employed for random effect Poisson regression to examine incident rate ratio (IRR) for intervention type (placebo or non-operative control). With this model, we

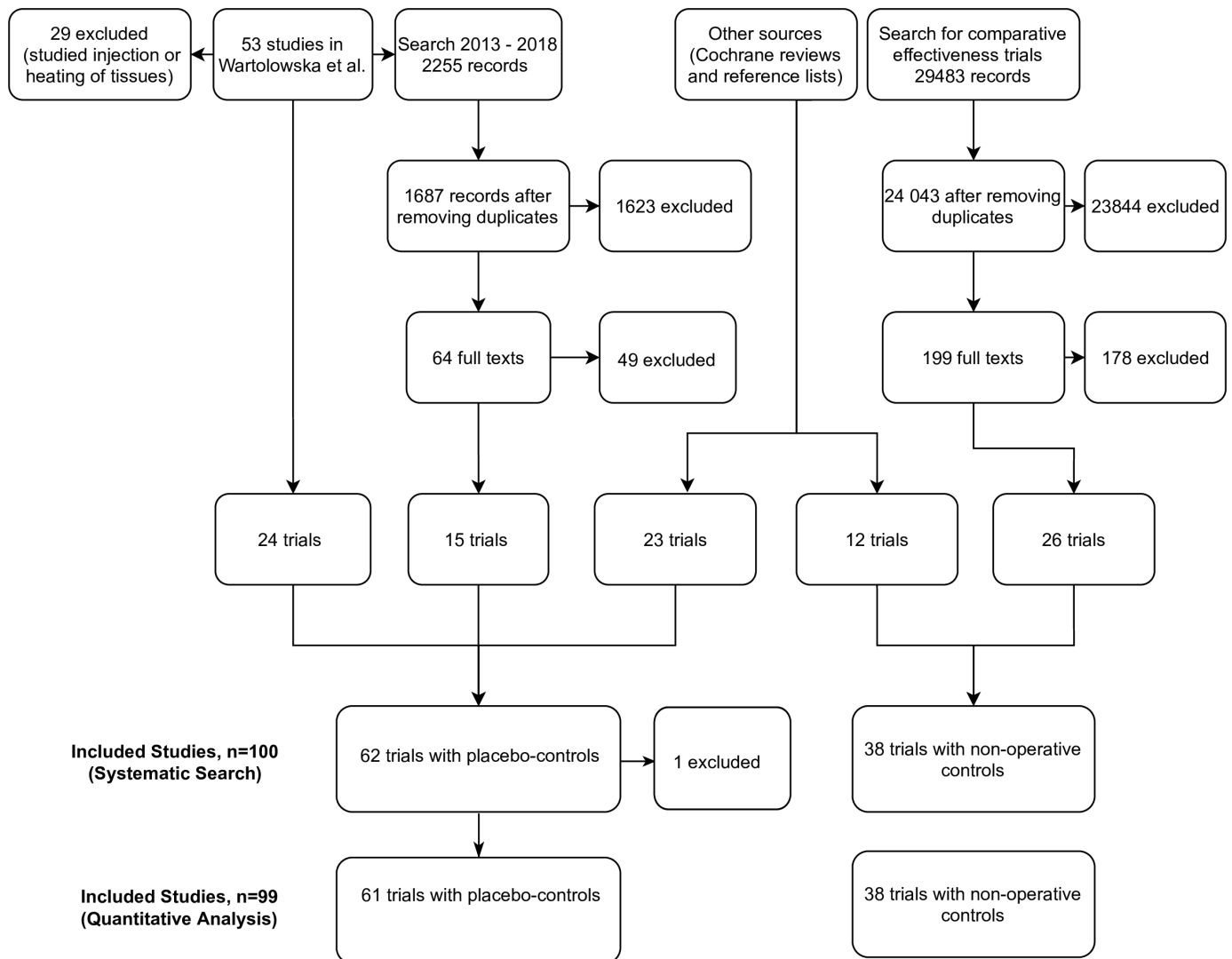


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of study selection.

also controlled for participant gender, follow-up duration and number of follow-up timepoints.

All trials with attrition and recruitment data were included in analyses. However, reporting biases were suspected in studies with 0% attrition and 100% recruitment and therefore sensitivity analyses excluding these studies were performed.

Funnel plot and Egger's test were used to assess publication bias, while meta regression was used to examine for the effect of covariates. Risk of bias was assessed according to Cochrane Risk of Bias Tool V.1.0. and detailed in a related publication by Karjalainen *et al.*¹²

Patient and public involvement

As this was a meta-epidemiological study and meta-analysis, there was no patient involvement in study design of conduct.

RESULTS

A total of 62 placebo control trials and 38 trials with non-operative controls (100 trials overall) were identified

(figure 1). 99 studies were included in the quantitative analysis (1 placebo control trial excluded due to unavailable full text at search date¹⁴). Detailed data on these included studies has been included in online supplemental appendix 2. Study cohorts were comparable between placebo and non-operative control trials; however, time to the primary outcome was shorter in studies with placebo controls (365 vs 274 days, $p=0.006$) (table 1). No significant covariates were identified in meta-regression analyses (online supplemental appendix 3).

Participant recruitment

Recruitment rate was available for 57 out of 99 included studies (36 (59.0%) placebo and 21 (55.3%) non-operative controls, respectively) and ranged between 9.3% and 100%.

The random effect pooled rate was similar between placebo and non-operative control trials (rate (95% CI): 76.9% (71.1% to 82.7%) vs 77.6% (66.7% to 88.4%), respectively, $p=0.915$). This included 10/36 (27.8%)

Table 1 Participant and follow-up characteristics

	Non-operative control	Placebo control	P value
N	38	61	
Age of study cohorts (mean±SD, n)			
Surgical intervention group	54.8±12.6, n=34	50.4±13.4, n=55	0.125
Control group	55.1±13.0, n=34	50.5±13.3, n=55	0.114
Other group*	48±8, n=3	47.8±5.8, n=4	0.807
Gender of study cohorts (mean±SD)			
Per cent female	62.7±24.8	61.8±30.9	0.87
Follow-up characteristics (median (IQR))			
Number of timepoints†	3 (2–5)	4 (2–6)	0.412
Timepoint (primary outcome), days	365 (183–730)	274 (91–365)	0.006
Timepoint (longest), days	365 (365–730)	365 (183–730)	0.193

*Other group only applicable to trials incorporating three treatment arms.
†Number of follow-up points was not available for five studies (one non-operative control and four placebo).
N, number of studies.

placebo and 3/21 (14.3%) non-operative control studies with 100% recruitment rates. When these studies were excluded, the recruitment rates decreased to 68.7% (59.3% to 78.1%) in the placebo and 74.1% (58.6% to 89.5%) in the non-operative controlled studies, respectively, with no between-group heterogeneity ($I^2=95\%$, $p=0.562$).

Participant attrition

Overall attrition rate was not available for 4 studies (2/61 placebo arms and 2/38 non-operative controls) and ranged from 0% to 80.0% in trials with available data.

Median (IQR) attrition rates were lower in placebo trials (12.4% (6.1%–29.8%)) compared with non-operative control trials (20.7% (9.1%–33.3%)); however, these did not reach statistical significance. These results also comprised 5/59 (8.5%) placebo arm studies and 2/36 (5.6%) of non-operative control studies with no participant attrition. For studies with attrition, the random effect pooled overall attrition (rate (95% CI)) did not differ significantly between placebo (21.2% (17.2% to 25.2%)) and non-operative (23.7% (18.8% to 28.6%)) controlled studies ($p=0.811$). This was also true for discrete components of attrition including loss to follow-up, dropout and cross-over rates (online supplemental appendices 4–6).

Random effect Poisson regression

The median (IQR) number of follow-up timepoints (4 (3–5.5) and 3.5 (2–6), $p=0.748$) was similar between non-operative and placebo control trials, respectively. Longest follow-up timepoint (365 (319.5–730) and 365 (183–456) days, $p=0.143$) was also similar between non-operative and placebo control trials, respectively.

Following correction for covariates especially the varied study durations, Poisson regression analyses showed significant between-group differences in the rates of dropouts, loss to follow-up and attrition (table 2). Poisson

regression demonstrated a higher attrition rate in placebo trials compared with non-operative control trials (IRR 1.8 (95% CI 1.1 to 3.0), $p=0.032$) and was predominantly seen in the medium term (500 days). The higher attrition rate in placebo trials was due to higher loss to follow-up (IRR 2.6 (95% CI 1.04 to 6.3), $p=0.042$) and higher dropout (IRR 3.5 (95% CI 1.1 to 11.3), $p=0.037$) as seen in figure 2.

The incorporation of just one additional follow-up timepoint (regardless of length of follow-up, that is, increased frequency of visits) is associated with a reduction in attrition (IRR (95% CI) of 0.64 (0.52 to 0.79), $p<0.001$) in placebo control surgical trials, largely driven by fewer losses to follow-up (IRR (95% CI) of 0.68 (0.52 to 0.89), $p=0.004$).

Publication bias

Egger test ($p<0.001$) indicated the presence of publication bias with the majority of included studies having low attrition rates (online supplemental appendix 7). Publication

Table 2 Association between attrition rates and type of control group (placebo or non-operative) in surgical trials

	Incident rate ratio (IRR)	95% CI		P value*
		Lower	Upper	
Attrition	1.8	1.1	3.0	0.032
Loss to follow-up	2.6	1.04	6.3	0.042
Dropout	3.5	1.1	11.3	0.037

IRRs expressed for placebo control trials as a ratio of incident rates for non-operative control trials.
*Poisson regression analysis using a generalised linear latent and mixed model to examine IRR, while controlling for participant gender, follow-up duration and number of follow-up timepoints.

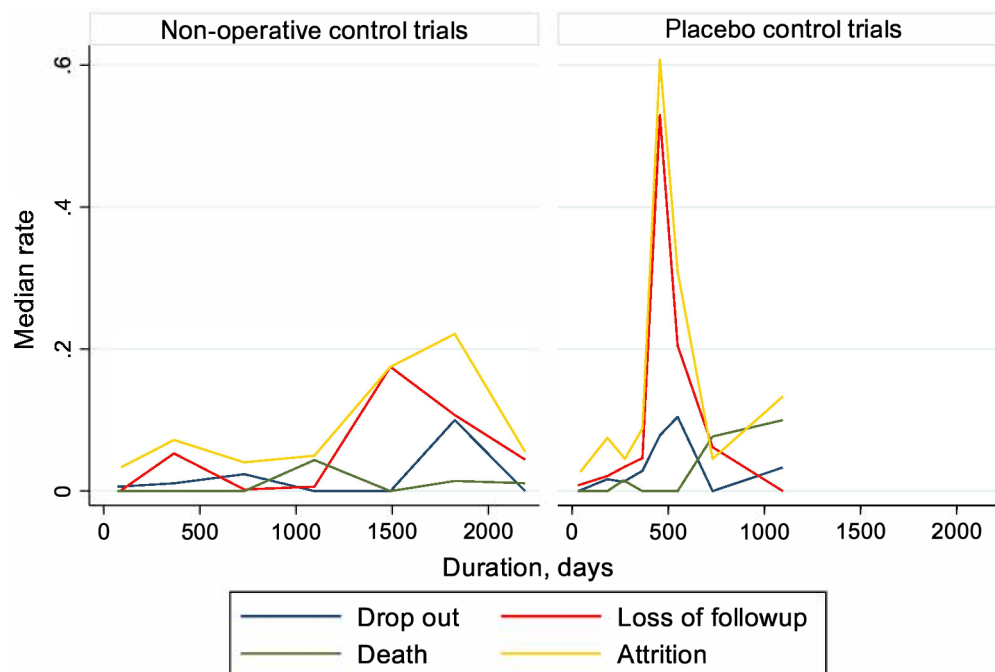


Figure 2 Poisson regression of median attrition rates (dropout, loss to follow-up, death, overall attrition) between placebo and non-operative controls.

bias was greater in placebo control trials compared with trials of non-operative trials (online supplemental appendices 8 and 9).

DISCUSSION

This review demonstrates key differences in participant recruitment and retainment when comparing placebo control and non-operative (non-placebo) control randomised trials of surgery. After adjustment for the number of follow-up timepoints and study duration, attrition losses were almost twice as high in placebo control compared with non-operative control trials. This was primarily driven by participant follow-up losses and dropouts.

Participant recruitment

Surgical randomised controlled trials can face recruitment rates as low as 8%,¹⁵ due to patients frequently failing to meet eligibility criteria for a small and specific target populations.^{3 16} Addition of a placebo component further exacerbates this problem by undermining willingness to participate.^{4 17 18} Participant surveys suggest this unwillingness stems from common perceptions that invasive surgical placebos are associated with greater risks (eg, infection).^{18 19} Data from previous randomised controlled trials as reported by Hare *et al*,⁴ indicate participant concerns regarding the possibility of receiving placebo surgery being the most common reason (38%) for non-participation despite eligibility. Contrary to these expectations, our results demonstrated no significant difference in recruitment rate between placebo control and non-operative control trials. Our findings may be

biased by sampling from published literature, with the non-representation of placebo control surgery trials that experienced stoppage and/or early termination due to recruitment failure.

Participant attrition

Our findings suggest placebo control surgery trials experience a twofold higher attrition rate (when considering cross-overs, dropouts and follow-up losses) compared with non-operative control surgery trials, after adjusting for the duration and number of follow-up timepoints. One possible cause for higher attrition rates in placebo control trials could be early unblinding. It is well-known that rigorous blinding is required to maintain equipoise (and fidelity) in placebo control surgery trials to ensure participant retention.^{11 20 21} Meta-analysis by Hróbjartsson *et al* found that non-blinded control groups suffer from 79% higher risk of dropouts and 55% higher risk of co-intervention use when compared with blinded control groups.²² The difficulties of appropriate blinding (and maintaining fidelity), especially in the context of not receiving treatment with persisting symptoms, likely account for the higher rates of attrition in placebo control surgery trials when compared with other control trials. Included trials in the present meta-analysis were published prior to the development of the Applying Surgical Placebo in Randomised Evaluations (ASPIRE) guidelines for acceptable surgical placebos, and therefore did not report on the fidelity and blinding of their surgical placebos.¹¹

Higher attrition rates in placebo control surgical trials were primarily driven by higher losses to follow-up and

participant dropout. With the inherent nature of surgical interventions being a 'one-time' irreversible change,²³ loss to follow-up and participant withdrawals may be higher when there is a long follow-up period with no concomitant treatments.²⁴ This is typical of placebo surgery trials, while non-operative trials tend to involve comparators that require ongoing intervention (therefore facilitating parallel follow-up).

We also found that differences in attrition rates between placebo and non-operative control trials of surgery arise primarily in the medium term (~500 days), suggestive of a 'participant demotivation' phenomenon that develops over moderate-term to longer-term study participation.^{25–29} Participant demotivation seems to be accelerated in placebo control trials, with the presence of additional uncertainty regarding potential allocation of a 'surgical placebo'. This demotivation likely peaks following the short-term optimism initially present at enrolment into a placebo control surgery trial. Moreover, the finding of additional follow-up timepoints correlating with a reduction in attrition suggests frequent follow-up timepoints may enable ongoing contact and thus participant retention, as positive relationships between participants and trial staff are fostered.^{28 30}

Publication bias

Trial discontinuation and non-publication is common and occurs more frequently in surgical than medical trials.^{31–35} Publication bias, or the selective submission or acceptance of a study into literature as such,^{36 37} is a likely limitation of the present findings. The majority of included studies had low attrition rates overall, indicating less publication of both placebo and non-operative control surgical trials with high attrition rates.⁸

Strengths and weaknesses

This study has several major strengths including a protocol-driven, preplanned, meta-epidemiological design that included all published surgical placebo trials until November 2018. Given our research question did not assess intervention effectiveness but rather described overall data from a methodological perspective, it is unlikely additional trials will change our conclusion. However, our findings are limited by missing data and non-reporting of recruitment (n=42) or attrition data (n=4) in some trials. Thus, our findings may be an underestimation of the true difference in attrition rates between placebo surgery trials and non-operative trials, as unfavourable attrition/recruitment data is less likely to be published.

Implications and future research

There is a need to investigate reasons why participant attrition occurs at a higher rate when placebo controls are employed in randomised trials of surgery. Future studies build on existing ASPIRE guidelines to explore the relationship between varying levels of placebo fidelity and rates of attrition.¹¹ Patient education and greater

transparency may promote confidence and willingness among eligible patients to participate. As such, future studies may also explore patient perceptions and attitudes towards placebo surgical procedures. Strategies to maximise continuous patient engagement may include guaranteeing placebo-exposed patients the surgical intervention if a statistically significant benefit is observed. This study also demonstrated that additional follow-up timepoints are associated with less attrition, thus closer follow-up is recommended in placebo control trials.

CONCLUSION

Placebo control trials of surgery have higher attrition rates when compared with trials with non-operative (non-placebo) controls. Our findings suggest that the design of surgical placebo trials should incorporate strategies with one key strategy being more frequent follow-up (for a given duration of follow-up) to mitigate losses to follow and dropout.

Transparency and ethical declaration

Authors affirm that this manuscript is an honest, accurate and transparent account of the study being reported; no important aspects of the study have been omitted; and any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Teemu Karjalainen, Pragadesh Natarajan, Spiro Menounos, Laura Harris, Masiath Monuja, Ian Harris, Rachelle Buchbinder, Manuela Ferreira, Rudolf Poolman, Alexandra Gorelik, Sam Adie

Title

Participant recruitment and attrition in placebo- versus non placebo-controlled randomised trials of surgery: a systematic review

Review Question

Is the problem of participant recruitment and attrition different in placebo-controlled surgical intervention trials, when compared to open-label, non-placebo-controlled surgical intervention trials?

Background

Despite widespread acceptance that a placebo control is essential to maintaining scientific rigour in the evaluation of clinical interventions, the use of surgical placebos introduces difficulties completing such randomised trials with a sufficient number of eligible patients (1, 2). In particular, the inherently invasive nature of surgical placebos often involving the risks of anaesthesia undermines patient willingness to participate in a procedure of potentially no benefit, thereby generating issues with recruitment and cohort retention (1-3).

Randomised control trials (RCTs) in surgery are well-known to suffer from these difficulties in recruitment, and the addition of a surgical placebo adds to especially lower rates of recruitment (1, 3). Indeed, only 15% of published RCTs involve surgical interventions and only 24% of currently used surgical therapies are supported by results of RCTs (2). While some authors suggest that these recruitment problems may be addressed by methods such as TV and newspaper advertising, recruitment usually remains slow and has been previously reported as the reason for early termination of multiple studies (2).

Retaining participants can also be problematic in randomised placebo-controlled trials of surgical intervention with participant withdrawals introducing attrition biases. Attrition refers to losses in participant information either due to drop-out or missing data over the duration of a longitudinal study (4). Such losses can create imbalances in study groups introducing methodological problems (attrition bias) and a reduction of statistical power due to a reduced sample size (4, 5). Although imputation methods exist that address this problem, none of these are replacements for lost information. Attrition compromises the strength of a study's findings in both internal validity and generalisability.

Previous studies have identified predictors of participant attrition, including longer delays between consent and first contact, lower patient education levels, minority race, prolonged duration of screening and symptom severity (6, 7). Other studies have also described study design characteristics that minimise the effects of attrition, including an intent-to-treat study design, participant reimbursement, intent-to-attend next visit discussion, study visit target windows and optimised quality care to limit participant burden (7, 8).

Despite the placebo control being the gold-standard for testing the effectiveness of an intervention, some studies have found that non-surgical placebo-controlled RCTs are characterised by higher subject drop-out rates when compared to non-placebo controlled RCTs (9, 10). Within placebo-controlled randomised trials, placebo arms face higher participant losses compared to treatment arms, possibly due to a lack of efficacy and/or patient perceived allocation of placebo prompting withdrawal (9-11). Moreover, the extent of attrition in placebo-controlled (or sham surgery) trials of surgical interventions has not been explored empirically, largely owing to the scarcity of placebo-controlled surgical trials. In comparison to placebo pills, placebo surgeries involve higher risks and are more invasive to participants, thus in theory possibly creating greater difficulties in retaining participants.

Our study will explore the problem of attrition and recruitment failure in placebo-controlled surgery trials in comparison to surgical trials that use a non-placebo comparator. The primary objective is to investigate differences in participant recruitment and attrition rates in placebo-controlled surgery trials in comparison to open-label, non-placebo-controlled surgery trials for the same intervention. Secondary analyses will explore study characteristics for their association with recruitment and attrition rates.

Methods

Search for studies

This review will include:

- 1.) Randomised placebo-controlled trials of surgical interventions
- 2.) Non-placebo-controlled (open-label) trials of similar surgical interventions and conditions

This study will utilise a previously identified set of randomised placebo-controlled trials of surgical interventions from an ongoing review (9) (PROSPERO ID CRD42019117364). We updated a previous electronic search for all published RCTs conducted on humans that compared a surgical intervention to a placebo surgical intervention (10). Surgery was defined as “any intervention that changes anatomy and requires a skin or other epithelial layer incision or suturing” (10). A surgical placebo, or sham surgery, was defined as an “imitation procedure” that cannot be differentiated by the patient, that lacks the key therapeutic step. RCTs will be grouped according to their surgical interventions and clinical conditions, and this informed the search for overlapping RCTs.

For each surgical intervention used in placebo-controlled RCTs we identified in the first search we conducted a systematic review of the literature to identify published RCTs conducted on humans assessing the *same surgical intervention and clinical condition*, but where the comparator was a non-surgical treatment group instead of placebo surgery.

The search to locate eligible non-placebo-controlled RCTs proceeded in the following order of preference: First, we used the Cochrane Database of Systematic Reviews, and DARE (from inception to current date) to identify any systematic review assessing the surgical procedure and condition of interest. We updated the search strategies of these reviews, and included eligible RCTs included in these reviews. Second, where we did not find a systematic review,

we formulated our own electronic search strategies with the help of a medical librarian, using a randomised trial/systematic review filter, combined with a filter specific to the clinical aspects of each group of placebo-controlled RCTs. For these, we searched MEDLINE, EMBASE and CENTRAL, from their inception to the present. The syntax of the search strategies is contained in Appendix 1 (NEED TO COLLATE FROM DROP BOX FOLDER)

Two investigators independently assessed the results of each search strategy, first screening titles and abstracts, and recording the reasons for exclusion. Two independent investigators conducted a full text review of papers included following the title/abstract screening. We resolved any discrepancies in included studies through discussion, and if necessary, using a third investigator for arbitration.

Data extraction

All data will be extracted independently by two investigators, and arbitrated by a third investigator if necessary. Cohen's kappa statistic and raw agreement scores will be calculated to determine inter-rater reliability.

General characteristics of included RCTs

- i) Year of study
- ii) The study population (age, sex, location, education level, ethnicity)
- iii) The total study sample size
- iv) The condition for which surgery was performed
- v) Type of intervention, dichotomised as open, or minimally invasive/percutaneous surgery.
- vi) Presence of a pilot or lead-in phase
- vii) Planned length of follow up
- viii) Number of follow up timepoints
- ix) Any reported methods or incentives to improve recruitment or follow up, including financial, gifts or lotteries, and reminders

Risk of bias

We will use the Cochrane Risk of Bias tool (11) to extract items not related to attrition.

Outcome data

- i) *Recruitment rate*, defined as the number enrolled expressed as a proportion of those eligible for the study
- ii) *Subject dropout*, defined as a refusal to progress further with the study. This will be reported as a proportion of total number recruited, and where available, will be characterised at different timepoints:
 - a. Prior to randomisation
 - b. Prior to the intervention
 - c. Prior to first follow up
 - d. Prior to final follow up
 - e. Overall

- iii) *Subject loss to follow up*, defined as the inability of investigators to obtain information at planned timepoints for reasons other than *subject dropout*. Where available, this will be characterised at different timepoints:
 - a. Prior to first follow up
 - b. Prior to final follow up
 - c. Overall
- iv) *Subject cross-over rates*, defined as an unplanned protocol violation resulting in subjects in the control group receiving the intervention, and vice versa. This will be reported as a proportion of the subject group, and characterised as:
 - a. Subjects crossing over into the surgical intervention
 - b. Subjects crossing over into the non-surgical intervention
 - c. Overall
- v) *Overall attrition of participants*, defined as a composite (or addition) of dropout, loss to follow up and cross-overs, expressed as a proportion of total sample size
- vi) Stoppage prior to recruitment of planned sample size. Where available, the reason for stoppage will be recorded, including due to poor recruitment rates.

The primary outcomes of interest will be rates of attrition (due to dropout, loss to follow up and cross-over), participant recruitment rates and number of studies with unplanned stoppage.

Statistical Analyses

The extracted data will be tested for heterogeneity and either fixed or random effect meta-analysis will be used to summarise attrition rates (overall, dropout, loss to follow up, and cross over) in placebo vs. non-placebo-controlled trials overall and stratified by trial groups (subject to data availability).

Due to the data nature (varying follow-up duration) mixed effect Poisson regression will be used to examine Incidents Rate Ratio (IRR) and Incident Rate Difference while controlling for potential confounders (e.g. age, type of intervention, etc.)

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Placebo effects in randomised trials of surgical interventions: a meta-epidemiological study

Citation

Teemu Karjalainen, Sam Adie, Lucy Busija, Ian Harris, Rachelle Buchbinder, Justine Naylor, Adriane Lewin, Juuso Heikkinen. Placebo effects in randomised trials of surgical interventions: a meta-epidemiological study. PROSPERO 2019 CRD42019117364 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019117364

Review question [1 change]

This review will address three specific questions:

- 1) What proportion of the surgical intervention effect size is represented by the placebo effect?
- 2) What is the size of the surgical placebo effect?
- 3) What is the difference between the surgical intervention effect size in placebo-controlled surgical trials compared to non-placebo-controlled surgical trials?

Secondary review questions are

- 1) Is there evidence of heterogenous treatment effect in musculoskeletal surgery, i.e. does the variance differ between active surgery groups versus non-surgery groups (due to subgroup of responders to surgery) ?
- 2) Is there difference in participant attrition rates between placebo-surgery and comparable open label studies

Searches [1 change]

We will perform an update of a previous electronic search (Wartolowska K, et al. Use of placebo controls in the evaluation of surgery: systematic review. BMJ. 2014 May 21;348:g3253; supplementary appendix 1), searching MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) for all published RCTs conducted on humans that have compared a surgical intervention to a placebo surgical intervention.

The updated search will be performed from 1st January 2013 until 21st November 2018.

We will not apply any language restrictions.

We will also screen the placebo-controlled surgical trials from the previous search (results up to 2013) for those which fulfil our inclusion criteria, and will also search the reference lists of the included articles to identify studies not captured in the original search

For each surgical intervention type for the placebo-controlled RCTs identified in the first search, we will search MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) to identify published RCTs conducted on humans assessing the same surgical intervention, but in which the comparator is a non-surgical treatment group (referred to hereafter as 'overlapping' RCTs).

We will also search for systematic reviews on same conditions from DARE from its inception until date of search.

The search strategy will include terms relating to or describing the intervention and the conditions. Full strategies for each condition will be developed after the first search is completed, and they will be published with the final manuscript.

Additional search strategy information can be found in the attached PDF document (link provided below).

Types of study to be included

Randomised controlled trials.

No language restrictions will be imposed.

Condition or domain being studied [1 change]

The placebo effect in surgical trials: any condition that is treated surgically and has been assessed in a placebo-surgery controlled trial. Primary analysis examines study effect size in placebo surgery; its components (non-specific versus therapeutic effect), and whether study design affects the effect size.

Secondary analyses will assess 1) magnitude of variance within groups (receiving surgery versus non-surgical) in musculoskeletal conditions. 2) attrition rates in placebo-surgery versus open label studies.

Participants/population

We will include populations as defined in the original placebo-surgery controlled trials.

Intervention(s), exposure(s)

Placebo-surgery.

Comparator(s)/control

- 1) Any surgical procedure against what the the placebo-surgery was compared in the trial.
- 2) Any non-active or non-operative control against which the surgical procedures identified in the placebo-controlled surgical trials were compared.

Main outcome(s) [2 changes]

The effect size from each included RCT.

We will use the same outcome for the analysis across the overlapping non-placebo-controlled RCTs (comparing surgery with non-surgical treatment in same conditions). The effect size selected will be, in order of priority: a measure of pain, function, disease specific quality of life, and generic quality of life. In conditions that are not painful, we will extract the outcome most often used as primary outcome in the included trials. We will use validated outcomes wherever possible. For pain, we will use measures of overall pain related to the anatomic region in preference to more specific measures (e.g. pain at rest, night pain, maximum pain). Similarly, for function, we will use measures of overall region-specific function in preference to more specific measures (e.g. walking distance, stiffness).

Measures of effect

We will give priority to any pre-specified timepoint described in the surgical placebo trial(s). Where this is not present, or is irregular across studies, a timepoint will be selected that reflects the maximum benefit (or harm) of the surgical intervention being assessed based on content expert opinion. If the exact timepoint is not uniform across studies, we will

extract the closest timepoint following the timepoint we selected as most important. Where the timepoints are also unclear, priority will be given to overall summary measures across all timepoints.

SMD is used as the summary measure in the primary analysis (comparing effect sizes in placebo-surgery trials versus open label trials)

Additional outcome(s) [2 changes]

In separate secondary analyses, we will use variability (SD) of the primary outcome and overall participant attrition rate (further divided to recruitment rate, subject drop out rate, loss to follow-up rate, cross over rates) as well as the rate of study early stoppage

Measures of effect

In separate secondary variability analysis assessing variances between active and non-active groups in musculoskeletal surgery, we will use variance ratio as summary measure (variance of active group versus variance in the placebo/inactive group).

In the secondary analysis assessing attrition rates in placebo-surgery trials versus open label surgery trials, we will use both incidence rate ratio and incidence ratio difference

Data extraction (selection and coding)

Two investigators (at minimum) will independently assess the results of each search strategy, first screening titles and abstracts, and recording the reasons for exclusion. Two independent investigators will conduct a full text review of papers included following the title/abstract screening. We will resolve any discrepancies in included studies through discussion, and if necessary, an independent investigator will act as an arbitrator.

Two independent investigators will extract one effect size from each included RCT. We will resolve any discrepancies in included studies through discussion, and if necessary, an independent investigator will act as an arbitrator.

For continuous outcomes, we will extract the mean change from baseline and standard deviation (SD) of the change in each group. Where change from baseline is not reported, we will extract the mean and SD of the outcome in the placebo and intervention groups at the specified follow-up time point. We will use information on baseline and final means to calculate the mean change in each group. We will use data available in the article, such as t and p-values from repeated measures tests to estimate standard deviation of change. If this information is not available, we will impute standard deviation of change using validated methods.

Two authors will also extract the following study characteristics independently:

- 1) The study population (age, sex, location);
- 2) The total study sample size;
- 3) The condition for which surgery was performed;
- 4) Type of intervention, dichotomised as open, or minimally invasive/percutaneous surgery;
- 5) Whether a primary outcome was specified, either explicitly by the study authors, or via a sample size calculation;
- 6) Type of outcome, dichotomised as either a prespecified primary (or an outcome that was used for a sample size calculation) or a prespecified secondary outcome.

Risk of bias (quality) assessment

We will assess reporting of allocation concealment, blinding of patients, care-givers, or outcome assessors, and attrition

(defined as a dropout rate or crossover rate of 20% or more). We will use the Cochrane risk of bias tool.

Strategy for data synthesis

We will standardise effect sizes using Hedges' g . We will convert the direction of effect of these standardised mean differences such that a positive value indicates improvement.

For dichotomous outcomes, we will calculate odds ratios for each study. If data for the same outcome are reported in continuous format in some studies and in dichotomous format in other studies, we will convert dichotomous effect sizes (odds ratios) into standardised mean differences.

We will use I^2 statistics to assess statistical heterogeneity when more than two studies are available. We will use random effects meta-analysis to combine results of individual studies.

If sufficient numbers of studies are available, we will also undertake meta-regression analysis to identify characteristics of study design that influence magnitude of placebo effect.

The review questions posed will be addressed as follows:

Question 1: we will calculate proportion attributable to contextual effect as a ratio of the change in the placebo group relative to change in the intervention group.

Question 2: we will perform this analysis in a subset of placebo-controlled surgical trials that also contain a non-operative control. We will calculate the placebo effect as difference between the change in the placebo group and change in the non-operative control group. We will also calculate the proportion of the total observed placebo effect (PPE) that is not accounted for by non-specific effects using the formula: $[1 - \text{change in the non-operative control group} / \text{change in the placebo group}]$.

Question 3: for each surgical intervention, we will compare summary effect sizes of the primary outcome from placebo-controlled RCTs to non-placebo RCTs. We will conduct a meta-regression analysis to estimate the difference between the magnitude of surgical effect from placebo-controlled and non-placebo-controlled trials, through the assessment of a multiplicative interaction between group allocation and the presence of placebo control.

Analysis of subgroups or subsets [1 change]

In all analyses, we will explore significant clinical or statistical heterogeneity through subgroup analyses using study level covariates including sample size (dichotomised as <100 or >100), type of intervention (dichotomised as open vs. endoscopic/minimally invasive/percutaneous surgery), allocation concealment (yes versus no/unclear), blinding of outcome assessors (yes versus no/unclear), and whether a primary outcome was specified (yes/no, either explicitly by the study authors, or a by inclusion of a sample size calculation). Sensitivity analysis will use the primary outcomes defined by the primary authors.

We will also perform a subgroup analysis comparing the magnitude of effect size in pain, function and global improvement in trials addressing musculoskeletal conditions.

Contact details for further information

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Organisational affiliation of the review [1 change]

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Type and method of review

Epidemiologic, Meta-analysis, Methodology, Systematic review, Other

Anticipated or actual start date

22 November 2018

Anticipated completion date [3 changes]

23 August 2022

Funding sources/sponsors

Teemu Karjalainen is being funded by a grant from the Finnish Medical Foundation and the Finnish Centre for Evidence Based Orthopaedics

The funding sources will not participate in the conduct of this review

Conflicts of interest

Language

English

Country

Australia, Finland

Published protocol

https://www.crd.york.ac.uk/PROSPEROFILES/117364_PROTOCOL_20200521.pdf

Stage of review [1 change]

Review Completed published

Details of final report/publication(s) or preprints if available [1 change]

Karjalainen T, Heikkinen J, Busija L, et al. Use of Placebo and Nonoperative Control Groups in Surgical Trials: A Systematic Review and Meta-analysis. JAMA Netw Open. 2022;5(7):e2223903.
doi:10.1001/jamanetworkopen.2022.23903
<https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2794704>

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

Epidemiologic Research Design; Epidemiologic Studies; Humans; Placebo Effect; Placebos; Randomized Controlled Trials as Topic; Reproducibility of Results; Research Design; Surgical Procedures, Operative; Treatment Outcome

Date of registration in PROSPERO

07 January 2019

Date of first submission

20 November 2018

Stage of review at time of this submission [3 changes]

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

Revision note

Review completed. Added publication and link to the paper

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

07 January 2019

15 May 2020

09 November 2020

23 August 2022

APPENDIX 1: Lists of key-words and terms used to search electronic databases

Placebo-controlled randomised trials of surgical interventions

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)

1. Clinical trial/
2. Randomized controlled trial/
3. Randomization/
4. Rct.tw.
5. random allocation.tw.
6. Randomly allocated.tw.
7. Allocated randomly.tw.
8. Randomized Controlled Trials as Topic/
9. randomized controlled trial/
10. Double Blind Method/
11. Single Blind Method/
12. clinical trial/
13. controlled clinical trial.pt.
14. randomized controlled trial.pt.
15. clinical trial.pt.
16. exp Clinical Trials as topic/
17. or/1-16
18. PLACEBOS/
19. placebo\$.tw.
20. sham.tw.
21. immitation.tw.
22. placebo effect\$.tw.
23. or/18-22
24. surgery.tw.
25. surgical.tw.
26. arthroscopy.tw.
27. endoscopy.tw.
28. transplantation.tw.
29. \$scopy.tw.
30. \$scopic.tw.
31. laparoscopy.tw.
32. Meta-Analysis as Topic/
33. meta analy\$.tw.
34. metaanaly\$.tw.
35. Review/
36. Comment/
37. Letter/
38. Editorial/
39. animal/
40. dose\$.tw.
41. pre\$medication.tw.
42. an\$esthesia.tw.
43. an\$esthetic\$.tw.
44. antibiotic\$.tw.
45. steroid\$.tw.
46. prophylaxis.tw.
47. prevention.tw.
48. preoperative.tw.
49. preanaesthetic\$.tw.
50. pre\$emptive.tw.
51. pre-operative.tw.
52. post-operative.tw.
53. postoperative.tw.
54. post\$surgery.tw.
55. (analgesic adj trial).tw.
56. oral\$.tw.
57. acupuncture.tw.
58. acupressure.tw.
59. scar.tw.
60. infection.tw.

61. dental.tw.
62. post\$surgical.tw.
63. pre\$surgical.tw.
64. case report.tw.
65. case study.tw.
66. pacing.tw.
67. stimulation.tw.
68. growth factor\$.tw.
69. hormon\$.tw.
70. or/24-31
71. or/32-69
72. 17 and 23
73. 72 and 70
74. 73 not 71

Ovid EMBASE

1. Clinical trial/
2. Randomized controlled trial/
3. Randomization/
4. Single blind procedure/
5. Double blind procedure/
6. Crossover procedure/
7. Randomi?ed controlled trial\$.tw.
8. Rct.tw.
9. random allocation.tw.
10. Randomly allocated.tw.
11. Allocated randomly.tw.
12. (allocated adj2 random).tw.
13. Single blind\$.tw.
14. Single blind\$.tw.
15. or/1-14
16. Placebo\$.tw.
17. placebo effect\$.tw.
18. sham.tw.
19. placebo.tw.
20. or/16-19
21. surgery.tw.
22. surgical.tw.
23. arthroscopy.tw.
24. endoscopy.tw.
25. \$scopy.tw.
26. \$scopic.tw.
27. laparoscopy.tw.
28. transplantation.tw.
29. or/21-28
30. letter/
31. Review/
32. animal/
33. editorial/
34. ((meta adj analy\$) or metaanalys\$).tw.
35. (analgesic adj trial).tw.
36. meta\$analysis.tw.
37. dose\$.tw.
38. oral\$.tw.
39. orally.tw.
40. dental.tw.
41. pre\$medication.tw.
42. pre\$surgical.tw.
43. post\$surgical.tw.
44. pre\$surgery.tw.
45. post\$surgery.tw.
46. antibiotic\$.tw.
47. an\$esthetic\$.tw.
48. steroid\$.tw.
49. peri\$operative.tw.
50. pre\$emptive.tw.

51. pre\$an\$esthetic\$.tw.
52. post\$operative.tw.
53. prophylaxis.tw.
54. prevention.tw.
55. acupuncture.tw.
56. accupressure.tw.
57. scar\$.tw.
58. infection\$.tw.
59. acupressure.tw.
60. pre\$operative.tw.
61. growth factor\$.tw.
62. pacing.tw.
63. stimulation.tw.
64. hormon\$.tw.
65. case report\$.tw.
66. case study.tw.
67. or/30-66
68. 15 and 20
69. 68 and 29
70. 69 not 67

Cochrane Central Register of Controlled Trials

http://onlinelibrary.wiley.com/o/cochrane/cochrane_clcentral_articles_fs.html

(placebo OR placebo effect OR sham OR imitation):ti,ab,kw and (surgery OR surgical OR laparoscopy OR endoscopy OR arthroscopy OR transplantation OR scopy):ti,ab,kw and (clinical trial OR randomised clinical trial OR RCT OR randomised controlled trial OR randomisation):ti,ab,kw not (drug OR dental OR oral OR infection OR steroids OR hormones OR growth factor OR prophylaxis OR anaesthesia OR pre-surgical OR post-surgical OR pre-emptive OR post-operative OR preoperative OR antibiotics OR acupuncture OR acupressure OR scar OR infection OR prevention):ti,ab,kw not (review OR animal OR stimulation):ti,ab,kw in Trials

ClinicalTrials.gov

Key words: interventional studies AND placebo NOT drug, stimulation, stimulator, acupuncture, acupressure, biological, behavioural, dietary supplements, genetic, analgesic, preconditioning, bone marrow, stem cells, and hormones

Non-operative controlled trials:**Abdominal pain/adhesiolysis (2016-current)**

Before 2016: Van Beukel et al (2017) (1)

MEDLINE

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. randomised.ab.
5. placebo.tw.
6. clinical trials as topic.sh.
7. randomly.ab.
8. trial.ti.
9. groups.tiab.
10. OR/1-9
11. exp animals/ not humans.sh.
12. 10 NOT 11
13. exp abdominal pain/
14. exp chronic pain/
15. exp Tissue Adhesions/
16. Adhesion\$.tw.
17. adhesi*.tiab.
18. OR/12-17
19. exp laparotomy
20. exp laparoscopy
21. laparoscop*.ti,ab.
22. laparotomy.ti,ab.
23. adhesiolysis.ti,ab.
24. ((abdomen or abdominal or abdomino*) and surgery).ti,ab.
25. OR/18-24
26. AND/11,18,25
27. limit 26 to yr="2016-Current"

Embase

1. Clinical Trial/
2. Randomized Controlled Trial/
3. exp randomization/
4. Single Blind Procedure/
5. Double Blind Procedure/
6. Crossover Procedure/
7. Placebo/
8. Randomi?ed controlled trial\$.tw.
9. Rct.tw.
10. random allocation.tw.
11. randomly allocated.tw.

12. allocated randomly.tw.
13. (allocated adj2 random).tw.
14. Single blind\$.tw.
15. Double blind\$.tw.
16. ((treble or triple) adj blind\$.ti.
17. placebo\$.tw.
18. prospective study/
19. OR/1-18
20. exp abdominal pain/
21. exp chronic pain/
22. exp Tissue Adhesions/
23. Adhesion\$.ti.
24. adhesi\$.ti,ab.
25. OR/20-24
26. exp laparoscopy/
27. exp laparotomy/
28. laparoscop\$.ti,ab.
29. laparotomy.ti,ab.
30. adhesiolysis.ti,ab.
31. (abdomen.ti,ab. or abdominal.ti,ab. or abdomino\$.ti,ab.) AND surgery.ti,ab.
32. OR/26-31
33. AND/19,25,32
34. limit 33 to yr="2016-current"

CENTRAL

1. (abdominal pain)
2. MeSH descriptor [chronic pain)] explode all trees
3. (Adhesion)
4. #1 OR #2 OR #3
5. MeSH descriptor [laparoscopy] explode all trees
6. MeSH descriptor [laparotomy] explode all trees
7. laparoscop\$
8. adhesiolysis
9. #5 OR #6 OR #7 OR #8
10. #4 AND #9

Reference List

1. van den Beukel BA, de Ree R, van Leuven S, Bakkum EA, Strik C, van Goor H, Ten Broek RP. Surgical treatment of adhesion-related chronic abdominal and pelvic pain after gynaecological and general surgery: a systematic review and meta-analysis. *Human Reproduction Update*. 2017 May 1;23(3):276-88.

Benign Prostatic Hyerplasia/ Urethral Lift

Medline

1. Exp Prostatic Hyperplasia/
2. prostat* adj3 hyperplasia*.tw.
3. Prostate* adj3 hypertroph*.tw.
4. Prostat* adj3 adenoma*.tw.
5. BPH or BPO or BPE.tw.
6. prostat* adj3 enlarg*.tw.
7. exp prostatism/
8. prostatism.tw
9. exp Urinary Bladder Neck Obstruction/
10. Bladder* adj3 obstruct*.tw.
11. BOO.tw.
12. OR/1-11
13. Prostatic urethral lift.tw
14. prost* ajd3 lift.tw.
15. Urolift.tw.
16. 13 or 14
17. 12 and 15
18. randomized controlled trial.pt.
19. controlled clinical trial.pt.
20. randomized
21. randomized
22. placebo.tw
23. clinical trials as topic.sh
24. randomly.ab.
25. trial.ti.
26. groups.ti,ab.
27. or/17-25
28. animals not (humans and animals).sh
29. 26 not 27
30. 16 and 28

EMBASE

Clinical Trial/
Randomized Controlled Trial/
exp randomization/
Single Blind Procedure/
Double Blind Procedure/
Crossover Procedure/
Placebo/
Randomi?ed controlled trial\$.tw.
Rct.tw.
random allocation.tw.

randomly allocated.tw.
allocated randomly.tw.
(allocated adj2 random).tw.
Single blind\$.tw.
Double blind\$.tw.
((treble or triple) adj blind\$).tw.
placebo\$.tw.
prospective study/
or/1-18
case study/
case report.tw.
abstract report/ or letter/
or/20-22
19 NOT 23
Prostatic urethral lift.tw
prost\$ lift.tw.
Urolift.tw.
OR/25-27
Exp Prostatic Hyperplasia/
prostat\$ adj3 hyperplasia\$.tw.
Prostate\$ adj3 hypertroph\$.tw.
Prostat\$ adj3 adenoma\$.tw.
BPH or BPO or BPE.tw.
prostat\$ adj3 enlarg\$.tw.
exp prostatism/
prostatism.tw.
exp Urinary Bladder Neck Obstruction/
Bladder\$ adj3 obstruct\$.tw.
BOO.tw.
OR/29-39
and/24,28,40

CENTRAL

1. MeSH description [benign prostatic hyperplasia] explode all trees
2. surgical procedures, operative explode all trees
3. surg* or surgical* or operat*:ti,ab
4. #2 or #3
5. #4 and #1

Callus Debridement

Medline

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. randomised.ab.
5. placebo.tw.
6. clinical trials as topic.sh.
7. randomly.ab.
8. trial.ti.
9. (crossover or cross-over or cross over).tw.
10. or/1-9
11. exp animals/ not humans.sh.
12. 10 NOT 11
13. Callosities/
14. callosities.mp.
15. callus.mp.
16. OR/13-15
17. surgical procedures, operative/
18. (surg* or surgical* or operat*).ti,ab.
19. debridement*.ti,ab.
20. OR/17-19
21. AND/12,16,20

EMBASE

1. Clinical Trial/
2. Randomized Controlled Trial/
3. exp randomization/
4. Single Blind Procedure/
5. Double Blind Procedure/
6. Crossover Procedure/
7. Placebo/
8. Randomi?ed controlled trial\$.tw.
9. Rct.tw.
10. random allocation.tw.
11. randomly allocated.tw.
12. allocated randomly.tw.
13. (allocated adj2 random).tw.
14. Single blind\$.tw.
15. Double blind\$.tw.
16. ((treble or triple) adj blind\$).tw.
17. placebo\$.tw.
18. prospective study/
19. or/1-18

20. case study/
21. case report.tw.
22. abstract report/ or letter/
23. or/20-22
24. 19 NOT 23
25. Callosities/
26. callosities.mp.
27. callus.mp.
28. OR/25-27
29. Exp surgical procedures, operative/
30. (surg\$ or surgical\$ or operat\$).ti,ab.
31. debridement*.ti,ab.
32. OR/29-31
33. AND/24,28,32

CENTRAL

1. MeSH description [Callosities] explode all trees
2. callosit*
3. callus
4. #1 or #2 or #3
5. surgical procedures, operative explode all trees
6. surg* or surgical* or operat*:ti,ab
7. debridement:kw,ti,ab
8. #5 or #6 or #7
9. #4 and #8

Cervical dystonia

Medline

randomized controlled trial.pt.
controlled clinical trial.pt.
randomized.ab.
randomised.ab.
placebo.tw.
clinical trials as topic.sh.
randomly.ab.
trial.ti.
(crossover or cross-over or cross over).tw.
or/1-9
exp animals/ not humans.sh.
10 NOT 11
cervical dystonia
Spasmodic Torticollis
focal dystonia
laterocollis or anterocollis or retrocollis):tw
OR/13-16
surgical procedures, operative/
(surg* or surgical* or operat*).ti,ab
deep brain stimulation.ti,ab
OR/18-20
and/12,17,21

EMBASE

1. Clinical Trial/
2. Randomized Controlled Trial/
3. exp randomization/
4. Single Blind Procedure/
5. Double Blind Procedure/
6. Crossover Procedure/
7. Placebo/
8. Randomi?ed controlled trial\$.tw.
9. Rct.tw.
10. random allocation.tw.
11. randomly allocated.tw.
12. allocated randomly.tw.
13. (allocated adj2 random).tw.
14. Single blind\$.tw.
15. Double blind\$.tw.
16. ((treble or triple) adj blind\$).tw.
17. placebo\$.tw.

18. prospective study/
19. or/1-18
20. case study/
21. case report.tw.
22. abstract report/ or letter/
23. or/20-22
24. 19 NOT 23
25. cervical dystonia/
26. spasmodic torticollis.tw.
27. dystonia.ti,ab.
28. laterocollis or anterocollis or retrocollis).tw.
29. OR/25-28
30. surgical procedures, operative/
31. (surg* or surgical* or operat*).ti,ab
32. Deep brain stimulation.ti,ab.
33. or/30-32
34. and/24,29,33

CENTRAL

1. MeSH Term: [Torticollis] explode all trees
2. dystonia:kw
3. #1 OR #2
4. MeSH Term [surgical procedures, operative] explode all trees
5. (surg* or surgical* or operat*):ti,ab
6. (deep brain stimulation):kw
7. #4 or #5 or #6
8. #3 and #7
9. limit to trials

Endometriosis

Medline

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. randomised.ab.
5. placebo.tw.
6. clinical trials as topic.sh.
7. randomly.ab.
8. trial.ti.
9. (crossover or cross-over or cross over).tw.
10. or/1-9
11. exp animals/ not humans.sh.
12. 10 NOT 11
13. exp Laparoscopy/ (146878)
14. Laparoscop\$.tw. (183770)
15. celioscop\$.tw. (580)
16. peritoneoscop\$.tw. (1176)
17. exp minimally invasive surgery/ (37349)
18. exp laser/ (123007)
19. exp diathermy/ (7154)
20. diathermy.tw. (4955)
21. LUNA.tw. (1395)
22. presacral neurectom\$.tw. (177)
23. laser\$.tw. (248739)
24. plasmajet.tw. (75)
25. plasma jet.tw. (342)
26. microlaparoscop\$.tw. (198)
27. minilaparoscop\$.tw. (342)
28. exp robotics/ (34612)
29. exp computer assisted surgery/ (11310)
30. Computer-Assisted Surg\$.tw. (1248)
31. da vinci.tw. (4710)
32. (keyhole adj3 surg\$.tw. (194)
33. Robot\$.tw. (56125)
34. remote surg\$.tw. (151)
35. microsurg\$.tw. (29971)
36. uterine nerve ablation\$.tw. (39)
37. uterosacral nerve ablation.tw. (38)
38. minimally invasive.tw. (84934)
39. (ablation or ablative).tw. (136843)
40. or/13-39 (748344)
41. exp endometriosis/ (36593)
42. exp infertility/ (121827)
43. endometrio\$.tw. (42667)

44. dyschezia.tw. (546)
45. dyspareunia.tw. (6811)
46. exp infertility/
47. or/41-46 (168951)
48. AND/12,40,47
49. limit 48 to yr="2013-current

EMBASE

1. Clinical Trial/
2. Randomized Controlled Trial/
3. exp randomization/
4. Single Blind Procedure/
5. Double Blind Procedure/
6. Crossover Procedure/
7. Placebo/
8. Randomi?ed controlled trial\$.tw.
9. Rct.tw.
10. random allocation.tw.
11. randomly allocated.tw.
12. allocated randomly.tw.
13. (allocated adj2 random).tw.
14. Single blind\$.tw.
15. Double blind\$.tw.
16. ((treble or triple) adj blind\$.tw.
17. placebo\$.tw.
18. prospective study/
19. or/1-18
20. case study/
21. case report.tw.
22. abstract report/ or letter/
23. or/20-22
24. 19 NOT 23
25. exp Laparoscopy/ (146878)
26. Laparoscop\$.tw. (183770)
27. celioscop\$.tw. (580)
28. peritoneoscop\$.tw. (1176)
29. exp minimally invasive surgery/ (37349)
30. exp laser/ (123007)
31. exp diathermy/ (7154)
32. diathermy.tw. (4955)
33. LUNA.tw. (1395)
34. presacral neurectom\$.tw. (177)
35. laser\$.tw. (248739)
36. plasmajet.tw. (75)
37. plasma jet.tw. (342)

38. microlaparoscop\$.tw. (198)
39. minilaparoscop\$.tw. (342)
40. exp robotics/ (34612)
41. exp computer assisted surgery/ (11310)
42. Computer-Assisted Surg\$.tw. (1248)
43. da vinci.tw. (4710)
44. (keyhole adj3 surg\$).tw. (194)
45. Robot\$.tw. (56125)
46. remote surg\$.tw. (151)
47. microsurg\$.tw. (29971)
48. uterine nerve ablation\$.tw. (39)
49. uterosacral nerve ablation.tw. (38)
50. minimally invasive.tw. (84934)
51. (ablation or ablative).tw. (136843)
52. exp hand assisted laparoscopy/ (712)
53. or/25-53 (748344)
54. exp endometriosis/ (36593)
55. exp infertility/ (121827)
56. endometrio\$.tw. (42667)
57. dyschezia.tw. (546)
58. dyspareunia.tw. (6811)
59. or/54-58 (168951)
60. AND/24,53,59
61. limit 60 to yr=" 2013-current"

CENTRAL

- 1 exp Laparoscopy/
- 2 Laparoscop\$.ti,ab,sh.
- 3 celioscop\$.tw.
- 4 peritoneoscop\$.tw.
- 5 exp Surgical Procedures, Minimally Invasive/
- 6 Lasers/
- 7 exp Diathermy/
- 8 LUNA
- 9 presacral neurectom*
- 10 (minimal\$ adj5 surg\$).tw.
- 11 laser\$.tw.
- 12 diathermy.tw.
- 13 plasmajet.tw.
- 14 plasma jet.tw.
- 15 excision.tw.
- 16 microlaparoscop\$.tw.
- 17 minilaparoscop\$.tw.
- 18 exp Robotics/
- 19 exp Surgery, Computer-Assisted/
- 20 Computer-Assisted Surg\$.tw.
- 21 da vinci.tw.

22 (keyhole near3 surg\$.tw.
23 Robot\$.tw.
24 remote surg\$.tw.
25 microsurg\$.tw.
26 minimally invasive.tw.
27 (ablation or ablative).tw.
28 or/1-27
29 exp Endometriosis/
30 endometrio\$.tw.
31 dyschezia.tw.
32 dyspareunia.tw.
33 infertility:kw
34 MeSH term infertility explode all trees
35 #29 or #30 or #31 or 32 #or 33
34 28 and 35

Transoral Incisionless Fundoplication

MEDLINE

randomized controlled trial.pt.
controlled clinical trial.pt.
randomized.ab.
randomised.ab.
placebo.tw.
clinical trials as topic.sh.
randomly.ab.
trial.ti.
(crossover or cross-over or cross over).tw.
or/1-9
exp animals/ not humans.sh.
10 NOT 11
transoral incisionless fundoplication.mp
EsophyX.mp.
Endocinch.mp.
transoral fundoplication.mp
endoscopic fundoplication.mp
OR/13-17
12 and 18

Embase

1. Clinical Trial/
2. Randomized Controlled Trial/
3. exp randomization/
4. Single Blind Procedure/
5. Double Blind Procedure/
6. Crossover Procedure/
7. Placebo/
8. Randomi?ed controlled trial\$.tw.
9. Rct.tw.
10. random allocation.tw.
11. randomly allocated.tw.
12. allocated randomly.tw.
13. (allocated adj2 random).tw.
14. Single blind\$.tw.
15. Double blind\$.tw.
16. ((treble or triple) adj blind\$).tw.
17. placebo\$.tw.
18. prospective study/
19. or/1-18
20. case study/
21. case report.tw.

22. abstract report/ or letter/
23. or/20-22
24. 19 NOT 23
25. transoral incisionless fundoplication.mp.
26. EsophyX.mp.
27. Endocinch.mp.
28. transoral fundoplication.mp.
29. endoscopic fundoplication.mp.
30. or/25-29
31. 24 and 30

CENTRAL

1. EsophyX
2. Endocinch
3. (transoral fundoplication) OR (transoral plication) OR (endoscopic plication) OR (endoscopic fundoplication)
4. TIF
5. #1 OR #2 OR #3 OR #4 OR #5

IMA ligation

Embase, Medline and Central

(internal mammary artery ligation) OR (internal-mammary-artery ligation) or division adj3 "internal mammary arter*"

Urinary Incontinence

Medline

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. randomised.ab.
5. placebo.tw.
6. clinical trials as topic.sh.
7. randomly.ab.
8. trial.ti.
9. (crossover or cross-over or cross over).tw.
10. or/1-9
11. exp animals/ not humans.sh.
12. 10 NOT 11
13. Urinary Incontinence, Stress/
14. ((stress* or mix* or urg* or urin*) adj3 incontinen\$).tw.
15. stress urinary incontinence*.mp.
16. occult urinary incontinence.mp.
17. OR/13-16
18. surgical procedures, operative/
19. (surg* or surgical* or operat*).ti,ab.
20. suburethral sling.mp.
21. abdominal sling.mp.
22. traditional sling procedure\$.tw.
23. suburethral sling procedure.tw.
24. mid\$urethral sling.tw.
25. retropubic sling procedure\$.tw.
26. transobturator sling procedure\$.tw.
27. TVT-Secur.mp.
28. mini-arc or mini-arc.mp.
29. ajust.mp.
30. needleless.mp.
31. solyx.mp.
32. single\$incision sling\$.mp.
33. mini\$sling.mp.
34. Ophira.mp.
35. Tissue Fixation System.mp.
36. OR/18-35
37. ((urethra* or periurethra* or transurethra*) adj3 (agent* or bulk* or injection* or injectable\$)).tw.
38. injection therapy.tw.
39. injectable\$.tw.
40. (injectable\$ adj2 agent\$).tw.
41. (bulk\$ adj3 agent\$).tw.
42. autologous fat.mp.
43. Peri\$urethral injection\$.mp.

44. OR/38-44
45. AND/12,17,36 (for the sling, limit 2018 – current)
46. AND/12, 17, 44 (2017-current)

EMBASE

1. Clinical Trial/
2. Randomized Controlled Trial/
3. exp randomization/
4. Single Blind Procedure/
5. Double Blind Procedure/
6. Crossover Procedure/
7. Placebo/
8. Randomi?ed controlled trial\$.tw.
9. Rct.tw.
10. random allocation.tw.
11. randomly allocated.tw.
12. allocated randomly.tw.
13. (allocated adj2 random).tw.
14. Single blind\$.tw.
15. Double blind\$.tw.
16. ((treble or triple) adj blind\$).tw.
17. placebo\$.tw.
18. prospective study/
19. or/1-18
20. case study/
21. case report.tw.
22. abstract report/ or letter/
23. or/20-22
24. 19 NOT 23
25. exp Urinary Incontinence, stress/
26. ((stress\$ or mix\$ or urg\$ or urin\$) adj3 incontinen\$).tw.
27. stress urinary incontinence*.mp.
28. occult urinary incontinence.mp.
29. OR/25-28
30. exp surgical procedures, operative/
31. (surg* or surgical* or operat*).ti,ab.
32. suburethral sling.mp.
33. abdominal sling.mp.
34. traditional sling procedure\$*.tw.
35. suburethral sling procedure.tw.
36. mid\$urethral sling.tw.
37. retropubic sling procedure\$*.tw.
38. transobturator sling procedure\$.tw.
39. TVT-Secur.mp.
40. mini-arc or mini-arc.mp.
41. ajust.mp.

42. needleless.mp.
43. solyx.mp.
44. single\$incision sling\$.mp.
45. mini\$sling.mp.
46. Ophira.mp.
47. Tissue Fixation System.mp.
48. OR/30-47
49. ((urethra* or periurethra* or transurethra*) adj3 (agent* or bulk* or injection* or injectable*)).tw.
50. injection therapy.tw.
51. injectable\$.tw.
52. (injectable\$ adj2 agent\$).tw.
53. (bulk\$ adj3 agent\$).tw.
54. autologous fat.mp.
55. Peri\$urethral injection\$.mp.
56. OR/38-44
57. AND/12,18,37 (this is for the sling, limit April 2018 – March 2019
58. AND/12, 18, 45 (2017-current)

CENTRAL

1. MeSH descriptor: [Urinary Incontinence, Stress] explode all trees
2. stres* near incontinen*:kw
3. stress near incontinence*:kw
4. mix* near incontinen*:kw
5. urg* near incontinen*:kw
6. stress urinary incontinence*:kw
7. occult urinary incontinence:kw
8. #1 or #2 or #3 or #4 or #5 or #6 or #7
9. MeSH descriptor: [Surgical Procedures, Operative] explode all trees
10. (surg* or surgical* or operat*):ti,ab
11. suburethral sling:kw
12. abdominal sling:kw
13. mid\$urethral sling:kw
14. retropubic sling:kw
15. transobturator sling:kw
16. "mini-arc" or "mini-arc"
17. ajust
18. needleless
19. solyx
20. single\$incision sling:kw
21. mini near sling:kw
22. Tissue Fixation System:kw
23. #9 or #10 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22
24. #8 and #23
25. with Publication Year from 2018 to 2019, in Trials

injectables

1. MeSH descriptor: [Urinary Incontinence, Stress] explode all trees
2. stres* near incontinen*:kw
3. stress near incontinence*:kw
4. mix* near incontinen*:kw
5. urg* near incontinen*:kw
6. stress urinary incontinence*:kw
7. occult urinary incontinence:kw
8. #1 or #2 or #3 or #4 or #5 or #6 or #7

Meniere's Disease

MEDLINE

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. randomised.ab.
5. placebo.tw.
6. clinical trials as topic.sh.
7. randomly.ab.
8. trial.ti.
9. (crossover or cross-over or cross over).tw.
10. or/1-9
11. exp animals/ not humans.sh.
12. 10 NOT 11
13. shunt.tw.
14. endolymphatic sac adj3 surgery
15. ((endolymphatic or sac) and shunt).ti,ab.
16. (endolymphatic and (surg* or decompress* or drainage)).ti,ab.
17. OR/13-15
18. endolymphatic hydrops.mp.
19. meniere disease/
20. vertigo.mp.
21. labyrinth or aural or endolymphatic adj3 syndrome or vertigo or hydrops
22. OR/18-21

EMBASE

1. Clinical Trial/
2. Randomized Controlled Trial/
3. exp randomization/
4. Single Blind Procedure/
5. Double Blind Procedure/
6. Crossover Procedure/
7. Placebo/
8. Randomi?ed controlled trial\$.tw.
9. Rct.tw.
10. random allocation.tw.
11. randomly allocated.tw.
12. allocated randomly.tw.
13. (allocated adj2 random).tw.
14. Single blind\$.tw.
15. Double blind\$.tw.
16. ((treble or triple) adj blind\$).tw.
17. placebo\$.tw.
18. prospective study/

19. or/1-18
20. case study/
21. case report.tw.
22. abstract report/ or letter/
23. shunt.tw.
24. endolymphatic sac adj3 surgery
25. ((endolymphatic or sac) and shunt).ti,ab.
26. (endolymphatic and (surg\$ or decompress\$ or drainage)).ti,ab.
27. OR/23-26
28. endolymphatic hydrops.mp.
29. meniere disease/
30. vertigo.mp.
31. labyrinth or aural or endolymphatic adj3 syndrome or vertigo or hydrops
32. OR/28-31

CENTRAL

1. surg* or decompression or drainage or shunt or operat* or surgical*
2. endolymphatic
3. #1 AND #2

Obesity

Medline

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. randomised.ab.
5. placebo.tw.
6. clinical trials as topic.sh.
7. randomly.ab.
8. trial.ti.
9. (crossover or cross-over or cross over).tw.
10. or/1-9
11. exp animals/ not humans.sh.
12. 10 NOT 11
13. exp obesity/
14. Overweight/
15. over?weight.ti,ab.
16. over weight.ti,ab.
17. overeating.ti,ab.
18. over?eating.ti,ab.
19. exp Weight Loss/
20. weight loss.ti,ab.
21. weight reduc\$.ti,ab.
22. or/13-21
23. bariatric surg\$.ti,ab.
24. exp bariatric surgery/
25. (surg\$ adj5 bariatric).ti,ab.
26. anti?obesity surg\$.ti,ab.
27. antiobesity surg\$.ti,ab.
28. (obesity adj5 surgery).ti,ab.
29. (obesity adj5 surgical).ti,ab.
30. (gastroplasty or gastro?gastostomy or "gastric bypass" or "gastric surgery" or "restrictive surgery").ti,ab.
31. exp gastric bypass/
32. gastroplasty/
33. ((gastric plication) or (vagal nerve stimulation) OR (vagal nerve block)).ti,ab.
34. stomach stapl\$.ti,ab.
35. obesity/su
36. exp Obesity, Morbid/su [Surgery]
37. OR/23-36
38. AND/12,22,37

EMBASE

1. Clinical Trial/

2. Randomized Controlled Trial/
3. exp randomization/
4. Single Blind Procedure/
5. Double Blind Procedure/
6. Crossover Procedure/
7. Placebo/
8. Randomi?ed controlled trial\$.tw.
9. Rct.tw.
10. random allocation.tw.
11. randomly allocated.tw.
12. allocated randomly.tw.
13. (allocated adj2 random).tw.
14. Single blind\$.tw.
15. Double blind\$.tw.
16. ((treble or triple) adj blind\$).tw.
17. placebo\$.tw.
18. prospective study/
19. or/1-18
20. case study/
21. case report.tw.
22. abstract report/ or letter/
23. or/20-22
24. 19 NOT 23
25. exp OBESITY/ or exp MORBID OBESITY/
26. over?weight.ti,ab.
27. over weight.ti,ab.
28. overeating.ti,ab.
29. over?eating.ti,ab.
30. exp Weight Reduction/
31. (weight adj1 los*).ti,ab.
32. (weight adj1 loos*).ti,ab.
33. weightloss.ti,ab.
34. weight?loss.ti,ab.
35. (weight adj3 reduc*).ti,ab.
36. weight?reduc*.ti,ab.
37. or/25-36
38. bariatric surg*.ti,ab.
39. exp Bariatric Surgery/
40. (surg* adj5 bariatric).ti,ab.
41. (anti?obesity adj3 surg*).ti,ab.
42. (antiobesity adj3 surg*).ti,ab.
43. anti obesity surg*.ti,ab.
44. (obesity adj5 surgery).ti,ab.
45. (obesity adj5 surgical).ti,ab.
46. (gastroplasty or gastrogastrostomy or gastro?gastrostomy or gastroenterostomy or gastric bypass or gastric surgery or
47. restrictive surgery).ti,ab.

48. exp GASTROPLASTY/
49. ("gastric plication" or "vagal nerve stimulation" OR "vagal nerve block").ti,ab.
50. gastric stapl*.ti,ab.
51. OR/38-50
52. 37 AND 51
53. OBESITY/su [Surgery]
54. Morbid Obesity/su [Surgery]
55. 53 OR 54
56. 37 AND 55
57. 52 OR 56

CENTRAL

- #1 MeSH descriptor: [Obesity] explode all trees
- #2 MeSH descriptor: [Overweight] this term only
- #3 MeSH descriptor: [Weight Loss] explode all trees
- #4 (obes* or overweight or "over weight")
- #5 #1 or #2 or #3 or #4
- #6 MeSH descriptor: [Bariatric Surgery] explode all trees
- #7 (bariatric near/5 surg*)
- #8 (obes* near/5 surg*)
- #9 antiobesity or anti-obesity or anti obesity near/5 (surg*)
- #10(gastroplasty or gastrogastrostomy or gastro?gastrostomy or gastroenterostomy or "gastric bypass" or "gastric surgery" or "restrictive surgery")
- #11 MeSH descriptor: [Gastric Bypass] explode all trees
- #12 MeSH descriptor: [Gastroplasty] explode all trees
- #13 stomach near/5 stapl*
- #14 gastric near/5 stapl*
- #15 (gastric plication):ti,ab OR (vagal nerve block):ti,ab OR (vagal nerve stimulation):ti,ab

Parkinson's Disease

Medline

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. randomised.ab.
5. placebo.tw.
6. clinical trials as topic.sh.
7. randomly.ab.
8. trial.ti.
9. (crossover or cross-over or cross over).tw.
10. or/1-9
11. exp animals/ not humans.sh.
12. 10 NOT 11
13. Parkinson's disease/
14. Parkinson's syndrome
15. Parkinson*.ti,ab
16. OR/13-15
17. surgical procedures, operative/
18. (surg* or surgical* or operat*).ti,ab
19. cell adj2 delivery.ti,ab.
20. gene adj delivery.ti,ab.
21. OR/17-20
22. and/12,16,21

EMBASE

1. Clinical Trial/
2. Randomized Controlled Trial/
3. exp randomization/
4. Single Blind Procedure/
5. Double Blind Procedure/
6. Crossover Procedure/
7. Placebo/
8. Randomi?ed controlled trial\$.tw.
9. Rct.tw.
10. random allocation.tw.
11. randomly allocated.tw.
12. allocated randomly.tw.
13. (allocated adj2 random).tw.
14. Single blind\$.tw.
15. Double blind\$.tw.
16. ((treble or triple) adj blind\$.tw.
17. placebo\$.tw.

18. prospective study/
19. or/1-18
20. case study/
21. case report.tw.
22. abstract report/ or letter/
23. or/20-22
24. 19 NOT 23
25. Parkinson's disease/
26. Parkinson's syndrome
27. Parkinson*.ti,ab
28. OR/25-27
29. surgical procedures, operative/
30. (surg* or surgical* or operat*).ti,ab
31. cell adj2 delivery.ti,ab.
32. gene adj delivery.ti,ab.
33. or/29-32
34. and/24,28,33

CENTRAL

1. MeSH Term: [Parkinson's disease] explode all trees
2. Parkinson*.ti,ab
3. #1 OR #2
4. MeSH Term [surgical procedures, operative] explode all trees
5. (surg* or surgical* or operat*).ti,ab
6. (cell adj2 delivery):ti,ab.
7. (gene adj delivery):ti,ab.
8. #4 or #5 or #6 or #7
9. #3 and #8

Sphincter of Oddi (Sphincterotomy)

Medline

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. randomised.ab.
5. placebo.tw.
6. clinical trials as topic.sh.
7. randomly.ab.
8. trial.ti.
9. (crossover or cross-over or cross over).tw.
10. or/1-9
11. exp animals/ not humans.sh.
12. 10 NOT 11
13. sphincter of oddi.mp.
14. endoscopic sphincterotomy.mp.
15. exp surgical procedures, operative/
16. (surg* or surgical* or operat*).ti,ab.
17. or/14-16
18. and/24-25,29 (240)

EMBASE

- 1 Clinical Trial/ (972204)
- 2 Randomized Controlled Trial/ (538693)
- 3 exp randomization/ (81721)
- 4 Single Blind Procedure/ (33954)
- 5 Double Blind Procedure/ (160406)
- 6 Crossover Procedure/ (58585)
- 7 Placebo/ (340669)
- 8 Randomi?ed controlled trial\$.tw. (196048)
- 9 Rct.tw. (31284)
- 10 random allocation.tw. (1931)
- 11 randomly allocated.tw. (31999)
- 12 allocated randomly.tw. (2439)
- 13 (allocated adj2 random).tw. (960)
- 14 Single blind\$.tw. (22514)
- 15 Double blind\$.tw. (200441)
- 16 ((treble or triple) adj blind\$).tw. (954)
- 17 placebo\$.tw. (290122)
- 18 prospective study/ (504017)
- 19 or/1-18 (2037125)
- 20 case study/ (68702)
- 21 case report.tw. (400876)
- 22 abstract report/ or letter/ (1086984)

- 23 or/20-22 (1547292)
- 24 19 not 23 (1986570)
- 25 sphincter of oddi.mp. (3272)
- 26 endoscopic sphincterotomy.mp. (5835)
- 27 exp surgical procedures, operative/ (4859006)
- 28 (surg* or surgical* or operat*).ti,ab. (3421933)
- 29 or/26-28 (6152758)
- 30 and/24-25,29 (240)

CENTRAL

- 1. sphincter of oddi
- 2. endoscopic sphincterotomy
- 3. sphincterotomy
- 4. surg* or surgical* or operative:kw
- 5. MeSH Term:[Surgical Procedures, Operative] explode all trees
- 6. #2 or #3 or #4 or #5
- 7. #1 and #6

Superior Labral Anterior-Posterior (SLAP) Lesions

Medline

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. randomised.ab.
5. placebo.tw.
6. clinical trials as topic.sh.
7. randomly.ab.
8. trial.ti.
9. (crossover or cross-over or cross over).tw.
10. or/1-9
11. exp animals/ not humans.sh.
12. 10 NOT 11
13. (SLAP or superior labral anterior-posterior).mp.
14. surgical procedures, operative/
15. (surg* or surgical* or operat*).ti,ab.
16. (biceps tenodesis OR biceps tenotomy OR repair OR suture OR debridement).ti,ab.
17. OR/13-16
18. 12 and 13 and 17

EMBASE

1. Clinical Trial/
2. Randomized Controlled Trial/
3. exp randomization/
4. Single Blind Procedure/
5. Double Blind Procedure/
6. Crossover Procedure/
7. Placebo/
8. Randomi?ed controlled trial\$.tw.
9. Rct.tw.
10. random allocation.tw.
11. randomly allocated.tw.
12. allocated randomly.tw.
13. (allocated adj2 random).tw.
14. Single blind\$.tw.
15. Double blind\$.tw.
16. ((treble or triple) adj blind\$).tw.
17. placebo\$.tw.
18. prospective study/
19. or/1-18
20. case study/
21. case report.tw.
22. abstract report/ or letter/

23. or/20-22
24. 19 NOT 23
25. (SLAP or superior labral anterior-posterior or superior labral anterior posterior).mp.
26. surgical procedures, operative/
27. (surg* or surgical* or operat*).ti,ab
28. (biceps tenodesis OR biceps tenotomy OR repair OR suture OR debridement).ti,ab.
29. OR/26-28
30. AND/24, 25,29

CENTRAL

1. SLAP
2. superior labral anterior-posterior or superior labral anterior posterior
3. #1 OR #2

Sleep Apnea

Medline

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. randomised.ab.
5. placebo.tw.
6. clinical trials as topic.sh.
7. randomly.ab.
8. trial.ti.
9. (crossover or cross-over or cross over).tw.
10. or/1-9
11. exp animals/ not humans.sh.
12. 10 NOT 11
13. palate/
14. palatal OR palate
15. 13 OR 14
16. implant*
17. 15 AND 16
18. septumplasty/
19. nasal adj3 surgery.ti,ab.
20. resection adj4 septum.tw.
21. OR/17-20
22. obstructive sleep apnea/
23. sleep apnea.ti,ab.
24. sleeping disorder.ti,ab
25. OR/22-24
26. AND/12,21,25

EMBASE

1. Clinical Trial/
2. Randomized Controlled Trial/
3. exp randomization/
4. Single Blind Procedure/
5. Double Blind Procedure/
6. Crossover Procedure/
7. Placebo/
8. Randomi?ed controlled trial\$.tw.
9. Rct.tw.
10. random allocation.tw.
11. randomly allocated.tw.
12. allocated randomly.tw.
13. (allocated adj2 random).tw.
14. Single blind\$.tw.

15. Double blind\$.tw.
16. ((treble or triple) adj blind\$).tw.
17. placebo\$.tw.
18. prospective study/
19. or/1-18
20. case study/
21. case report.tw.
22. abstract report/ or letter/
23. or/20-22
24. 19 NOT 23
25. palate/
26. palatal OR palate.mp.
27. 25 OR 26
28. implant*.mp.
29. 27 and 28
30. exp septumplasty/
31. nasal surgery/
32. nasal adj3 surgery.ti,ab.
33. resection adj4 septum.tw.
34. OR/29-33
35. exp obstructive sleep apnea/
36. sleep apnea.ti,ab.
37. sleeping disorder*.ti,ab
38. OR/35-37
39. AND/24,34,38

CENTRAL

1. MeSH descriptor: [Palate] explode all trees
2. palatal or palate:kw
3. implant*
4. #1 or #2
5. #3 and #4
6. MeSH descriptor: [Nasal Surgical Procedures] explode all trees
7. nasal adj3 surgery:ti,ab
8. septum adj4 resection
9. #5 OR #6 OR #7 OR #8
10. MeSH descriptor: [Sleep Apnea, Obstructive] explode all trees
11. sleep apnea:ti,ab
12. sleep disorder*:kw
13. #10 or #11 or #12
14. #9 and #13

Spinal Cord Injury

Medline

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. randomised.ab.
5. placebo.tw.
6. clinical trials as topic.sh.
7. randomly.ab.
8. trial.ti.
9. (crossover or cross-over or cross over).tw.
10. or/1-9
11. exp animals/ not humans.sh.
12. 10 NOT 11
13. exp Spinal Cord Injuries/
14. exp Central Cord Syndrome/
15. (myelopathy adj3 (traumatic or post-traumatic)).ab,ti.
16. ((spine or spinal or vertebrae) adj3 (fracture* or wound* or trauma* or injur* or damag*)).ab,ti.
17. (spinal cord adj3 (contusion or laceration or transaction or trauma or ischemia)).ab,ti.
18. central cord injury syndrome.ab,ti.
19. central spinal cord syndrome.ab,ti.
20. exp Paraplegia/
21. exp Quadriplegia/
22. OR/13-21
23. cell adj3 transplantation
24. Lamina Propria Transplantation
25. transplant*
26. regenerative surgery
27. AND/12,22,26

EMBASE

1. Clinical Trial/
2. Randomized Controlled Trial/
3. exp randomization/
4. Single Blind Procedure/
5. Double Blind Procedure/
6. Crossover Procedure/
7. Placebo/
8. Randomi?ed controlled trial\$.tw.
9. Rct.tw.
10. random allocation.tw.
11. randomly allocated.tw.
12. allocated randomly.tw.

13. (allocated adj2 random).tw.
14. Single blind\$.tw.
15. Double blind\$.tw.
16. ((treble or triple) adj blind\$).tw.
17. placebo\$.tw.
18. prospective study/
19. or/1-18
20. case study/
21. case report.tw.
22. abstract report/ or letter/
23. or/20-22
24. 19 NOT 23
25. exp Spinal Cord Injuries/
26. exp Central Cord Syndrome/
27. (myelopathy adj3 (traumatic or post-traumatic)).ab,ti.
28. ((spine or spinal or vertebrae) adj3 (fracture\$ or wound\$ or trauma\$ or injur\$ or damage\$)).ab,ti.
29. (spinal cord adj3 (contusion or laceration or transaction or trauma or ischemia)).ab,ti.
30. central cord injury syndrome.ab,ti.
31. central spinal cord syndrome.ab,ti.
32. exp Paraplegia/
33. exp Quadriplegia/
34. OR/25-33
35. cell adj3 transplantation
36. Lamina Propria/
37. transplant\$
38. regenerative surgery
39. OR/35-38
40. AND/24,34,39

CENTRAL

1. MeSH descriptor: [Spinal Cord Injuries] explode all trees
2. MeSH descriptor: [Central Cord Syndrome] explode all trees
3. myelopathy near3 (traumatic or post-traumatic)
4. (spine or spinal or vertebrae) near3 (fracture* or wound* or trauma* or injur* or damag*)
5. (spinal cord) near3 (contusion or laceration or transaction or trauma or ischemia)
6. central cord injury syndrome
7. central spinal cord syndrome
8. paraplegi* or quadriplegi* or tetraplegi*
9. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
10. transplant*:kw
11. cell near3 transplantation
12. regenerative surgery
13. MeSH descriptor: [Mucous Membrane] explode all trees
14. lamina propria transplant*:kw
15. #10 or #11 or #12 #13 or #14

16. #9 and #15 (in trials)

Migraine

MEDLINE

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. randomised.ab.
5. placebo.tw.
6. clinical trials as topic.sh.
7. randomly.ab.
8. trial.ti.
9. (crossover or cross-over or cross over).tw.
10. or/1-9
11. exp animals/ not humans.sh.
12. 10 NOT 11
13. Headache/ OR exp Headache Disorders/
14. exp Migraine Disorders/
15. (headach* OR migrain* OR cephalgi* OR cephalalgi*).ti,ab.
16. OR/13-15
17. surgical procedure, operative/
18. (surger* OR surgical* or operat*).tw.
19. ((nerve decompr*) OR (surgical decompr*) OR (surgical treat*)).tw.
20. OR/17-19
21. AND/12,16,20

EMBASE

1. Clinical Trial/
2. Randomized Controlled Trial/
3. exp randomization/
4. Single Blind Procedure/
5. Double Blind Procedure/
6. Crossover Procedure/
7. Placebo/
8. Randomi?ed controlled trial\$.tw.
9. Rct.tw.
10. random allocation.tw.
11. randomly allocated.tw.
12. allocated randomly.tw.
13. (allocated adj2 random).tw.
14. Single blind\$.tw.
15. Double blind\$.tw.
16. ((treble or triple) adj blind\$).tw.
17. placebo\$.tw.

18. prospective study/
19. or/1-18
20. case study/
21. case report.tw.
22. abstract report/ or letter/
23. or/20-22
24. 19 NOT 23
25. surgical procedure/
26. (surger\$ OR surgical\$ or operat\$).tw.
27. OR/25-27
28. Headache/ OR exp Headache and facial pain/
29. exp Migraine/
30. (headach* OR migrain* OR cephalgi* OR cephalalgi*).ti
31. OR/29-31
32. AND/24,27,31

CENTRAL

MeSH descriptor Headache/ OR MeSH descriptor Headache Disorders explode all trees

MeSH descriptor Migraine Disorders explode all trees

(headach* OR migrain* OR cephalgi* OR cephalalgi*):ti,ab,kw.

#1 OR #2 OR #3

surgical procedures, operative/

(surg* OR surgical* or operat*):kw,ab,ti

Tardive dystonia

MEDLINE

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. randomised.ab.
5. placebo.tw.
6. clinical trials as topic.sh.
7. randomly.ab.
8. trial.ti.
9. (crossover or cross-over or cross over).tw.
10. or/1-9
11. exp animals/ not humans.sh.
12. 10 NOT 11
13. dystonia/
14. tardive dystonia.ti,ab.
15. OR/13-14
16. surgical procedures, operative/
17. (surg* or surgical* or operat*).ti,ab
18. deep brain stimulation.ti,ab
19. OR/16-18
20. AND/12,15,19

EMBASE

Clinical Trial/
Randomized Controlled Trial/
exp randomization/
Single Blind Procedure/
Double Blind Procedure/
Crossover Procedure/
Placebo/
Randomi?ed controlled trial\$.tw.
Rct.tw.
random allocation.tw.
randomly allocated.tw.
allocated randomly.tw.
(allocated adj2 random).tw.
Single blind\$.tw.
Double blind\$.tw.
((treble or triple) adj blind\$).tw.
placebo\$.tw.
prospective study/

or/1-18
case study/
case report.tw.
abstract report/ or letter/
or/20-22
19 NOT 23
Exp dystonia/
tardive dystonia.ti,ab.
OR/25-26
surgical procedures, operative/
(surg* or surgical* or operat*).ti,ab
Deep brain stimulation.ti,ab.
or/28-30
and/24,27,31

CENTRAL

1. dystonia:kw
2. (tardive dystonia):kw
3. (tarvide dyskinesia):kw
4. #1 OR #2 OR #3
5. MeSH Term [surgical procedures, operative] explode all trees
6. (surg* or surgical* or operat*).ti,ab
7. (deep brain stimulation):kw
8. #5 or #6 or #7
9. #4 and #8
10. limit to trials

Tennis Elbow

Medline

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. randomised.ab.
5. placebo.tw.
6. clinical trials as topic.sh.
7. randomly.ab.
8. trial.ti.
9. (crossover or cross-over or cross over).tw.
10. or/1-9
11. exp animals/ not humans.sh.
12. 10 NOT 11
13. exp Tennis Elbow/
14. exp Tendinopathy/
15. exp Tendon Injuries/
16. exp Elbow Joint/
17. exp Pain/
18. 16 and 17
19. tennis elbow.tw.
20. (Tendinitis or Tendinosis or Tendonitis).tw.
21. (pain\$ and lateral elbow).tw.
22. epicondylitis.tw.
23. common extensor origin.tw.
24. epicondylalgia.tw.
25. or/13-15,18-24
26. exp Surgery/
27. (surgery\$ or surgeries or surgical or operat\$).tw.
28. (tenotomy or tendon release or ECRB release or extensor carpi radialis brevis release).ti,ab.
29. or/26-28
30. AND/12,25,29

EMBASE

1. Clinical Trial/
2. Randomized Controlled Trial/
3. exp randomization/
4. Single Blind Procedure/
5. Double Blind Procedure/
6. Crossover Procedure/
7. Placebo/
8. Randomi?ed controlled trial\$.tw.
9. Rct.tw.
10. random allocation.tw.
11. randomly allocated.tw.

12. allocated randomly.tw.
13. (allocated adj2 random).tw.
14. Single blind\$.tw.
15. Double blind\$.tw.
16. ((treble or triple) adj blind\$).tw.
17. placebo\$.tw.
18. prospective study/
19. or/1-18
20. case study/
21. case report.tw.
22. abstract report/ or letter/
23. or/20-22
24. 19 NOT 23
25. exp Tennis Elbow/
26. exp Tendinopathy/
27. exp Tendon Injuries/
28. exp Elbow Joint/
29. exp Pain/
30. 28 and 29
31. tennis elbow.tw.
32. (Tendinitis or Tendinosis or Tendonitis).tw.
33. (pain\$ and lateral elbow).tw.
34. epicondylitis.tw.
35. common extensor origin.tw.
36. epicondylalgia.tw.
37. or/25-27,30-36
38. exp Surgery/
39. (surgery\$ or surgeries or surgical or operat\$).ti,ab.
40. (tenotomy or tendon release or ECRB release or extensor carpi radialis brevis release).ti,ab.
41. or/26-28
42. AND/12,25,29

CENTRAL

1. MeSH descriptor: [Tennis Elbow] explode all trees
2. MeSH descriptor: [Elbow Tendinopathy] explode all trees
3. MeSH descriptor: [Tendon Injuries] explode all trees
4. MeSH descriptor: [Tendon Injuries] explode all trees
5. MeSH descriptor: [Pain] explode all trees
6. #4 and #5
7. tennis elbow:ti,ab
8. (Tendinitis or Tendinosis or Tendonitis):ti,ab
9. (pain* and "lateral elbow"):ti,ab
10. epicondylitis:ti,ab
11. "common extensor origin":ti,ab
12. epicondylalgia:ti,ab
13. (#1 OR #2 OR #3 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12)
14. MeSH descriptor: [Surgical Procedures, Operative] explode all trees

15. (surgery* or surgeries or surgical or operat*):ti,ab
16. (tenotomy or tendon release or ECRB release or extensor carpi radialis brevis release):ti,ab
17. #14 or #15 or #16
18. #13 and #17

Vertebroplasty

Medline

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. randomised.ab.
5. placebo.tw.
6. clinical trials as topic.sh.
7. randomly.ab.
8. trial.ti.
9. (crossover or cross-over or cross over).tw.
10. or/1-9
11. exp animals/ not humans.sh.
12. 10 NOT 11
13. exp Spine/
14. (spine or spinal or vertebra\$).tw.
15. exp Fractures, Bone/
16. fractur\$.ti.
17. 13 or 14
18. 16 or 16
19. 17 and 18
20. exp Spinal Fractures/
21. 19 or 20
22. exp Bone Cements/
23. exp Methylmethacrylates/
24. methacrylate\$.tw.
25. bone cement\$.tw.
26. exp Fracture Fixation, Internal/
27. exp Vertebroplasty/
28. vertebroplast\$.tw.
29. cementoplast\$.tw.
30. sacroplast\$.tw. (114)
31. or/22-30
32. and/12,21,31
- 2017-current

EMBASE

1. Clinical Trial/
2. Randomized Controlled Trial/
3. exp randomization/
4. Single Blind Procedure/
5. Double Blind Procedure/
6. Crossover Procedure/
7. Placebo/

8. Randomised controlled trial\$.tw.
9. Rct.tw.
10. random allocation.tw.
11. randomly allocated.tw.
12. allocated randomly.tw.
13. (allocated adj2 random).tw.
14. Single blind\$.tw.
15. Double blind\$.tw.
16. ((treble or triple) adj blind\$).tw.
17. placebo\$.tw.
18. prospective study/
19. or/1-18
20. case study/
21. case report.tw.
22. abstract report/ or letter/
23. or/20-22
24. 19 NOT 23
33. exp Spine/
34. (spine or spinal or vertebra\$).tw.
35. exp Fractures, Bone/
36. fractur\$.ti.
37. 33 or 34
38. 35 or 36
39. 37 and 38
40. exp Spinal Fractures/
41. 39 or 40
42. exp Bone Cements/
43. exp Methylmethacrylates/
44. methacrylate\$.tw.
45. bone cement\$.tw.
46. exp Fracture Fixation, Internal/
47. exp Vertebroplasty/
48. vertebroplast\$.tw.
49. cementoplast\$.tw.
50. sacroplast\$.tw. (114)
51. or/42-50
52. and/12,41,51
- 2017-current

CENTRAL

- 1 exp Spine/ (4032)
- 2 (spine or spinal or vertebra\$).tw. (20306)
- 3 exp Fractures, Bone/ (3949)
- 4 fractur\$.ti. (6791)
- 5 1 or 2 (21641)
- 6 3 or 4 (8007)

7 5 and 6 (1504)
8 exp Spinal Fractures/ (561)
9 7 or 8 (1528)
10 exp Bone Cements/ (769)
11 exp Methylmethacrylates/ (389)
12 methacrylate\$.tw. (251)
13 bone cement\$.tw. (201)
14 exp Fracture Fixation, Internal/ (1077)
15 exp Vertebroplasty/ (112)
16 vertebroplast\$.tw. (202)
17 cementoplast\$.tw. (10)
18 sacroplast\$.tw. (2)
19 or/10-18 (2421)
20 9 and 19 (244)

Natarajan P, et al. *BMJ Open* 2024; 14:e080258. doi: 10.1136/bmjopen-2023-080258

Natarajan P, et al. *BMJ Open* 2024; 14:e080258. doi: 10.1136/bmjopen-2023-080258

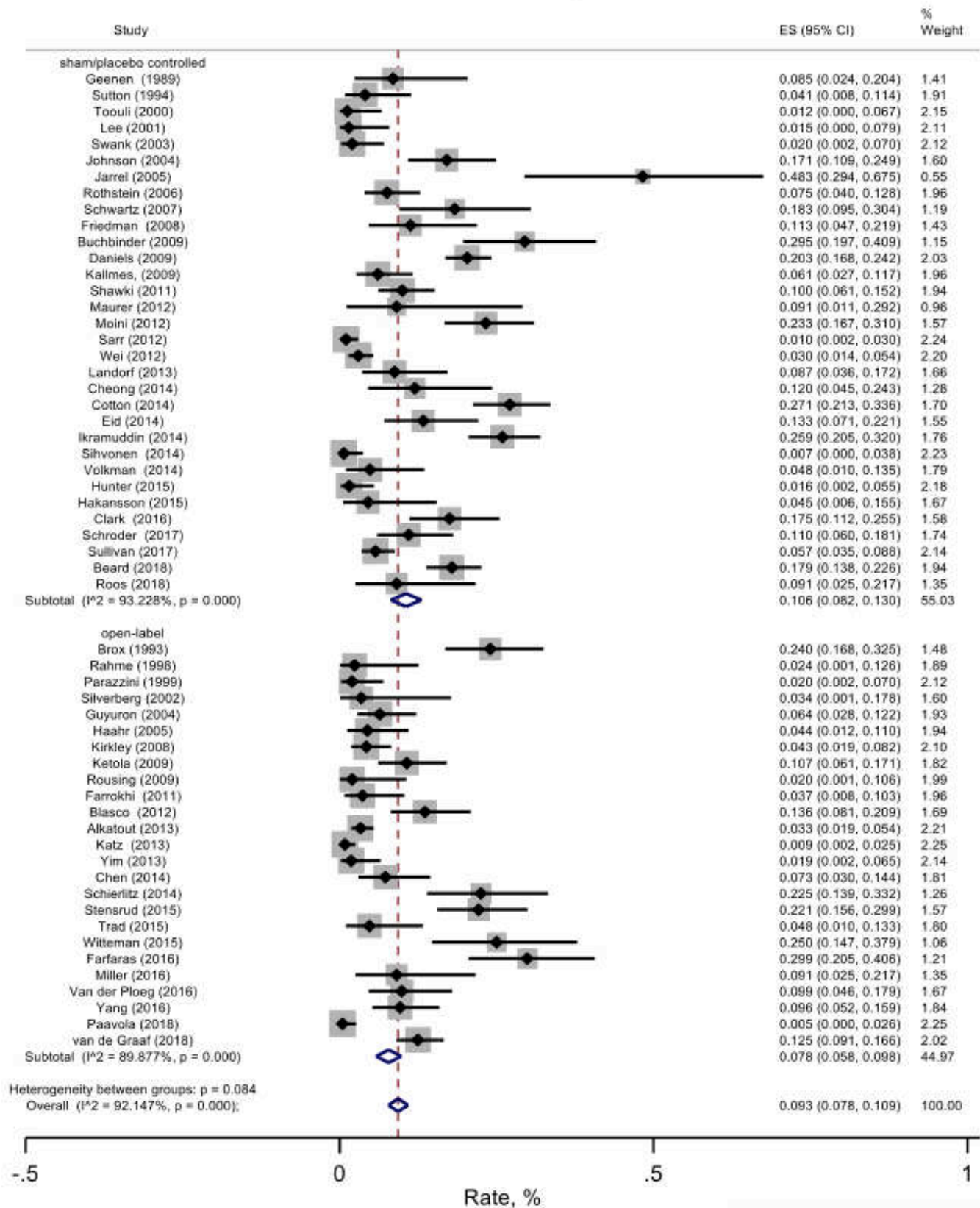
Appendix 2. Meta-regression for confounders including female proportion of study participants, number enrolled and number of follow-up points

	Attrition rate effect size	Dropout rate effect size	Loss to follow-up effect size
Placebo Control Trials*	-0.17 (-0.66 to 0.32)	-0.24 (-0.86 to 0.37)	0.17 (-0.59 to 0.93)
Longest follow-up	0.0002 (-0.0004 to 0.0007)	-0.0003 (-0.0010 to 0.0004)	0.0002 (-0.0008 to 0.0011)
Female rate	-0.69 (-1.61 to 0.24)	-0.12 (-1.24 to 1.00)	0.44 (-0.94 to 1.82)
Number enrolled	-0.0001 (-0.0025 to 0.0024)	0.001 (-0.002 to 0.004)	-0.0001 (-0.0037 to 0.0036)
Number of follow-up points	0.009 (-0.075 to 0.094)	0.058 (-0.041 to 0.157)	0.057 (-0.074 to 0.187)
Note: *non-operative control trials used as a reference category			

Appendix 3: Pooled (random effects) recruitment and attrition rates for studies with attrition > 0% and recruitment < 100%.

	Group	Rate (%)	95% Confidence Interval		P
			Lower (%)	Upper (%)	
Recruitment	Placebo control (n=36)	68.7	59.3	78.1	0.562
	Non-operative control (n=21)	74.1	58.6	89.5	
Attrition (Overall)	Placebo control (n= 54)	21.2	17.2	25.2	0.811
	Non-operative control (n=34)	23.7	18.8	28.6	
Cross-over	Placebo control (n= 54)	8.8	6.3	11.4	0.174
	Non-operative control (n=34)	11.8	8.4	15.2	
Drop-out	Placebo control (n= 54)				
	Non-operative control (n=34)				
Follow-up	Placebo control (n= 54)	10.6	8.2	13.0	0.084
	Non-operative control (n=34)	7.8	5.8	9.8	

overall follow-up rate



overall cross-over rate

