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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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Keywords

Randomised controlled trials, attrition, recruitment, surgery, placebo.

Key Points

Question

What are the differences in recruitment and attrition rates between placebo control randomised trials of surgery and trials of the same surgical interventions and conditions that used non-operative (non-placebo) controls.

Findings

The unadjusted pooled recruitment and attrition rates were similar between placebo and non-operative control trials. 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 (IRR 1.8 [95% CI 1.1-3.0] p=0.032).

Meaning

Placebo control trials of surgery have similar recruitment issues but higher attrition compared with non-operative (non-placebo) control trials.

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 CENTRAL from their inception date to 21st 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. 25730 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, drop out 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 (IRR 1.8 [95% CI 1.1-3.0] p=0.032). The incorporation of one additional follow-up time point (regardless of follow-up duration) was associated with reduced attrition in placebo control surgical trials (IRR [95% CI] 0.64 [0.52-0.79], 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 given follow-up duration to mitigate losses to follow and dropout.

Strengths and limitations of this study

- The difficulties of participant recruitment and high attrition experienced by placebo control trials evaluating efficacy of any surgical intervention has not been empirically explored previously.
- This is the first study to quantify the difficulties of conducting placebo controlled trials of surgery, and offer strategies to mitigate these issues in future trials.
- To minimise bias, data was extracted independently by pairs of investigators and arbitrated by a third investigator if necessary.
- Findings 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.

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 drop-out 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). 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, e.g. 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, that lacks the key surgical element(s) [11].

This study involves the search strategy and eligibility criteria from a related publication by Karjalainen et al (2022) [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 (2022) [12].

Our search included eligible placebo control trials from a published systematic review by Wartolowska et al (2014) [1] as well as an extension of its search until 21st 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 to March 13 to March 15, 2019. Where no relevant

Cochrane review was identified, a search algorithm was devised and applied to the Cochrane Central Register of Controlled Trials (CENTRAL), 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

The extracted data were tested for heterogeneity and random effect meta-analysis was used to summarise attrition rates (overall, dropout, loss to follow up, and cross over) in placebo vs. non-operative control trials, stratified by trial groups. Due to the nature of the data (with varying follow-up duration), a Generalized Linear Latent and Mixed (GLLAM) Model was employed for random effect Poisson regression to examine Incidents Rate Ratio (IRR) and Incident Rate Differences, while controlling for potential covariates: participant gender, intervention type (placebo or non-operative control), follow-up duration and number of follow-up timepoints. Descriptive statistics were used to summarise key aspect of the selected studies. The 'metaprop' command in Stata 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 studies heterogeneity all analyses were based on the random effect model.

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 (2022) [12].

Results

A total of 62 placebo control trials and 38 trials with non-operative controls (100 trials overall) identified. 99 studies were included in the quantitative analysis (1 placebo control trial excluded due to unavailable full text at search date [13]). Detailed data on these included studies has been included in Appendix 1. 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 (Appendix 2).

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% to 100%.

The random effect pooled rate was similar between placebo and non-operative control trials (rate [95% CI]: 76.9% [95% CI 71.1%-82.7%] vs 77.6% [95% CI 66.7%-88.4%], respectively, p=0.915). This included 10/36 (27.8%) placebo and 3/21 (14.3%) non-operative control studies with 100% recruitment rates. When these studies were excluded, the adjusted recruitment rates decreased to 68.7% [59.3%-78.1%] in the placebo and 74.1% [58.6%-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 to 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%) sham/placebo arm studies and 2/36 (5.6%) of open-label 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% - 25.2%]) and non-operative (23.7% [18.8% - 28.6%]) controlled studies (p=0.811). This was also true for discrete components of attrition including loss to follow-up, drop-out and cross-over rates (Appendix 3).

Poisson Analysis

The median (IQR) number of follow up timepoints (4 [3-5.5] and 3.5 [2-6], p=0.748) were similar between non-operative and placebo control trials respectively. Longest follow-up timepoint was also similar (365 [319.5-730] and 365 [183-456] days, p=0.143) However, the follow-up time to the primary endpoint was significantly longer in non-operative control trials (365 [183-730] vs 274 [91-365] days, p=0.06).

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 to non-operative control trials (IRR 1.8 [95% CI 1.1-3.0], 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 1.04-6.3], p=0.042) and higher dropout (IRR 3.5 [95% CI 1.1-11.3], p=0.037) as seen in Figure 1.

The incorporation of just one additional follow-up timepoint point (regardless of length of follow up i.e. increased frequency of visits) is associated with a reduction in attrition (IRR [95% CI] of 0.64 [0.52-0.79], p<0.001) in placebo control surgical trials, largely driven by fewer losses to follow-up (IRR [95% CI] of 0.68 [0.52-0.89], 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 (Appendix 4). Publication bias was greater in placebo control trials compared to trials of non-operative trials (Appendix 5, 6).

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 to non-operative control trials. This was primarily driven by participant follow-up losses and drop-outs.

Participant Recruitment

Surgical randomised controlled trials can face recruitment rates as low as 8% [14], due to patients frequently failing to meet eligibility criteria for a small and specific target populations [3,15]. Addition of a placebo component further exacerbates this problem by undermining willingness to participate [4,16,17]. Participant surveys suggest this unwillingness stems from common perceptions that invasive surgical placebos are associated with greater risks (e.g., infection) [17,18]. Previous trials such as Hare *et al.* [4], which reported 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 two-fold higher attrition rate (when considering cross-overs, drop-outs and follow-up losses) compared to 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 [11,19,20]. Metanalysis by Hróbjartsson et al., found nonblinded control groups suffer from 79% higher risk of drop-outs and 55% higher risk of co-intervention use when compared to blinded control groups [21]. 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 to other-control trials. Included trials in the present meta-analysis were published prior to development of the 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 drop-out. With the inherent nature of surgical interventions being a "one-time" irreversible change [22], loss to follow-up and participant withdrawals may be

higher when there is a long follow-up period with no concomitant treatments [23]. This is typical of placebo surgery trials, whilst 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 to longer-term study participation [24-28]. 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 [27,29].

Publication Bias

Trial discontinuation and non-publication is common and occurs more frequently in surgical than medical trials [30-34]. Publication bias, or the selective submission or acceptance of a study into literature as such [35,36], is a likely limitation of the present findings. The majority of included studies had a small attrition rates overall, indicating non-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, pre-planned, 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 non-operative trials.

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 upon 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 to 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.

Figure Legends

Figure 1. Poisson Regression of Median Attrition Rates (Drop-out, Loss to Follow-up, Death, Overall Attrition) between placebo and non-operative controls.

Appendix Legends

Appendix 1. Detailed data on included studies.

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

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

Appendix 4. Funnel Plot for All Included Trials. Effect sizes: 0 = 50%, +2 = ~88% and -2 = ~12 % attrition rate.

Appendix 5. Funnel Plot for Placebo Control Surgery Trials. Effect sizes: 0 = 50%, +2 = ~88% and -2 = ~12 % attrition rate.

Appendix 6. Funnel Plot for Non-Operative Control Surgery Trials. Effect sizes: 0 = 50%, +2 = ~88% and -2 = ~12 % attrition rate.

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Table 1: Participant and Follow-up Characteristics

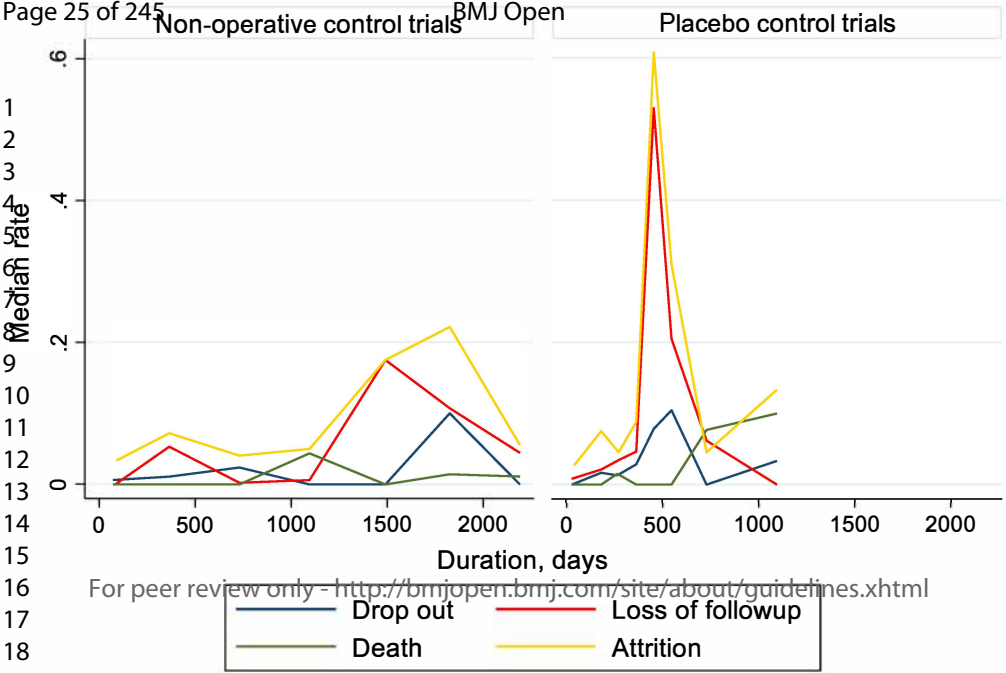
	Non-operative control	Placebo control	p-value
n	38	61	
Age of study cohorts (mean ± SD, n)			
Surgical intervention group	54.8 ± 12.6, (n=34)	50.4 ± 13.4, (n=55)	0.125
Control group	55.1 ± 13.0, (n=34)	50.5 ± 13.3, (n=55)	0.114
Other group [1]	48 ± 8, (n=3)	47.8 ± 5.8, (n=4)	0.807
Gender of study cohorts (mean + SD)			
% 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

*number of follow-up points was not available for 5 studies (1 non-operative control and 4 placebo);
[1]Other group only applicable to trials incorporating 3 treatment arms;
SD = standard deviation, n = number of studies.

Table 2: Association between attrition rates and type of control group (placebo or non-operative) in surgical trials. Incident rate ratios (IRR) expressed for placebo control trials as a ratio of incident rates for non-operative control trials.

	Incident Rate Ratio (IRR)	95% Confidence Interval		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
Drop out	3.5	1.1	11.3	0.037

* Poisson regression analysis using a Generalized Linear Latent and Mixed (GLLAM) Model to examine Incidents Rate Ratio (IRR) and Incident Rate Differences, while controlling for participant gender, intervention type (placebo or non-operative control), follow-up duration and number of follow-up timepoints.



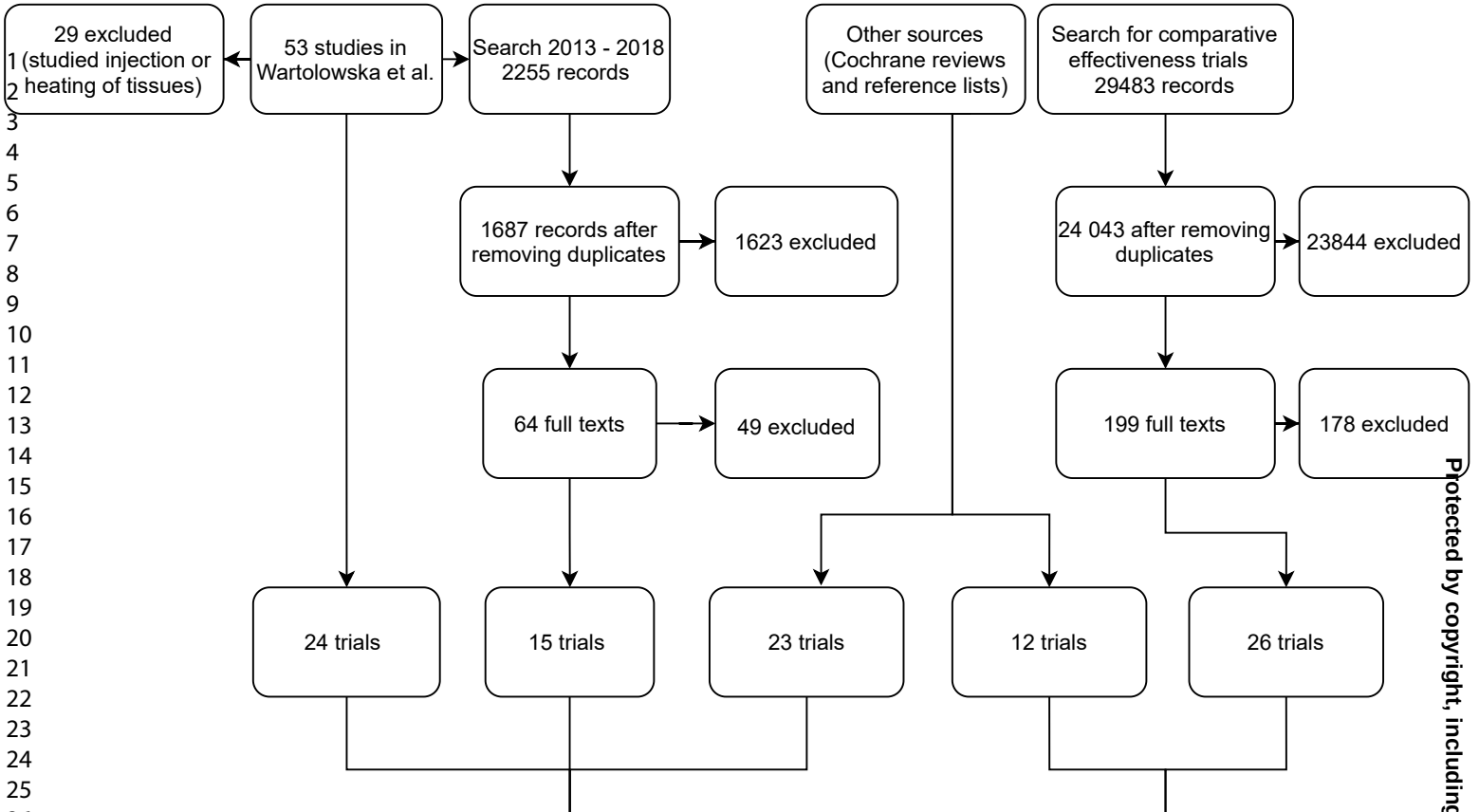


Figure 1. PRISMA flowchart of study selection

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Timepoint (primary outcome), days	365 (183-730)	274 (91-365)	**0.006**
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*number of follow-up points was not available for 5 studies (1 non-operative control and 4 placebo);
[1]Other group only applicable to trials incorporating 3 treatment arms;
SD = standard deviation, n = number of studies.

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* Poisson regression analysis using a Generalized Linear Latent and Mixed (GLLAM) Model to examine Incidents Rate Ratio (IRR) and Incident Rate Differences, while controlling for participant gender, intervention type (placebo or non-operative control), follow-up duration and number of follow-up timepoints.

id	author	year	control	lot/lead_phas	prim_tps
1	Abbot	2004	1	0	183
2	Beard	2018	1	0	183
3	Buchbinder	2009	1	0	91
4	Cheong	2014	1	0	183
5	Clark	2016	1	0	14
6	Cobb	1959	1	0	274
7	Cotton	2014	1	1	365
8	Daniels	2009	1	0	365
9	Davys	2005	1	0	1
10	Dimond	1960	1	0	.
11	Eid	2014	1	0	365
12	Firanescu	2018	1	0	365
13	Freed	2001	1	0	365
14	Friedman	2008	1	0	91
15	Geenen	1989	1	0	1460
16	Gillespie	2011	1	0	91
17	Gross	2011	1	0	365
18	Gruber	2018	1	0	91
19	Guyuron	2009	1	0	365
20	Hansen	2016	1	0	91
21	Hunter	2015	1	0	183
22	Hakansson	2015	1	0	183
23	Ikramuddin	2014	1	0	365
24	Jarrel	2005	1	1	365
25	Johnson	2004	1	0	365
26	Kalapala	2018	1	0	91
27	Kallmes,	2009	1	0	30
28	Koutzourelakis	2008	1	0	106
29	Kroslak	2018	1	0	183
30	Kupsch	2006	1	0	91
31	Landorf	2013	1	0	42
32	Lee	2001	1	0	91
33	LeWitt	2011	1	1	183
34	Lichten	1987	1	0	365
35	Marks	2010	1	1	365
36	Maurer	2012	1	0	91
37	Moini	2012	1	0	274
38	MONTGOMERY	2006	1	0	365
39	Moseley	1996	1	1	183
40	**Moseley**	**2002**	**1**	**1**	**730**
41	Moseley	2002	1	1	730
42	Olanow	2015	1	1	456
43	Olanow	2003	1	0	730
45	Roehrborn	2013	1	0	91
46	Roos	2018	1	0	730

47	Rothstein	2006	1	0	91
48	Sarr	2012	1	0	365
49	Schroder	2017	1	0	730
50	Schwartz	2007	1	0	365
51	Shawki	2011	1	0	365
52	**Sihvonen**	**2014**	**1**	**0**	**730**
53	Steward	2008	1	0	91
54	Sullivan	2017	1	1	365
55	Sutton	1994	1	0	183
56	**Swank**	**2003**	**1**	**0**	**365**
57	Thompson	2013	1	1	183
58	Thomsen	1981	1	0	365
59	Toouli	2000	1	0	730
61	Volkman	2014	1	0	91
62	Wang	2016	1	0	1095
63	Wei	2012	1	0	91
64	Alkatout	2013	0	0	730
67	Blasco	2012	0	0	365
68	Brox	1993	0	1	183
69	Chen	2014	0	0	365
70	Chen	2014	0	0	183
71	Farfaras	2016	0	0	30
72	Farrokhi	2011	0	0	1095
73	Fuentes	2011	0	0	730
74	Gad	2012	0	0	548
75	Gauffin	2014	0	0	365
76	Guyuron	2004	0	1	365
77	Haahr	2005	0	0	365
78	Herrlin	2006	0	0	183
79	Katz	2013	0	1	183
80	Ketola	2009	0	0	730
81	Kirkley	2008	0	0	730
82	Klazen	2010	0	0	365
83	Marcoux	1997	0	0	274
84	Merchan	1993	0	0	1095
85	Miller	2016	0	0	365
86	Osteras	2012	0	1	91
87	Paavola	2018	0	0	730
88	Parazzini	1999	0	0	365
89	Peters	1992	0	0	365
90	Peters	1997	0	0	1460
90	**Peters**	**1997**	**0**	**0**	**48**
91	Rahme	1998	0	0	183
92	Rousing	2009	0	0	91
93	Schierlitz	2014	0	0	183
94	Siddle	2012	0	0	548

95	Spencer	1992	0	0	365
96	Stensrud	2015	0	0	730
97	Trad	2015	0	0	183
99	van de Graaf	2018	0	0	730
100	Van der Ploeg	2016	0	0	365
101	Witteman	2015	0	1	183
102	Yang	2016	0	0	365
103	Yim	2013	0	1	730
105	Silverberg	2002	0	1	365
106	Silverberg	2008	1	1	274

long_tps	total_tps	n_tps	plan_sample	ndom_sampalysed_sam	n_female
365	183, 365	2	50	52	39	39
365	183, 365	2	300	313	274	158
730	, 91, 183, 365	6	164	78	73	62
365	91, 183, 365	3	100	50	43	50
183	14, 30, 91, 18	5	120	120	112	88
456	274, 456	2	.	17	17	5
365	l, 183, 274, 36	4	214	214	173	197
1825	365, 730, 109	6	420	487	379	487
1	1	1	38	38	37	33
365	.	.	.	18	18	.
365	183, 213, 243	12	150	90	74	83
365	, 30, 91, 183,	6	180	180	176	133
365	122, 243, 365	3	.	40	39	19
91	14, 91	2	60	62	62	29
1460	55, 730, 1095,	5	.	47	47	45
91	91	1	100	51	50	8
1825	61, 91, 183, 2	7	68	76	67	24
183	91, 183	2	48	25	23	21
365	l, 183, 274, 36	4	.	76	75	.
.	.	.	.	52	46	.
183	14, 91, 198	3	120	129	129	66
183	183	1	.	44	44	20
1825	, 152, 183, 21	18	233	239	239	203
365	l, 183, 274, 36	4	100	29	16	29
365	1, 91, 365	3	130	123	123	123
.	.	.	.	13	.	.
91	3, 14, 30, 91	4	250	131	128	99
122	91, 122	.	48	49	47	19
913	42, 84, 183, 9	5	80	26	26	19
183	91, 183	2	40	40	40	13
42	14, 21, 28, 34,	6	80	80	80	50
730	183, 274, 36	8	90	68	.	68
183	30, 91, 183	3	40	45	37	10
365	91, 365	2	.	21	21	21
548	83, 274, 365,	7	51	58	57	15
91	91	1	.	22	20	22
274	274	1	146	146	76	146
365	46, 91, 365	3	.	46	43	31
183	.5, 46, 91, 183	4	10	10	9	0
730	**91, 183, 365, 5**	**7**	**180**	**180**	**165**	**13**
730	91, 183, 365, 5	7	180	180	165	13
730	74, 365, 456,	9	52	51	47	16
730	74, 365, 456,	9	.	34	31	10
91	14, 30, 91	3	.	206	206	0
730	91, 730	2	100	44	42	21

91	91	1	.	159	144	69
365	152, 183, 213	15	222	294	253	165
730	l, 183, 365, 73	4	120	118	118	47
365	0, 91, 183, 36	4	60	60	57	24
365	91, 183, 365	3	.	190	171	190
730	**1,183,365, 73**	**4**	**140**	**146**	**144**	**57**
91	7, 30, 91	3	100	100	100	21
730	91, 183, 9, 27	7	.	332	332	296
183	91, 183	2	.	74	63	74
365	**91,183,365**	**3**	**120**	**100**	**100**	**87**
183	l, 183, 127, 91	6	132	77	.	73
1095	3, 213, 243, 2	13	.	30	30	12
730	183, 365, 548,	5	.	81	79	73
183	91, 183	2	60	62	62	35
1095	3, 365, 730, 1(	4	.	12	12	2
365	91, 183, 365	3	300	337	327	337
730	152, 365, 730	3	.	450	410	450
365	4, 61, 183, 36	4	128	125	95	97
183	91, 183, 913	3	108	125	120	71
365	1, 7, 30, 91,	6	.	96	89	62
183	183	1	.	28	7	2
168	30, 168	2	120	87	55	28
1095	183, 365, 730	6	.	82	82	60
730	183, 365, 730	3	.	60	60	60
548	.	.	.	41	.	.
365	183, 365	2	150	150	150	41
365	l, 183, 274, 36	4	.	125	108	.
2190	, 183, 365, 21	4	100	90	84	58
183	56, 183	2	80	99	90	35
365	91, 183, 366	3	340	351	330	187
144	04, 365, 730, 1	7	140	140	134	88
730	183, 365, 548,	5	186	188	168	112
365	, 30, 91, 183,	6	200	202	163	140
274	2, 152, 183, 24	6	330	348	341	348
1095	365, 730, 1095	3	.	80	73	53
730	33,243,304,36	11	44	44	39	34
91	91	1	20	17	17	4
730	l, 183, 365, 73	4	210	210	186	135
365	365	1	.	101	96	101
365	365	1	.	48	48	48
1460	1460	1	.	72	.	26
48	**12, 24, 36, 48**	**4**	**.**	**72**	**48**	**26**
365	183, 365	2	.	42	39	23
91	91	1	40	50	47	41
1490	5, 730, 1095,	7	62	80	74	80
548	26, 183, 274,	7	64	65	64	48

548	91,183,548	3	.	7	6	3
730	91, 365, 730	3	140	140	140	54
183	14, 91, 183	3	42	63	60	33
730	l, 183, 365, 73	4	320	321	289	161
365	365	1	320	91	89	91
365	30, 91, 183, 3	5	120	60	57	22
365	30, 91, 183, 3(	5	96	135	107	69
730	l, 183, 365, 73	4	108	108	102	81
365	l, 183, 274, 36	4	.	29	23	14
274	0, 91, 183, 27	4	256	230	164	95

age_int1	age_int2	age_int3	n_screened	n_eligible	n_enrolled	recruit_rate
32.1	32.1	.	.	168	52	30.952381
52.9	53.7	53.2	2975	740	313	42.2972973
74.2	78.9	.	468	219	78	35.6164384
31	30	.	.	94	50	53.1914894
80	81	.	302	154	120	77.9220779
64	54	.	.	.	17	.
38	39	.	1584	286	214	74.8251748
30.6	30.5	.	592	487	487	100
60.2	57.5	.	55	51	38	74.5098039
.	.	.	.	.	18	.
51	50	.	763	275	90	32.7272727
74.7	76.9	.	1280	336	180	53.5714286
57.5	57.5	.	.	.	40	.
48.1	39	.	112	80	62	77.5
49	49	.	289	51	47	92.1568627
52.3	51.1	.	.	.	51	.
56.4	55.4	.	157	83	76	91.5662651
62	55.1	.	29	25	25	100
45.1	44.6	.	317	76	76	100
.	.	.	.	.	52	.
52	55	.	696	.	129	.
41	62	.	121	63	44	69.8412698
47	47	.	420	327	239	73.088685
28.9	29.4	.	36	29	29	100
29.5	29	.	200	123	123	100
.	.	.	.	.	.	.
73.4	74.3	.	1813	431	131	30.3944316
39	37.6	.	.	51	49	96.0784314
53	51	.	.	27	27	100
40.5	38.4	.	60	48	40	83.3333333
71.8	73.3	.	157	.	80	.
57.2	56.9	.	.	.	68	.
61.8	60.6	.	66	49	45	91.8367347
.	.	.	39	21	21	100
60.1	57.3	.	.	.	58	.
48.9	53.3	.	.	.	22	.
27.8	27.7	.	160	.	146	.
42	41	.	.	.	46	.
.	.	.	.	.	10	.
51.2	**52**	**53.6**	**.**	**324**	**180**	**55.5555556**
53.6	52	51.2	.	324	180	55.5555556
59.7	58.7	.	.	.	51	.
58.75	58	.	.	.	34	.
67	65	.	430	220	206	93.6363636
47.2	46.4	.	586	68	44	64.7058824

48.1	46.3	.	.	.	159	.
46	46	.	503	.	294	.
42	40	40	445	118	118	100
45	47	47	.	.	60	.
30.25	31.9	.	280	.	190	.
52	**52**	**.**	**.**	**205**	**146**	**71.2195122**
47.2	51.5	.	968	100	100	100
44.2	45.3	.	587	.	332	.
29	29.5	.	.	.	74	.
45.4	**47.8**	**.**	**121**	**103**	**100**	**97.0873786**
47.6	47.6	.	358	129	77	59.6899225
49.9	53.9	.	.	30	30	100
.	.	.	.	.	81	.
57.1	56.6	.	85	77	62	80.5194805
29.25	38.75	.	207	.	12	.
63.4	62.2	.	517	.	337	.
.	.	.	523	499	450	90.1803607
71.33	75.27	.	219	125	125	100
48	48	47	444	155	125	80.6451613
64.63	66.49	.	.	.	96	.
.	.	.	64	28	28	100
52.4	49.9	48.9	95	.	87	.
72	74	.	105	84	82	97.6190476
.	.	.	.	.	60	.
.	.	.	.	.	41	.
54	54	.	179	155	150	96.7741935
43.4	42.9	.	.	.	125	.
44.3	44.5	.	.	.	90	.
56	56	.	180	99	90	90.9090909
59	57.8	.	14,430	1330	351	26.3909774
46.4	47.8	.	.	.	140	.
58.6	60.6	.	277	219	188	85.8447489
75.2	75.4	.	934	434	202	46.5437788
31	30	.	717	348	348	100
57	56	.	.	.	80	.
38.3	38.5	.	50	49	44	89.7959184
52.7	47	.	29	19	17	89.4736842
50.5	50.8	50.4	281	213	210	98.5915493
30.6	30.3	.	.	.	101	.
35.5	35.7	.	.	.	48	.
56	59	.	.	.	72	.
56	**59**	**.**	**.**	**.**	**72**	**.**
42	42	.	.	.	42	.
80	80	.	.	.	50	.
67	66	.	845	146	80	54.7945205
55.6	55.1	.	258	71	65	91.5492958

52	54.7	.	.	.	7	.
50.2	48.9	.	341	226	140	61.9469027
54.8	50.1	.	196	95	63	66.3157895
57.6	57.3	.	.	.	321	.
61	63.7	.	2000	.	91	.
42.4	49.3	.	.	.	60	.
77.1	76.2	.	158	153	135	88.2352941
54.9	57.9	.	162	157	108	68.7898089
71.4	73.5	.	529	313	29	9.26517572
74.5	74	.	394	277	230	83.032491

i1_tp1_dura	i1_tp1_drop	i1_tp1_follow	1_tp1_death	i1_tp2_dura	i1_tp2_drop	1_tp2_follow
365	4	0	0	.	.	.
183	6	10	0	365	0	12
7	0	1	0	30	0	3
0	.	.	.	91	.	.
3	1	2	0	14	2	3
61	0	0	1	.	.	.
274	.	17	.	365	.	14
365	5	51	0	.	.	.
.	.	.	.	.	.	.
.	.	.	.	.	.	.
365	4	10	0	.	.	.
0	1	0	0	1	0	0
243	0	0	1	.	.	.
14	0	0	0	91	0	2
.	.	.	.	.	.	.
.	.	.	.	.	.	.
14	0	0	0	30	0	0
91	1	0	0	183	1	0
91	2	.	.	183	.	.
.	.	.	.	.	.	.
0	6	0	0	198	4	1
183	0	1	0	.	.	.
0	5	0	0	365	1	9
76	1	1	0	167	0	6
1	0	1	0	91	0	2
.	.	.	.	.	.	.
30	.	1	.	91	.	4
.	.	.	.	.	.	.
.	.	.	.	.	.	.
.	.	.	.	.	.	.
42	0	1	0	.	.	.
.	.	.	.	.	.	.
0	6	0	0	.	.	.
.	.	.	.	.	.	.
365	2	0	2	.	.	.
91	0	1	0	.	.	.
274	16	19	0	.	.	.
46	.	.	.	91	.	.
91	1	.	.	.	.	.
14	**.**	**2**	**.**	**46**	**.**	**5**
.	.	.	.	.	.	.
456	1	14	0	.	.	.
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91	6	9	0	.	.	.
365	12	2	0	.	.	.
91	.	1	.	183	.	.
91	0	4	0	365	2	1
365	0	9	0	.	.	.
.	.	.	.	.	.	.
7	0	0	0	30	0	0
365	7	7	0	.	.	.
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12	.	**1**	.	.	.	.
.	.	.	.	.	.	.
1095	1	0	1	.	.	.
.	.	.	.	.	.	.
91	1	1	.	183	.	.
.	.	.	.	.	.	.
91	0	2	0	365	0	1
152	10	3	0	.	.	.
0	7	.	.	14	.	6
91	0	14	0	183	0	4
365	0	4	0	.	.	.
183	.	.	.	.	.	.
30	6	2	1	168	0	2
7	0	0	0	61	0	0
.	.	.	.	.	.	.
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.	.	.	.	.	.	.
0	9	0	0	.	.	.
0	4	0	0	2190	0	1
56	.	.	.	183	.	.
91	12	0	1	365	4	1
0	1	0	0	730	2	0
0	2	0	0	730	1	2
0	2	0	0	1	0	0
0	5	0	0	100	9	0
1095	0	0	5	.	.	.
0	.	.	.	7	.	.
.	.	.	.	.	.	.
0	17	0	0	730	0	0
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365	**0**	**6**	**0**	**730**	**0**	**0**
183	0	0	0	365	0	0
91	0	1	1	.	.	.
183	0	0	2	1490	0	6
42	0	0	0	84	0	0

183	0	.	1	365	.	.
91	.	7	.	365	.	7
183	.	1	.	.	.	.
0	1	0	0	91	1	2
0	2	0	0	365	1	3
183	0	10	0	365	0	5
0	2	0	0	365	0	8
730	3	1	0	.	.	.
0	1	0	0	365	1	1
0	7	0	0	274	4	0

i1_tp2_death	i1_tp3_dura	i1_tp3_drop	1_tp3_follow	1_tp3_death	i1_tp4_dura	i1_tp4_drop
.	.	.	.	.	.	.
0	.	.	.	.	.	.
0	91	0	1	1	183	0
.	183	.	3	.	.	.
0	30	2	1	0	91	1
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0	61	0	0	0	91	0
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.	274	.	.	.	365	.
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0	.	.	.	.	.	.
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0	548	13	27	0	.	.
0	259	0	1	0	350	0
0	365	0	10	0	.	.
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.	**91**	**.**	**4**	**.**	**183**	**.**
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0	183	0	0	0	365	0
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i1_tp4_follow	i1_tp4_death	i1_tp5_dura	i1_tp5_drop	i1_tp5_follow	i1_tp5_death	i1_tp6_dura
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1	1	365	1	1	1	730
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7	**.**	**365**	**.**	**5**	**.**	**548**
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i1_tp6_drop	i1_tp6_follow	i1_tp6_death	i1_tp7_dura	i1_tp7_drop	i1_tp7_follow	i1_tp7_death
0	3	2	.	.	.	.
4	0	4	.	.	.	.
0	0	0	365	4	0	4
.	**10**	.	**730**	.	**9**	.

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3	0	2	365	1	0	2
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i1_tp8_dura	i1_tp8_drop	i1_tp8_follow	i1_tp8_death	i1_tp9_dura	i1_tp9_drop	1_tp9_follow
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i1_tp9_deathi	1_tp10_durai	1_tp10_drop	1_tp10_follov	1_tp10_deathi	2_tp1_dura	i2_tp1_drop
.	.	.	.	.	365	1
.	.	.	.	.	183	2
.	.	.	.	.	7	0
.	.	.	.	.	0	.
.	.	.	.	.	3	0
.	.	.	.	.	243	0
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.	.	.	.	.	91	0
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.	.	.	.	.	0	3
.	.	.	.	.	730	0
.	.	.	.	.	0	2
.	.	.	.	.	0	8

i2_tp1_follow	2_tp1_death	i2_tp2_dura	i2_tp2_drop	2_tp2_follow	i2_tp2_death	i2_tp3_dura
0	0	.	.	.	.	.
7	0	365	1	7	0	.
3	0	30	0	1	1	91
.	.	91	.	.	.	183
4	0	14	0	2	0	30
0	1	.	.	.	.	.
13	.	365	.	9	.	.
48	0	.	.	.	.	.
.	.	.	.	.	.	.
.	1	.	.	.	.	.
2	0	.	.	.	.	.
0	0	1	0	0	0	30
.	.	.	.	.	.	.
0	0	91	0	5	0	.
.	.	.	.	.	.	.
.	.	.	.	.	.	.
0	0	30	0	0	0	61
0	0	183	1	0	0	.
.	.	183	.	.	.	274
.	.	.	.	.	.	.
0	0	198	9	1	0	.
1	0	.	.	.	.	.
0	0	365	6	4	0	548
3	0	167	0	2	0	259
0	0	91	0	1	0	365
.	.	.	.	.	.	.
1	.	91	.	2	.	.
.	.	.	.	.	.	.
.	.	.	.	.	.	.
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1	0	.	.	.	.	.
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0	0	.	.	.	.	.
1	0	.	.	.	.	.
15	0	.	.	.	.	.
.	.	91	3	.	.	365
0	.	.	.	.	.	.
.	**.**	**46**	**0**	**3**	**.**	**91**
.	.	.	.	.	.	.
13	0	.	.	.	.	.
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2	0	730	0	2	0	.

3	0	.	.	.	.	.
1	0	.	.	.	.	.
1	.	183	.	1	.	365
2	0	365	1	2	0	.
10	0	.	.	.	.	.
1	**1**	**.**	**.**	**.**	**.**	**.**
0	0	30	0	0	91	3
12	0	.	.	.	.	.
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1	**.**	**.**	**.**	**.**	**.**	**.**
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1	0	365	0	6	0	.
11	0	.	.	.	.	.
.	2	61	1	2	.	183
3	0	183	0	0	0	.
3	0	.	.	.	.	.
.	.	.	.	.	.	.
10	0	168	0	3	0	.
0	0	61	0	0	0	183
0	0	.	.	.	.	.
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0	0	2190	0	3	0	.
.	.	183	.	.	.	.
2	1	365	5	0	0	.
0	0	730	4	0	0	1825
0	0	730	0	6	0	.
0	0	1	0	0	1	7
0	0	132	12	0	0	.
0	2	.	.	.	.	.
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1	0	.	.	.	.	.
0	1	.	.	.	.	.
4	0	1490	0	8	0	.
0	0	84	0	0	0	126

.	.	365	.	.	.	548
10	.	365	.	9	.	730
2	.	.	.	.	.	.
0	0	91	1	2	0	181
0	0	365	0	5	0	.
0	0	.	.	.	.	.
0	0	365	2	5	0	.
1	0	.	.	.	.	.
0	0	365	1	0	0	.
0	0	274	2	0	4	.

i2_tp3_drop	i2_tp3_follow	i2_tp3_death	i2_tp4_dura	i2_tp4_drop	2_tp4_follow	i2_tp4_death
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0	2	0	183	1	1	1
1	3	.	.	.	.	.
1	1	0	91	2	3	1
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i2_tp5_dura	i2_tp5_drop	i2_tp5_follow	i2_tp5_death	i2_tp6_dura	i2_tp6_drop	i2_tp6_follow
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365	0	2	1	730	0	4
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183	2	0	1	365	1	0
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183	0	0	.	365	1	0
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730	0	0	0	1095	0	0
91	5	0	1	183	5	0
121	.	.	.	183	.	.
274	0	0	0	365	0	0

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i2_tp6_death	i2_tp7_dura	i2_tp7_drop	i2_tp7_follow	i2_tp7_death	i2_tp8_dura	i2_tp8_drop
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.	**730**	**.**	**15**	**.**	**.**	**.**
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i2_tp8_followi	2_tp8_death	i2_tp9_dura	i2_tp9_drop	2_tp9_followi	2_tp9_death	i2_tp10_dura
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i2_tp10_drop	2_tp10_follov	2_tp10_deatl	i3_tp1_dura	i3_tp1_drop	i3_tp1_follow	i3_tp1_death
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i3_tp2_dura	i3_tp2_drop	i3_tp2_follow	i3_tp2_death	i3_tp3_dura	i3_tp3_drop	i3_tp3_follow
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183	.	1	.	365	.	.
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i3_tp3_death	i3_tp4_dura	i3_tp4_drop	i3_tp4_followi	i3_tp4_death	i3_tp5_dura	i3_tp5_drop
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i3_tp5_followi3_tp5_death		i3_tp6_dura	i3_tp6_drop	i3_tp6_followi3_tp6_death		i3_tp7_dura
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11	**.**	**548**	**.**	**14**	**.**	**730**
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i3_tp7_drop	i3_tp7_followi	i3_tp7_death	i3_tp8_dura	i3_tp8_drop	i3_tp8_followi	i3_tp8_death
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i3_tp9_dura	i3_tp9_drop	i3_tp9_follow	i3_tp9_death	i3_tp10_dura	i3_tp10_drop	3_tp10_follov
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3_tp10_death	overall_drop	drop_rate	overall_follow	follow_rate	overall_death	death_rate
.	18	34.6153846	0	0	0	0
.	16	5.11182109	56	17.8913738	0	0
.	2	2.56410256	23	29.4871795	12	15.3846154
.	1	2	6	12	0	0
.	11	9.16666667	21	17.5	6	5
.	0	0	0	0	2	11.7647059
.	1	0.46728972	58	27.1028037	0	0
.	9	1.84804928	99	20.3285421	0	0
.	0	0	0	0	0	0
.	.	.	.	.	1	5.55555556
.	4	4.44444444	12	13.3333333	0	0
.	15	8.33333333	0	0	13	7.22222222
.	0	0	0	0	1	2.5
.	0	0	7	11.2903226	0	0
.	3	6.38297872	4	8.5106383	0	0
.	.	.	.	.	0	0
.	5	6.57894737	0	0	5	6.57894737
.	4	16	0	0	0	0
.	3	3.94736842	.	.	.	.
.	6	11.5384615	0	0	0	0
.	23	17.8294574	2	1.5503876	0	0
.	3	6.81818182	2	4.54545455	0	0
.	28	11.7154812	62	25.9414226	0	0
.	1	3.44827586	14	48.2758621	0	0
.	0	0	21	17.0731707	0	0
.	.	.	.	.	.	.
.	1	0.76335878	8	6.10687023	0	0
.	2	4.08163265	0	0	0	0
.	1	3.7037037	0	0	0	0
.	2	5	0	0	0	0
.	0	0	7	8.75	0	0
.	10	14.7058824	1	1.47058824	2	2.94117647
.	8	17.7777778	0	0	0	0
.	0	0	0	0	0	0
.	.	.	.	.	.	.
.	0	0	2	9.09090909	0	0
.	36	24.6575342	34	23.2876712	0	0
.	3	6.52173913	0	0	0	0
.	1	10	0	0	.	.
.	**15**	**8.33333333**	**0**	**0**	**0**	**0**
.	.	.	.	.	.	.
.	.	.	.	.	.	.
.	1	2.94117647	0	0	2	5.88235294
.	0	0	0	0	0	0
.	14	31.8181818	4	9.09090909	0	0

.	16	10.0628931	12	7.54716981	0	0
.	16	5.44217687	3	1.02040816	0	0
.	0	0	13	11.0169492	0	0
.	7	11.6666667	11	18.3333333	0	0
.	0	0	19	10	0	0
.	**0**	**0**	**1**	**0.68493151**	**1**	**0.68493151**
.	0	0	0	0	0	0
.	11	3.31325301	19	5.72289157	0	0
.	8	10.8108108	3	4.05405405	0	0
.	**2**	**2**	**2**	**2**	**0**	**0**
.	.	.	.	.	0	0
.	1	3.33333333	0	0	3	10
.	1	1.2345679	1	1.2345679	0	0
.	1	1.61290323	3	4.83870968	0	0
.	0	0	0	0	0	0
.	0	0	10	2.96735905	0	0
.	25	5.55555556	15	3.33333333	0	0
.	10	8	17	13.6	9	7.2
.	4	3.2	30	24	0	0
.	0	0	7	7.29166667	0	0
.	.	.	.	.	.	.
.	11	12.6436782	26	29.8850575	2	2.29885057
.	0	0	3	3.65853659	3	3.65853659
.	8	13.3333333	.	.	.	.
.	.	.	.	.	.	.
.	.	.	.	.	0	0
.	9	7.2	8	6.4	0	0
.	6	6.66666667	4	4.44444444	1	1.11111111
.	6	6.66666667	.	.	.	.
.	26	7.40740741	3	0.85470085	2	0.56980057
.	22	15.7142857	15	10.7142857	2	1.42857143
.	11	5.85106383	8	4.25531915	1	0.53191489
.	24	11.8811881	0	0	11	5.44554455
.	30	8.62068966	0	0	0	0
.	0	0	0	0	7	8.75
.	1	2.27272727	4	9.09090909	0	0
.	0	0	0	0	0	0
.	22	10.4761905	1	0.47619048	1	0.47619048
.	5	4.95049505	2	1.98019802	0	0
.	0	0	0	0	0	0
.	.	.	.	.	.	.
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.	3	7.14285714	1	2.38095238	0	0
.	0	0	1	2	2	4
.	0	0	18	22.5	2	2.5
.	0	0	0	0	1	1.53846154

.	0	0	0	0	1	14.2857143
.	16	11.4285714	31	22.1428571	0	0
.	0	0	3	4.76190476	0	0
.	31	9.65732087	40	12.4610592	1	0.31152648
.	4	4.3956044	9	9.89010989	0	0
.	0	0	15	25	0	0
.	7	5.18518519	13	9.62962963	0	0
.	3	2.77777778	2	1.85185185	0	0
.	5	17.2413793	1	3.44827586	1	3.44827586
.	72	31.3043478	0	0	7	3.04347826

overall_loss	cross_surg	ross_nonsur	overall_cross	cross_rate	verall_attritio	attrition_rate
34.6153846	1	0	1	1.92307692	19	36.5384615
23.0031949	26	43	69	22.0447284	141	45.0479233
32.0512821	0	0	0	0	37	47.4358974
14	0	0	0	0	7	14
26.6666667	0	0	0	0	38	31.6666667
0	0	0	0	0	2	11.7647059
27.5700935	1	0	1	0.46728972	60	28.0373832
22.1765914	0	5	5	1.02669405	136	27.926078
0	0	0	0	0	0	0
.	0	0	0	0	1	5.55555556
17.7777778	0	0	0	0	16	17.7777778
8.33333333	0	0	0	0	28	15.5555556
0	0	0	0	0	1	2.5
11.2903226	0	0	0	0	7	11.2903226
14.893617	12	0	12	25.5319149	19	40.4255319
.	0	0	0	0	1	1.96078431
6.57894737	0	0	0	0	10	13.1578947
16	0	0	0	0	4	16
.	0	0	0	0	3	3.94736842
11.5384615	0	0	0	0	6	11.5384615
19.379845	12	10	22	17.0542636	47	36.4341085
11.3636364	0	0	0	0	5	11.3636364
37.6569038	1	0	1	0.41841004	91	38.0753138
51.7241379	0	0	0	0	15	51.7241379
17.0731707	0	0	0	0	21	17.0731707
.	.	.	.	.	.	.
6.87022901	9	29	38	29.0076336	47	35.8778626
4.08163265	0	0	0	0	2	4.08163265
3.7037037	0	0	0	0	1	3.84615385
5	0	0	0	0	2	5
8.75	0	0	0	0	7	8.75
16.1764706	0	0	0	0	13	19.1176471
17.7777778	0	0	0	0	8	17.7777778
0	0	0	0	0	0	0
.	.	.	.	.	44	75.862069
9.09090909	0	0	0	0	2	9.09090909
47.9452055	0	0	0	0	70	47.9452055
6.52173913	0	0	0	0	3	6.52173913
10	0	0	0	0	.	.
8.33333333	**0**	**0**	**0**	**0**	**15**	**8.33333333**
.	.	.	.	.	15	8.33333333
.	0	0	0	0	40	78.4313725
2.94117647	0	0	0	0	3	8.82352941
0	0	0	0	0	0	0
40.9090909	8	0	8	18.1818182	26	59.0909091

17.6100629	.	.	.	.	28	17.6100629
6.46258503	0	0	0	0	19	6.46258503
11.0169492	20	0	20	16.9491525	33	27.9661017
30	30	.	30	50	48	80
10	.	.	.	.	19	10
0.68493151	**5**	**0**	**5**	**3.42465753**	**7**	**4.79452055**
0	0	0	0	0	0	0
9.03614458	.	.	.	.	30	9.03614458
14.8648649	0	0	0	0	11	14.8648649
4	**2**	**0**	**2**	**2**	**6**	**6**
.	0	2	2	2.5974026	10	12.987013
3.33333333	0	0	0	0	4	13.3333333
2.4691358	.	.	.	.	2	2.4691358
6.4516129	0	0	0	0	4	6.4516129
0	0	0	0	0	0	0
2.96735905	9	2	11	3.26409496	21	6.23145401
8.88888889	.	.	.	.	40	8.88888889
21.6	0	0	0	0	36	28.8
27.2	0	26	26	20.8	60	48
7.29166667	4	0	4	4.16666667	11	11.4583333
.	.	.	.	.	.	.
42.5287356	3	0	3	3.44827586	42	48.2758621
3.65853659	20	0	20	24.3902439	26	31.7073171
.	.	.	.	.	8	13.3333333
.	.	.	.	.	.	.
.	16	9	25	16.6666667	73	48.6666667
13.6	.	.	.	.	17	13.6
11.1111111	11	0	11	12.2222222	22	24.4444444
.	3	0	3	3.33333333	9	9.09090909
8.26210826	59	9	68	19.3732194	99	28.2051282
26.4285714	18	12	30	21.4285714	88	62.8571429
10.106383	0	6	6	3.19148936	26	13.8297872
11.8811881	10	6	16	7.92079208	51	25.2475248
8.62068966	0	0	0	0	30	8.62068966
0	0	0	0	0	7	8.75
11.3636364	0	0	0	0	5	11.3636364
0	0	0	0	0	0	0
10.952381	8	0	8	3.80952381	55	26.1904762
6.93069307	.	.	.	.	7	6.93069307
0	0	0	0	0	0	0
.	.	.	.	.	24	33.3333333
.	**.**	**.**	**.**	**.**	**32**	**44.4444444**
9.52380952	13	0	13	30.952381	17	40.4761905
2	0	0	0	0	3	6
22.5	0	0	0	0	20	25
0	0	0	0	0	6	9.23076923

0	0	0	0	0	1	14.2857143
33.5714286	13	0	13	9.28571429	60	42.8571429
4.76190476	0	0	0	0	3	4.76190476
22.1183801	47	8	55	17.1339564	127	39.5638629
14.2857143	.	.	.	.	13	14.2857143
25	20	0	20	33.3333333	35	58.3333333
14.8148148	8	0	8	5.92592593	28	20.7407407
4.62962963	1	0	1	0.92592593	6	5.55555556
20.6896552	0	0	0	0	7	24.137931
31.3043478	0	0	0	0	79	34.3478261

opped_recruminated_follttrition_reasc	retainment
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0	1	1	.

id	author	year	control	lot/lead_phas	prim_tps
1	Abbot	2004	1	0	183
2	Beard	2018	1	0	183
3	Buchbinder	2009	1	0	91
4	Cheong	2014	1	0	183
5	Clark	2016	1	0	14
6	Cobb	1959	1	0	274
7	Cotton	2014	1	1	365
8	Daniels	2009	1	0	365
9	Davys	2005	1	0	1
10	Dimond	1960	1	0	.
11	Eid	2014	1	0	365
12	Firanescu	2018	1	0	365
13	Freed	2001	1	0	365
14	Friedman	2008	1	0	91
15	Geenen	1989	1	0	1460
16	Gillespie	2011	1	0	91
17	Gross	2011	1	0	365
18	Gruber	2018	1	0	91
19	Guyuron	2009	1	0	365
20	Hansen	2016	1	0	91
21	Hunter	2015	1	0	183
22	Hakansson	2015	1	0	183
23	Ikramuddin	2014	1	0	365
24	Jarrel	2005	1	1	365
25	Johnson	2004	1	0	365
26	Kalapala	2018	1	0	91
27	Kallmes,	2009	1	0	30
28	Koutzourelakis	2008	1	0	106
29	Kroslak	2018	1	0	183
30	Kupsch	2006	1	0	91
31	Landorf	2013	1	0	42
32	Lee	2001	1	0	91
33	LeWitt	2011	1	1	183
34	Lichten	1987	1	0	365
35	Marks	2010	1	1	365
36	Maurer	2012	1	0	91
37	Moini	2012	1	0	274
38	MONTGOMERY	2006	1	0	365
39	Moseley	1996	1	1	183
40	**Moseley**	**2002**	**1**	**1**	**730**
41	Moseley	2002	1	1	730
42	Olanow	2015	1	1	456
43	Olanow	2003	1	0	730
45	Roehrborn	2013	1	0	91
46	Roos	2018	1	0	730

47	Rothstein	2006	1	0	91
48	Sarr	2012	1	0	365
49	Schroder	2017	1	0	730
50	Schwartz	2007	1	0	365
51	Shawki	2011	1	0	365
52	**Sihvonen**	**2014**	**1**	**0**	**730**
53	Steward	2008	1	0	91
54	Sullivan	2017	1	1	365
55	Sutton	1994	1	0	183
56	**Swank**	**2003**	**1**	**0**	**365**
57	Thompson	2013	1	1	183
58	Thomsen	1981	1	0	365
59	Toouli	2000	1	0	730
61	Volkman	2014	1	0	91
62	Wang	2016	1	0	1095
63	Wei	2012	1	0	91
106	Silverberg	2008	1	1	274

long_tps	total_tps	n_tps	plan_sampl e	ndom_samp	alysed_samp	n_female
365	183, 365	2	50	52	39	39
365	183, 365	2	300	313	274	158
730	, 91, 183, 365,	6	164	78	73	62
365	91, 183, 365	3	100	50	43	50
183	, 14, 30, 91, 18	5	120	120	112	88
456	274, 456	2	.	17	17	5
365	1, 183, 274, 36	4	214	214	173	197
1825	, 365, 730, 109	6	420	487	379	487
1	1	1	38	38	37	33
365	.	.	.	18	18	.
365	, 183, 213, 243	12	150	90	74	83
365	', 30, 91, 183,	6	180	180	176	133
365	122, 243, 365	3	.	40	39	19
91	14, 91	2	60	62	62	29
1460	65, 730, 1095,	5	.	47	47	45
91	91	1	100	51	50	8
1825	61, 91, 183, 2	7	68	76	67	24
183	91, 183	2	48	25	23	21
365	1, 183, 274, 36	4	.	76	75	.
.	.	.	.	52	46	.
183	14, 91, 198	3	120	129	129	66
183	183	1	.	44	44	20
1825	, 152, 183, 21	18	233	239	239	203
365	1, 183, 274, 36	4	100	29	16	29
365	1, 91, 365	3	130	123	123	123
.	.	.	.	13	.	.
91	3, 14, 30, 91	4	250	131	128	99
122	91, 122	.	48	49	47	19
913	, 42, 84, 183, 9	5	80	26	26	19
183	91, 183	2	40	40	40	13
42	14, 21, 28, 34,	6	80	80	80	50
730	183, 274, 36	8	90	68	.	68
183	30, 91, 183	3	40	45	37	10
365	91, 365	2	.	21	21	21
548	83, 274, 365,	7	51	58	57	15
91	91	1	.	22	20	22
274	274	1	146	146	76	146
365	46, 91, 365	3	.	46	43	31
183	15, 46, 91, 183	4	10	10	9	0
730	**91, 183, 365, 5**	**7**	**180**	**180**	**165**	**13**
730	91, 183, 365, 5	7	180	180	165	13
730	74, 365, 456, 5	9	52	51	47	16
730	74, 365, 456, 5	9	.	34	31	10
91	14, 30, 91	3	.	206	206	0
730	91, 730	2	100	44	42	21

91	91	1	.	159	144	69
365	, 152, 183, 213	15	222	294	253	165
730	1, 183, 365, 73	4	120	118	118	47
365	0, 91, 183, 36	4	60	60	57	24
365	91, 183, 365	3	.	190	171	190
730	**1,183,365, 73**	**4**	**140**	**146**	**144**	**57**
91	7, 30, 91	3	100	100	100	21
730	91, 183, 9, 27	7	.	332	332	296
183	91, 183	2	.	74	63	74
365	**91,183,365**	**3**	**120**	**100**	**100**	**87**
183	1, 183, 127, 91	6	132	77	.	73
1095	3, 213, 243, 2	13	.	30	30	12
730	183, 365, 548,	5	.	81	79	73
183	91, 183	2	60	62	62	35
1095	3, 365, 730, 1	4	.	12	12	2
365	91, 183, 365	3	300	337	327	337
274	0, 91, 183, 27	4	256	230	164	95

age_int1	age_int2	age_int3	n_screened	n_eligible	n_enrolled	recruit_rate
32.1	32.1	.	.	168	52	30.952381
52.9	53.7	53.2	2975	740	313	42.2972973
74.2	78.9	.	468	219	78	35.6164384
31	30	.	.	94	50	53.1914894
80	81	.	302	154	120	77.9220779
64	54	.	.	.	17	.
38	39	.	1584	286	214	74.8251748
30.6	30.5	.	592	487	487	100
60.2	57.5	.	55	51	38	74.5098039
.	.	.	.	.	18	.
51	50	.	763	275	90	32.7272727
74.7	76.9	.	1280	336	180	53.5714286
57.5	57.5	.	.	.	40	.
48.1	39	.	112	80	62	77.5
49	49	.	289	51	47	92.1568627
52.3	51.1	.	.	.	51	.
56.4	55.4	.	157	83	76	91.5662651
62	55.1	.	29	25	25	100
45.1	44.6	.	317	76	76	100
.	.	.	.	.	52	.
52	55	.	696	.	129	.
41	62	.	121	63	44	69.8412698
47	47	.	420	327	239	73.088685
28.9	29.4	.	36	29	29	100
29.5	29	.	200	123	123	100
.	.	.	.	.	.	.
73.4	74.3	.	1813	431	131	30.3944316
39	37.6	.	.	51	49	96.0784314
53	51	.	.	27	27	100
40.5	38.4	.	60	48	40	83.3333333
71.8	73.3	.	157	.	80	.
57.2	56.9	.	.	.	68	.
61.8	60.6	.	66	49	45	91.8367347
.	.	.	39	21	21	100
60.1	57.3	.	.	.	58	.
48.9	53.3	.	.	.	22	.
27.8	27.7	.	160	.	146	.
42	41	.	.	.	46	.
.	.	.	.	.	10	.
51.2	**52**	**53.6**	**.**	**324**	**180**	**55.5555556**
53.6	52	51.2	.	324	180	55.5555556
59.7	58.7	.	.	.	51	.
58.75	58	.	.	.	34	.
67	65	.	430	220	206	93.6363636
47.2	46.4	.	586	68	44	64.7058824

48.1	46.3	.	.	.	159	.
46	46	.	503	.	294	.
42	40	40	445	118	118	100
45	47	47	.	.	60	.
30.25	31.9	.	280	.	190	.
52	**52**	**.**	**.**	**205**	**146**	**71.2195122**
47.2	51.5	.	968	100	100	100
44.2	45.3	.	587	.	332	.
29	29.5	.	.	.	74	.
45.4	**47.8**	**.**	**121**	**103**	**100**	**97.0873786**
47.6	47.6	.	358	129	77	59.6899225
49.9	53.9	.	.	30	30	100
.	.	.	.	.	81	.
57.1	56.6	.	85	77	62	80.5194805
29.25	38.75	.	207	.	12	.
63.4	62.2	.	517	.	337	.
74.5	74	.	394	277	230	83.032491

i1_tp1_dura	i1_tp1_drop	i1_tp1_follow	i1_tp1_death	i1_tp2_dura	i1_tp2_drop	i1_tp2_follow
365	4	0	0	.	.	.
183	6	10	0	365	0	12
7	0	1	0	30	0	3
0	.	.	.	91	.	.
3	1	2	0	14	2	3
61	0	0	1	.	.	.
274	.	17	.	365	.	14
365	5	51	0	.	.	.
.	.	.	.	.	.	.
.	.	.	.	.	.	.
365	4	10	0	.	.	.
0	1	0	0	1	0	0
243	0	0	1	.	.	.
14	0	0	0	91	0	2
.	.	.	.	.	.	.
.	.	.	.	.	.	.
14	0	0	0	30	0	0
91	1	0	0	183	1	0
91	2	.	.	183	.	.
.	.	.	.	.	.	.
0	6	0	0	198	4	1
183	0	1	0	.	.	.
0	5	0	0	365	1	9
76	1	1	0	167	0	6
1	0	1	0	91	0	2
.	.	.	.	.	.	.
30	.	1	.	91	.	4
.	.	.	.	.	.	.
.	.	.	.	.	.	.
.	.	.	.	.	.	.
42	0	1	0	.	.	.
.	.	.	.	.	.	.
0	6	0	0	.	.	.
.	.	.	.	.	.	.
365	2	0	2	.	.	.
91	0	1	0	.	.	.
274	16	19	0	.	.	.
46	.	.	.	91	.	.
91	1	.	.	.	.	.
14	**.**	**2**	**.**	**46**	**.**	**5**
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456	1	14	0	.	.	.
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91	6	9	0	.	.	.
365	12	2	0	.	.	.
91	.	1	.	183	.	.
91	0	4	0	365	2	1
365	0	9	0	.	.	.
.	.	.	.	.	.	.
7	0	0	0	30	0	0
365	7	7	0	.	.	.
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12	.	**1**	.	.	.	.
.	.	.	.	.	.	.
1095	1	0	1	.	.	.
.	.	.	.	.	.	.
91	1	1	.	183	.	.
.	.	.	.	.	.	.
91	0	2	0	365	0	1
0	7	0	0	274	4	0

i1_tp2_death	i1_tp3_dura	i1_tp3_drop	i1_tp3_followi	i1_tp3_death	i1_tp4_dura	i1_tp4_drop
.	.	.	.	.	.	.
0	.	.	.	.	.	.
0	91	0	1	1	183	0
.	183	.	3	.	.	.
0	30	2	1	0	91	1
.	.	.	.	.	.	.
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0	30	0	0	0	91	1
.	.	.	.	.	.	.
0	.	.	.	.	.	.
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.	.	.	.	.	.	.
0	61	0	0	0	91	0
0	.	.	.	.	.	.
.	274	.	.	.	365	.
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0	.	.	.	.	.	.
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0	548	13	27	0	.	.
0	259	0	1	0	350	0
0	365	0	10	0	.	.
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0	91	0	0	0	.	.
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i1_tp4_followi	i1_tp4_death	i1_tp5_dura	i1_tp5_drop	i1_tp5_followi	i1_tp5_death	i1_tp6_dura
.	.	.	.	.	.	.
.	.	.	.	.	.	.
1	1	365	1	1	1	730
.	.	.	.	.	.	.
3	0	183	0	2	3	.
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.	.	.	.	.	.	.
.	.	.	.	.	.	.
0	2	183	1	0	2	365
.	.	.	.	.	.	.
.	.	.	.	.	.	.
.	.	.	.	.	.	.
.	.	.	.	.	.	.
0	0	183	0	0	0	274
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7	**.**	**365**	**.**	**5**	**.**	**548**
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i1_tp6_drop	i1_tp6_followi	i1_tp6_death	i1_tp7_dura	i1_tp7_drop	i1_tp7_followi	i1_tp7_death
0	3	2	.	.	.	.
4	0	4	.	.	.	.
0	0	0	365	4	0	4
.	**10**	.	**730**	.	**9**	.

i1_tp8_dura	i1_tp8_drop	i1_tp8_follow	i1_tp8_death	i1_tp9_dura	i1_tp9_drop	i1_tp9_follow
.	.	.	.	.	.	.
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i1_tp9_deathi1_tp10_durai1_tp10_drop1_tp10_follov1_tp10_deathi2_tp1_dura	i2_tp1_drop
. 365	1
. 183	2
. 7	0
. 0	.
. 3	0
. 243	0
. 274	.
. 365	4
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. 42	.
. 365	0
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. 14	0
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. 183	3
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. 91	2
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i2_tp1_followi	i2_tp1_death	i2_tp2_dura	i2_tp2_drop	i2_tp2_followi	i2_tp2_death	i2_tp3_dura
0	0	.	.	.	.	.
7	0	365	1	7	0	.
3	0	30	0	1	1	91
.	.	91	.	.	.	183
4	0	14	0	2	0	30
0	1	.	.	.	.	.
13	.	365	.	9	.	.
48	0	.	.	.	.	.
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.	1	.	.	.	.	.
2	0	.	.	.	.	.
0	0	1	0	0	0	30
.	.	.	.	.	.	.
0	0	91	0	5	0	.
.	.	.	.	.	.	.
.	.	.	.	.	.	.
0	0	30	0	0	0	61
0	0	183	1	0	0	.
.	.	183	.	.	.	274
.	.	.	.	.	.	.
0	0	198	9	1	0	.
1	0	.	.	.	.	.
0	0	365	6	4	0	548
3	0	167	0	2	0	259
0	0	91	0	1	0	365
.	.	.	.	.	.	.
1	.	91	.	2	.	.
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15	0	.	.	.	.	.
.	.	91	3	.	.	365
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13	0	.	.	.	.	.
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2	0	730	0	2	0	.

3	0	.	.	.	.	.
1	0	.	.	.	.	.
1	.	183	.	1	.	365
2	0	365	1	2	0	.
10	0	.	.	.	.	.
1	**1**	**.**	**.**	**.**	**.**	**.**
0	0	30	0	0	91	3
12	0	.	.	.	.	.
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1	0	365	0	6	0	.
0	0	274	2	0	4	.

i2_tp3_drop	i2_tp3_followi	i2_tp3_death	i2_tp4_dura	i2_tp4_drop	i2_tp4_followi	i2_tp4_death
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i2_tp5_dura	i2_tp5_drop	i2_tp5_follow	i2_tp5_death	i2_tp6_dura	i2_tp6_drop	i2_tp6_follow
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365	0	2	1	730	0	4
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183	2	0	1	365	1	0
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183	0	0	.	365	1	0
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i2_tp6_death	i2_tp7_dura	i2_tp7_drop	i2_tp7_followi2_tp7_death		i2_tp8_dura	i2_tp8_drop
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i2_tp8_follow	i2_tp8_death	i2_tp9_dura	i2_tp9_drop	i2_tp9_follow	i2_tp9_death	i2_tp10_dura
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i2_tp10_drop	2_tp10_follov	2_tp10_deatl	i3_tp1_dura	i3_tp1_drop	i3_tp1_followi	3_tp1_death
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i3_tp2_dura	i3_tp2_drop	i3_tp2_follow	i3_tp2_death	i3_tp3_dura	i3_tp3_drop	i3_tp3_follow
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365	0	13	0	.	.	.
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i3_tp3_death	i3_tp4_dura	i3_tp4_drop	i3_tp4_followi3_tp4_death		i3_tp5_dura	i3_tp5_drop
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i3_tp5_followi	i3_tp5_death	i3_tp6_dura	i3_tp6_drop	i3_tp6_followi	i3_tp6_death	i3_tp7_dura
11	.	**548**	.	**14**	.	**730**

i3_tp7_drop	i3_tp7_follow	i3_tp7_death	i3_tp8_dura	i3_tp8_drop	i3_tp8_follow	i3_tp8_death
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i3_tp9_dura	i3_tp9_drop	i3_tp9_follow	i3_tp9_death	i3_tp10_dura	i3_tp10_drop	3_tp10_follov
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3_tp10_death	overall_drop	drop_rate	overall_follow	follow_rate	overall_death	death_rate
.	18	34.6153846	0	0	0	0
.	16	5.11182109	56	17.8913738	0	0
.	2	2.56410256	23	29.4871795	12	15.3846154
.	1	2	6	12	0	0
.	11	9.16666667	21	17.5	6	5
.	0	0	0	0	2	11.7647059
.	1	0.46728972	58	27.1028037	0	0
.	9	1.84804928	99	20.3285421	0	0
.	0	0	0	0	0	0
.	.	.	.	.	1	5.55555556
.	4	4.44444444	12	13.3333333	0	0
.	15	8.33333333	0	0	13	7.22222222
.	0	0	0	0	1	2.5
.	0	0	7	11.2903226	0	0
.	3	6.38297872	4	8.5106383	0	0
.	.	.	.	.	0	0
.	5	6.57894737	0	0	5	6.57894737
.	4	16	0	0	0	0
.	3	3.94736842	.	.	.	.
.	6	11.5384615	0	0	0	0
.	23	17.8294574	2	1.5503876	0	0
.	3	6.81818182	2	4.54545455	0	0
.	28	11.7154812	62	25.9414226	0	0
.	1	3.44827586	14	48.2758621	0	0
.	0	0	21	17.0731707	0	0
.	.	.	.	.	.	.
.	1	0.76335878	8	6.10687023	0	0
.	2	4.08163265	0	0	0	0
.	1	3.7037037	0	0	0	0
.	2	5	0	0	0	0
.	0	0	7	8.75	0	0
.	10	14.7058824	1	1.47058824	2	2.94117647
.	8	17.7777778	0	0	0	0
.	0	0	0	0	0	0
.	.	.	.	.	.	.
.	0	0	2	9.09090909	0	0
.	36	24.6575342	34	23.2876712	0	0
.	3	6.52173913	0	0	0	0
.	1	10	0	0	.	.
.	**15**	**8.33333333**	**0**	**0**	**0**	**0**
.	.	.	.	.	.	.
.	.	.	.	.	.	.
.	1	2.94117647	0	0	2	5.88235294
.	0	0	0	0	0	0
.	14	31.8181818	4	9.09090909	0	0

.	16	10.0628931	12	7.54716981	0	0
.	16	5.44217687	3	1.02040816	0	0
.	0	0	13	11.0169492	0	0
.	7	11.6666667	11	18.3333333	0	0
.	0	0	19	10	0	0
.	**0**	**0**	**1**	**0.68493151**	**1**	**0.68493151**
.	0	0	0	0	0	0
.	11	3.31325301	19	5.72289157	0	0
.	8	10.8108108	3	4.05405405	0	0
.	**2**	**2**	**2**	**2**	**0**	**0**
.	.	.	.	.	0	0
.	1	3.33333333	0	0	3	10
.	1	1.2345679	1	1.2345679	0	0
.	1	1.61290323	3	4.83870968	0	0
.	0	0	0	0	0	0
.	0	0	10	2.96735905	0	0
.	72	31.3043478	0	0	7	3.04347826

overall_loss	cross_surg	ross_nonsur	overall_cross	cross_rate	verall_attritio	attrition_rate
34.6153846	1	0	1	1.92307692	19	36.5384615
23.0031949	26	43	69	22.0447284	141	45.0479233
32.0512821	0	0	0	0	37	47.4358974
14	0	0	0	0	7	14
26.6666667	0	0	0	0	38	31.6666667
0	0	0	0	0	2	11.7647059
27.5700935	1	0	1	0.46728972	60	28.0373832
22.1765914	0	5	5	1.02669405	136	27.926078
0	0	0	0	0	0	0
.	0	0	0	0	1	5.55555556
17.7777778	0	0	0	0	16	17.7777778
8.33333333	0	0	0	0	28	15.5555556
0	0	0	0	0	1	2.5
11.2903226	0	0	0	0	7	11.2903226
14.893617	12	0	12	25.5319149	19	40.4255319
.	0	0	0	0	1	1.96078431
6.57894737	0	0	0	0	10	13.1578947
16	0	0	0	0	4	16
.	0	0	0	0	3	3.94736842
11.5384615	0	0	0	0	6	11.5384615
19.379845	12	10	22	17.0542636	47	36.4341085
11.3636364	0	0	0	0	5	11.3636364
37.6569038	1	0	1	0.41841004	91	38.0753138
51.7241379	0	0	0	0	15	51.7241379
17.0731707	0	0	0	0	21	17.0731707
.	.	.	.	.	.	.
6.87022901	9	29	38	29.0076336	47	35.8778626
4.08163265	0	0	0	0	2	4.08163265
3.7037037	0	0	0	0	1	3.84615385
5	0	0	0	0	2	5
8.75	0	0	0	0	7	8.75
16.1764706	0	0	0	0	13	19.1176471
17.7777778	0	0	0	0	8	17.7777778
0	0	0	0	0	0	0
.	.	.	.	.	44	75.862069
9.09090909	0	0	0	0	2	9.09090909
47.9452055	0	0	0	0	70	47.9452055
6.52173913	0	0	0	0	3	6.52173913
10	0	0	0	0	.	.
8.33333333	**0**	**0**	**0**	**0**	**15**	**8.33333333**
.	.	.	.	.	15	8.33333333
.	0	0	0	0	40	78.4313725
2.94117647	0	0	0	0	3	8.82352941
0	0	0	0	0	0	0
40.9090909	8	0	8	18.1818182	26	59.0909091

17.6100629	.	.	.	.	28	17.6100629
6.46258503	0	0	0	0	19	6.46258503
11.0169492	20	0	20	16.9491525	33	27.9661017
30	30	.	30	50	48	80
10	.	.	.	.	19	10
0.68493151	**5**	**0**	**5**	**3.42465753**	**7**	**4.79452055**
0	0	0	0	0	0	0
9.03614458	.	.	.	.	30	9.03614458
14.8648649	0	0	0	0	11	14.8648649
4	**2**	**0**	**2**	**2**	**6**	**6**
.	0	2	2	2.5974026	10	12.987013
3.33333333	0	0	0	0	4	13.3333333
2.4691358	.	.	.	.	2	2.4691358
6.4516129	0	0	0	0	4	6.4516129
0	0	0	0	0	0	0
2.96735905	9	2	11	3.26409496	21	6.23145401
31.3043478	0	0	0	0	79	34.3478261

topped_recr	uminated_foll	ttrition_reaso	retainment
0	0	1	.
0	0	.	.
1	0	1	.
1	0	6	.
0	0	1	4
0	0	1	.
0	0	.	5
0	0	6	4
0	0	.	.
0	0	1	.
1	0	6	.
0	0	1	.
0	0	1	.
0	0	6	.
0	0	4	.
0	0	.	.
0	0	6	.
0	0	6	.
0	0	6	.
0	0	3	.
0	0	.	5
0	0	2	.
0	0	5	.
1	0	.	.
0	0	.	.
.	.	.	.
1	0	.	.
0	0	3	.
1	0	.	.
0	0	.	.
0	0	.	.
0	1	1	.
0	0	.	.
0	0	.	.
0	0	1	.
0	0	6	.
0	0	3	.
0	0	5	.
0	0	6	.
0	**0**	**.**	**.**
0	0	.	.
0	0	5	.
0	0	1	.
0	0	.	.
1	0	4	.

0	0	6	.
0	0	5	.
0	0	6	.
0	0	3	.
0	0	.	.
0	**0**	**3**	**.**
0	0	.	.
0	0	5	5
0	0	1	.
0	**0**	**6**	**.**
1	0	6	.
0	0	1	.
0	0	1	.
0	0	.	.
0	0	.	.
0	1	3	.
0	1	1	.

5	3	56
56	58	61
		5

8.19672131 4.91803279

id	author	year	control	lot/lead_phas	prim_tps
64	Alkatout	2013	0	0	730
67	Blasco	2012	0	0	365
68	Brox	1993	0	1	183
69	Chen	2014	0	0	365
70	Chen	2014	0	0	183
71	Farfaras	2016	0	0	30
72	Farrokhi	2011	0	0	1095
73	Fuentes	2011	0	0	730
74	Gad	2012	0	0	548
75	Gauffin	2014	0	0	365
76	Guyuron	2004	0	1	365
77	Haahr	2005	0	0	365
78	Herrlin	2006	0	0	183
79	Katz	2013	0	1	183
80	Ketola	2009	0	0	730
81	Kirkley	2008	0	0	730
82	Klazen	2010	0	0	365
83	Marcoux	1997	0	0	274
84	Merchan	1993	0	0	1095
85	Miller	2016	0	0	365
86	Osteras	2012	0	1	91
87	Paavola	2018	0	0	730
88	Parazzini	1999	0	0	365
89	Peters	1992	0	0	365
90	Peters	1997	0	0	1460
90	**Peters**	**1997**	**0**	**0**	**48**
91	Rahme	1998	0	0	183
92	Rousing	2009	0	0	91
93	Schierlitz	2014	0	0	183
94	Siddle	2012	0	0	548
95	Spencer	1992	0	0	365
96	Stensrud	2015	0	0	730
97	Trad	2015	0	0	183
99	van de Graaf	2018	0	0	730
100	Van der Ploeg	2016	0	0	365
101	Witteman	2015	0	1	183
102	Yang	2016	0	0	365
103	Yim	2013	0	1	730
105	Silverberg	2002	0	1	365

long_tps	total_tps	n_tps	plan_sampl e	ndom_samp	alysed_samp	n_female
730	152, 365, 730	3	.	450	410	450
365	4, 61, 183, 365	4	128	125	95	97
183	91, 183, 913	3	108	125	120	71
365	1, 7, 30, 91,	6	.	96	89	62
183	183	1	.	28	7	2
168	30, 168	2	120	87	55	28
1095	183, 365, 730,	6	.	82	82	60
730	183, 365, 730	3	.	60	60	60
548	.	.	.	41	.	.
365	183, 365	2	150	150	150	41
365	1, 183, 274, 36	4	.	125	108	.
2190	., 183, 365, 21	4	100	90	84	58
183	56, 183	2	80	99	90	35
365	91, 183, 366	3	340	351	330	187
144	04, 365, 730, 1	7	140	140	134	88
730	183, 365, 548,	5	186	188	168	112
365	', 30, 91, 183, 3	6	200	202	163	140
274	2, 152, 183, 24	6	330	348	341	348
1095	365, 730, 1095	3	.	80	73	53
730	33,243,304,36	11	44	44	39	34
91	91	1	20	17	17	4
730	1, 183, 365, 73	4	210	210	186	135
365	365	1	.	101	96	101
365	365	1	.	48	48	48
1460	1460	1	.	72	.	26
48	**12, 24, 36, 48**	**4**	**.**	**72**	**48**	**26**
365	183, 365	2	.	42	39	23
91	91	1	40	50	47	41
1490	5, 730, 1095,	7	62	80	74	80
548	26, 183, 274,	7	64	65	64	48
548	91,183,548	3	.	7	6	3
730	91, 365, 730	3	140	140	140	54
183	14, 91, 183	3	42	63	60	33
730	1, 183, 365, 73	4	320	321	289	161
365	365	1	320	91	89	91
365	30, 91, 183, 3	5	120	60	57	22
365	30, 91, 183, 36	5	96	135	107	69
730	1, 183, 365, 73	4	108	108	102	81
365	1, 183, 274, 36	4	.	29	23	14

age_int1	age_int2	age_int3	n_screened	n_eligible	n_enrolled	recruit_rate
.	.	.	523	499	450	90.1803607
71.33	75.27	.	219	125	125	100
48	48	47	444	155	125	80.6451613
64.63	66.49	.	.	.	96	.
.	.	.	64	28	28	100
52.4	49.9	48.9	95	.	87	.
72	74	.	105	84	82	97.6190476
.	.	.	.	.	60	.
.	.	.	.	.	41	.
54	54	.	179	155	150	96.7741935
43.4	42.9	.	.	.	125	.
44.3	44.5	.	.	.	90	.
56	56	.	180	99	90	90.9090909
59	57.8	.	14,430	1330	351	26.3909774
46.4	47.8	.	.	.	140	.
58.6	60.6	.	277	219	188	85.8447489
75.2	75.4	.	934	434	202	46.5437788
31	30	.	717	348	348	100
57	56	.	.	.	80	.
38.3	38.5	.	50	49	44	89.7959184
52.7	47	.	29	19	17	89.4736842
50.5	50.8	50.4	281	213	210	98.5915493
30.6	30.3	.	.	.	101	.
35.5	35.7	.	.	.	48	.
56	59	.	.	.	72	.
56	**59**	**.**	**.**	**.**	**72**	**.**
42	42	.	.	.	42	.
80	80	.	.	.	50	.
67	66	.	845	146	80	54.7945205
55.6	55.1	.	258	71	65	91.5492958
52	54.7	.	.	.	7	.
50.2	48.9	.	341	226	140	61.9469027
54.8	50.1	.	196	95	63	66.3157895
57.6	57.3	.	.	.	321	.
61	63.7	.	2000	.	91	.
42.4	49.3	.	.	.	60	.
77.1	76.2	.	158	153	135	88.2352941
54.9	57.9	.	162	157	108	68.7898089
71.4	73.5	.	529	313	29	9.26517572

i1_tp1_dura	i1_tp1_drop	i1_tp1_follow	i1_tp1_death	i1_tp2_dura	i1_tp2_drop	i1_tp2_follow
152	10	3	0	.	.	.
0	7	.	.	14	.	6
91	0	14	0	183	0	4
365	0	4	0	.	.	.
183	.	.	.	.	.	.
30	6	2	1	168	0	2
7	0	0	0	61	0	0
.	.	.	.	.	.	.
.	.	.	.	.	.	.
.	.	.	.	.	.	.
0	9	0	0	.	.	.
0	4	0	0	2190	0	1
56	.	.	.	183	.	.
91	12	0	1	365	4	1
0	1	0	0	730	2	0
0	2	0	0	730	1	2
0	2	0	0	1	0	0
0	5	0	0	100	9	0
1095	0	0	5	.	.	.
0	.	.	.	7	.	.
.	.	.	.	.	.	.
0	17	0	0	730	0	0
.	.	.	.	.	.	.
.	.	.	.	.	.	.
.	.	.	.	.	.	.
365	**0**	**6**	**0**	**730**	**0**	**0**
183	0	0	0	365	0	0
91	0	1	1	.	.	.
183	0	0	2	1490	0	6
42	0	0	0	84	0	0
183	0	.	1	365	.	.
91	.	7	.	365	.	7
183	.	1	.	.	.	.
0	1	0	0	91	1	2
0	2	0	0	365	1	3
183	0	10	0	365	0	5
0	2	0	0	365	0	8
730	3	1	0	.	.	.
0	1	0	0	365	1	1

i1_tp2_death	i1_tp3_dura	i1_tp3_drop	i1_tp3_followi	i1_tp3_death	i1_tp4_dura	i1_tp4_drop
.	.	.	.	.	.	.
.	61	.	2	1	183	.
0	.	.	.	.	.	.
.	.	.	.	.	.	.
.	.	.	.	.	.	.
0	.	.	.	.	.	.
0	183	0	0	0	365	0
.	.	.	.	.	.	.
.	.	.	.	.	.	.
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.	.	.	.	.	.	.
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i1_tp4_followi	i1_tp4_death	i1_tp5_dura	i1_tp5_drop	i1_tp5_followi	i1_tp5_death	i1_tp6_dura
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0	2	730	0	0	0	1095
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0	1	91	4	0	0	183
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9	0	730	11	0	0	.
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i1_tp6_drop	i1_tp6_followi	i1_tp6_death	i1_tp7_dura	i1_tp7_drop	i1_tp7_followi	i1_tp7_death
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i1_tp8_dura	i1_tp8_drop	i1_tp8_follow	i1_tp8_death	i1_tp9_dura	i1_tp9_drop	i1_tp9_follow
304	.	.	.	365	1	3

i1_tp9_deathi	i1_tp10_durai	i1_tp10_drop	1_tp10_follov	1_tp10_deatl	i2_tp1_dura	i2_tp1_drop
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.	.	.	.	.	183	0
.	.	.	.	.	0	3
.	.	.	.	.	730	0
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i2_tp1_followi	i2_tp1_death	i2_tp2_dura	i2_tp2_drop	i2_tp2_followi	i2_tp2_death	i2_tp3_dura
11	0	.	.	.	.	.
.	2	61	1	2	.	183
3	0	183	0	0	0	.
3	0	.	.	.	.	.
.	.	.	.	.	.	.
10	0	168	0	3	0	.
0	0	61	0	0	0	183
0	0	.	.	.	.	.
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.	.	.	.	.	.	.
0	0	2190	0	3	0	.
.	.	183	.	.	.	.
2	1	365	5	0	0	.
0	0	730	4	0	0	1825
0	0	730	0	6	0	.
0	0	1	0	0	1	7
0	0	132	12	0	0	.
0	2	.	.	.	.	.
.	.	7	.	.	.	30
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1	0	.	.	.	.	.
0	1	.	.	.	.	.
4	0	1490	0	8	0	.
0	0	84	0	0	0	126
.	.	365	.	.	.	548
10	.	365	.	9	.	730
2	.	.	.	.	.	.
0	0	91	1	2	0	181
0	0	365	0	5	0	.
0	0	.	.	.	.	.
0	0	365	2	5	0	.
1	0	.	.	.	.	.
0	0	365	1	0	0	.

i2_tp3_drop	i2_tp3_followi	i2_tp3_death	i2_tp4_dura	i2_tp4_drop	i2_tp4_followi	i2_tp4_death
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.	.	2	365	1	3	2
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0	0	0	365	0	2	1
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10	7	1	.	.	.	.
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1	0	0	30	1	0	0
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3	10	1	365	6	14	0
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i2_tp5_dura	i2_tp5_drop	i2_tp5_follow	i2_tp5_death	i2_tp6_dura	i2_tp6_drop	i2_tp6_follow
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730	0	0	0	1095	0	0
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91	5	0	1	183	5	0
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121	.	.	.	183	.	.
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274	0	0	0	365	0	0
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730	2	0	0	.	.	.
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i2_tp6_death	i2_tp7_dura	i2_tp7_drop	i2_tp7_followi	i2_tp7_death	i2_tp8_dura	i2_tp8_drop
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0	365	0	0	4	.	.
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i2_tp8_followi	2_tp8_death	i2_tp9_dura	i2_tp9_drop	i2_tp9_followi	2_tp9_deathi	2_tp10_dura
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i2_tp10_drop	2_tp10_follov	2_tp10_deatl	i3_tp1_dura	i3_tp1_drop	i3_tp1_follow	i3_tp1_death
.	.	.	152	1	1	0
.	.	.	.	.	.	.
.	.	.	91	0	8	0
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i3_tp2_dura	i3_tp2_drop	i3_tp2_follow	i3_tp2_death	i3_tp3_dura	i3_tp3_drop	i3_tp3_follow
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183	0	1	0	.	.	.
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168	0	5	0	.	.	.
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i3_tp3_death	i3_tp4_dura	i3_tp4_drop	i3_tp4_follow	i3_tp4_death	i3_tp5_dura	i3_tp5_drop
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i3_tp5_followi	i3_tp5_death	i3_tp6_dura	i3_tp6_drop	i3_tp6_followi	i3_tp6_death	i3_tp7_dura
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i3_tp7_drop	i3_tp7_followi	i3_tp7_death	i3_tp8_dura	i3_tp8_drop	i3_tp8_followi	i3_tp8_death
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i3_tp9_dura	i3_tp9_drop	i3_tp9_follow	i3_tp9_death	i3_tp10_dura	i3_tp10_drop	3_tp10_follov
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3_tp10_death	overall_drop	drop_rate	overall_follow	follow_rate	overall_death	death_rate
.	25	5.55555556	15	3.33333333	0	0
.	10	8	17	13.6	9	7.2
.	4	3.2	30	24	0	0
.	0	0	7	7.29166667	0	0
.	.	.	.	.	.	.
.	11	12.6436782	26	29.8850575	2	2.29885057
.	0	0	3	3.65853659	3	3.65853659
.	8	13.3333333	.	.	.	.
.	.	.	.	.	.	.
.	.	.	.	.	0	0
.	9	7.2	8	6.4	0	0
.	6	6.66666667	4	4.44444444	1	1.11111111
.	6	6.66666667	.	.	.	.
.	26	7.40740741	3	0.85470085	2	0.56980057
.	22	15.7142857	15	10.7142857	2	1.42857143
.	11	5.85106383	8	4.25531915	1	0.53191489
.	24	11.8811881	0	0	11	5.44554455
.	30	8.62068966	0	0	0	0
.	0	0	0	0	7	8.75
.	1	2.27272727	4	9.09090909	0	0
.	0	0	0	0	0	0
.	22	10.4761905	1	0.47619048	1	0.47619048
.	5	4.95049505	2	1.98019802	0	0
.	0	0	0	0	0	0
.	.	.	.	.	.	.
.	.	.	.	.	.	.
.	3	7.14285714	1	2.38095238	0	0
.	0	0	1	2	2	4
.	0	0	18	22.5	2	2.5
.	0	0	0	0	1	1.53846154
.	0	0	0	0	1	14.2857143
.	16	11.4285714	31	22.1428571	0	0
.	0	0	3	4.76190476	0	0
.	31	9.65732087	40	12.4610592	1	0.31152648
.	4	4.3956044	9	9.89010989	0	0
.	0	0	15	25	0	0
.	7	5.18518519	13	9.62962963	0	0
.	3	2.77777778	2	1.85185185	0	0
.	5	17.2413793	1	3.44827586	1	3.44827586

overall_loss	cross_surg	ross_nonsur	overall_cross	cross_rate	verall_attritio	attrition_rate
8.88888889	.	.	.	.	40	8.88888889
21.6	0	0	0	0	36	28.8
27.2	0	26	26	20.8	60	48
7.29166667	4	0	4	4.16666667	11	11.4583333
.	.	.	.	.	.	.
42.5287356	3	0	3	3.44827586	42	48.2758621
3.65853659	20	0	20	24.3902439	26	31.7073171
.	.	.	.	.	8	13.3333333
.	.	.	.	.	.	.
.	16	9	25	16.6666667	73	48.6666667
13.6	.	.	.	.	17	13.6
11.1111111	11	0	11	12.2222222	22	24.4444444
.	3	0	3	3.33333333	9	9.09090909
8.26210826	59	9	68	19.3732194	99	28.2051282
26.4285714	18	12	30	21.4285714	88	62.8571429
10.106383	0	6	6	3.19148936	26	13.8297872
11.8811881	10	6	16	7.92079208	51	25.2475248
8.62068966	0	0	0	0	30	8.62068966
0	0	0	0	0	7	8.75
11.3636364	0	0	0	0	5	11.3636364
0	0	0	0	0	0	0
10.952381	8	0	8	3.80952381	55	26.1904762
6.93069307	.	.	.	.	7	6.93069307
0	0	0	0	0	0	0
.	.	.	.	.	24	33.3333333
.	**.**	**.**	**.**	**.**	**32**	**44.4444444**
9.52380952	13	0	13	30.952381	17	40.4761905
2	0	0	0	0	3	6
22.5	0	0	0	0	20	25
0	0	0	0	0	6	9.23076923
0	0	0	0	0	1	14.2857143
33.5714286	13	0	13	9.28571429	60	42.8571429
4.76190476	0	0	0	0	3	4.76190476
22.1183801	47	8	55	17.1339564	127	39.5638629
14.2857143	.	.	.	.	13	14.2857143
25	20	0	20	33.3333333	35	58.3333333
14.8148148	8	0	8	5.92592593	28	20.7407407
4.62962963	1	0	1	0.92592593	6	5.55555556
20.6896552	0	0	0	0	7	24.137931

topped_recr	uminated_foll	ttrition_reaso	retainment
0	0	4	.
0	0	6	.
0	0	3	.
0	0	6	.
0	0	.	.
1	0	1	.
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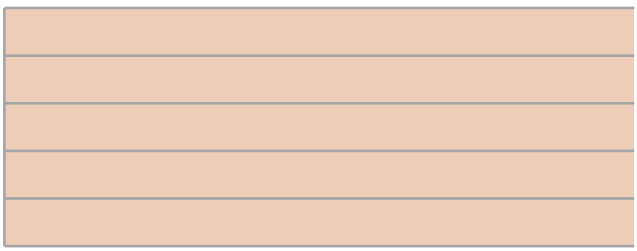
0	0	.	.
0	0	2	4
1	1	.	.
0	1	6	.
0	0	2	.
0	0	3	.
0	0	6	.
2	2		2
5.26315789	5.26315789		

KEY

Issue/Symbol	Explanation	Notes
Days duration		
91	3 months	Each duration timpoint was calculated with "Google conversion months to days" and the value was rounded to the nearest full number
183	6 months	
274	9 months	
365	1 year	
Dot (.)	Unknown information	Either information not given or could not be derived

Variable Type
STUDY INFORMATION
INVESTIGATION VARIABLES
POPULATION VARIABLES
RECRUITMENT VARIABLES
SUBJECT LOSSES (Drop-out & Lost to Follow-Up)
SUBJECT CROSS-OVER RATES
ATTRITION RATES



Variable
Article ID number
Author
Year
Control Intervention
Pilot/Lead-in Phase
Primary Outcome Timepoint Follow-up
Longest Follow-up
Follow-up Timepoints
Follow-up Timepoints
Planned Sample Size
Randomised Sample Size
Analysed Sample Size
Sex
Mean Age (Intervention 1)
Mean Age (Intervention 2)
Mean Age (Intervention 3)
Screened
Eligible
Overall Recruited (enrolled)
Recruitment Rate
Intervention 1
Intervention 2
Intervention 3
Timepoint (duration)
Timepoint (drop-out)
Timepoint (lost to follow-up)
Timepoint (death)
Overall Drop-Out
Drop-out Rate
Overall Lost to Follow-Up
Subject Loss Rate
Overall Lost to Follow-Up
Overall Death
Overall Subject Loss Rate
Cross-over into surgical intervention
Cross-over into non-surgical intervention
Overall Cross-Over
Cross-Over Rate
Overall Attrition Losses
Overall Attrition Rate

Reported Reasons for Attrition
Stoppage at point of recruitment (Y/N)
Stoppage at point of follow up (Y/N)
Reported Participant Retainment Strategies
Notes

Variable Abbreviation (Data)
id
author
year
control
pilot/lead_phase
prim_tps
long_tps
total_tps
n_tps
plan_sample
randomised_sample
analysed_sample
n_female
age_int1
age_int2
age_int3
n_screened
n_eligible
n_enrolled
recruit_rate
in_tpm_dura (n=1-3; m=1-10)
in_tpm_drop (n=1-3; m=1-10)
in_tpm_follow (n=1-3; m=1-10)
in_tpm_death (n=1-3; m=1-10)
overall_drop
drop_rate
overall_follow
follow_rate
overall_death
death_rate
overall_loss
cross_surg
cross_nonsurg
overall_cross
cross_rate
overall_attrition
attrition_rate

attrition_reason
stopped_recruit
terminated_follow
retainment

Units/ Formulae
(placebo/sham-controlled = 1/open-label = 0)
(Y = 1/N = 0)
(days)
(days)
(Interval Months)
(no.)
(no.)
(no.)
(no.)
(no. females)
(years)
(years)
(years)
(no.)
(no.)
(no.)
(overall recruited / total eligible %)
(days)
(no.)
(no.)
(no.)
(no.)
(overall drop-out / overall recruited %)
(overall subject loss / overall recruited %)
(overall death / overall recruited %)
(Follow-up Loss % + Drop-out %)
(no.)
(no.)
(no.)
(overall cross-over / overall recruited %)
verall Attrition Losses / Randomised Sample Size

Definition
Number given to article in the randomisation document (eg. Abbot 2004 = 1, Beard 2018 = 2, etc)
Last name of first published author
Year in which study was published
Placebo/sham surgical intervention controlled RCT or Open-Label Trial
lead-in phase: a study or part of a study conducted on a smaller scale in order to assess feas
Duration of time before follow-up for primary outcome (months)
Duration before final follow-up
Timepoints at which follow-up data was collected
Number of times data was collected from participants during follow-up
ed/aimed for sample size via statistical analysis. Includes 10% for losses - if these calculations
The number of participants beginning the randomisation process.
The number of participants with complete data, and so analysed for trials results.
The number of females in randomised sample size.
The average age in the surgical intervention group of the study.
The average age in the control/placebo group of the study.
The average age in the third group (other intervention)- leave blank if not applicable
l number of participants that were screened via baseline assessments for commencement of t
The total number of potential and eligible participants invited to participate in the study
he number of participants who were assessed as eligible and commenced participation in stud
The proportion of those eligible participants invited that were enrolled into the study
Surgical intervention group
Control group
Other Group
The duration of time after which outcome were collected.
he number of participants that gave refusal to progress further with the study within RCT group
igators to obtain primary outcomes information at planned primary outcome timepoint for parti
icipants who died in RCT group at planned timepint for primary outcomes information collecti
umber that dropped out (in all intervention groups) before trial completion (including follow-up
rcentage of people who quit treatment before its completion, including subsequent follow-up s
The overall no. of participants lost to follow-up.
The rate of loss of participants to follow-up.
The overall no. of participants lost to death.
The rate of loss of participants to death.
nt losses (either active/drop-out or passive/follow-up loss) as a proportion of randomised sam
umber of participants that underwent unplanned protocol violation and received surgical interve
ber of participants that underwent unplanned protocol violation and received non-surgical inte
that underwent unplanned protocol violation resulting in subjects in the control group receivin
overall rate of randomised participants that underwent unplanned protocol violation (cross-ov
Total number of patients lost to follow-up and drop-out in the study
Overall rate at which participants were lost from study.

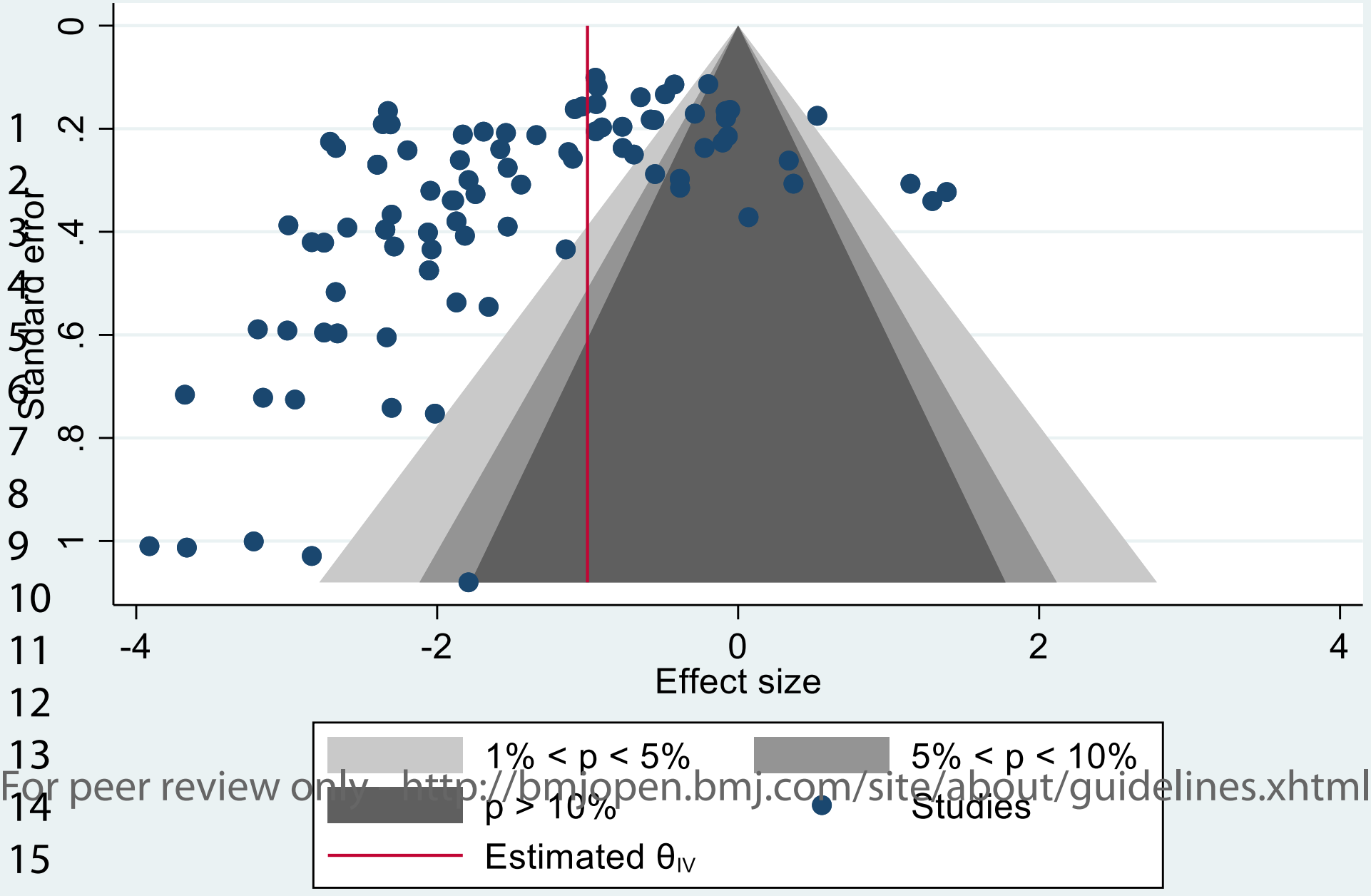
Reported reasons why participants left study.
Trial recruitment stopped early before reaching planned sample size.
llow-up terminated earlier than planned (prior to completion of all planned follow-up timepoints
Methods reported to be used to retain participants and actively affect attrition losses from study
Any other comments?

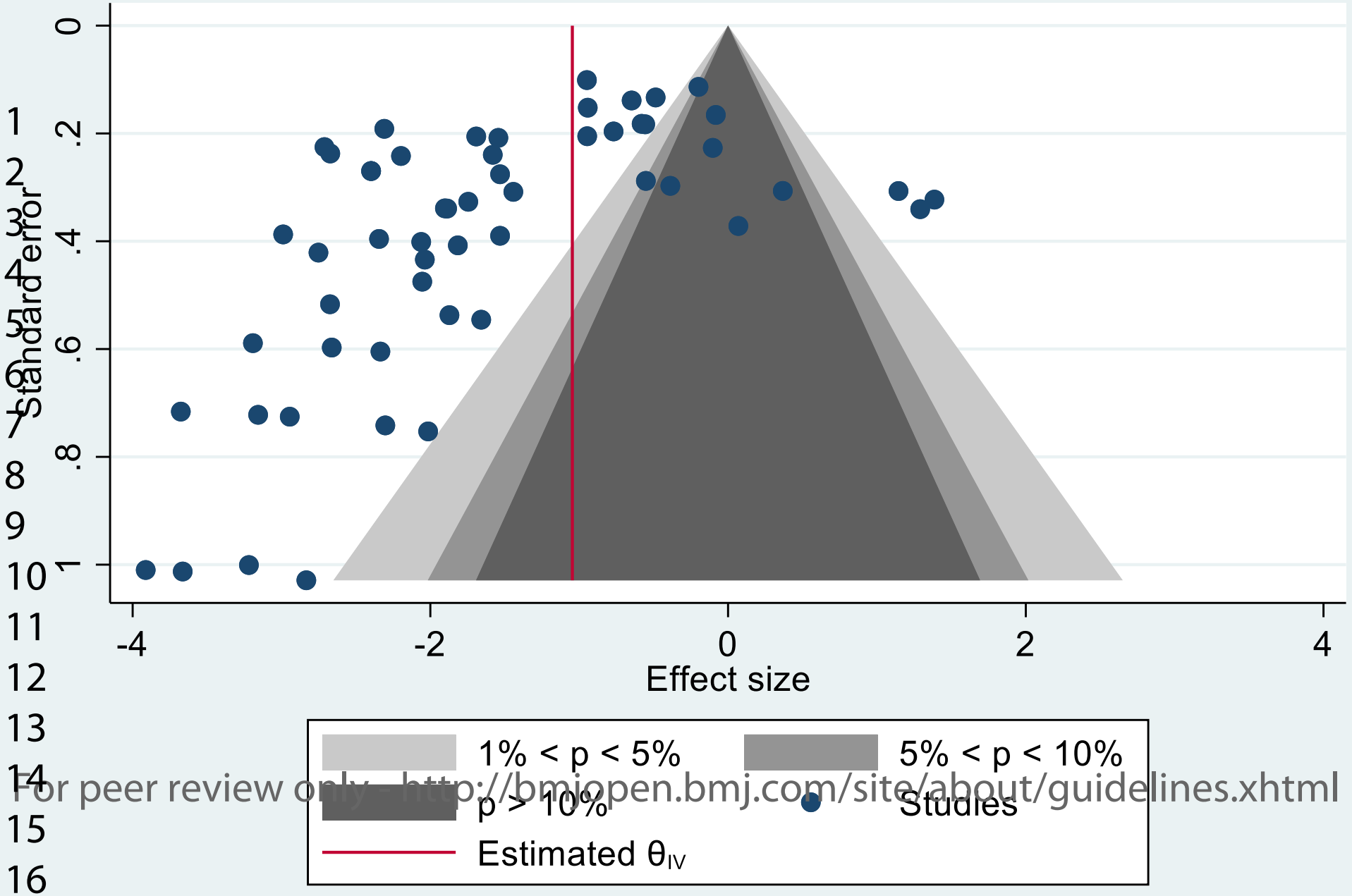
Appendix 2. Meta-regression for confounders including female proportion of study participants, number enrolled and number of follow-up points

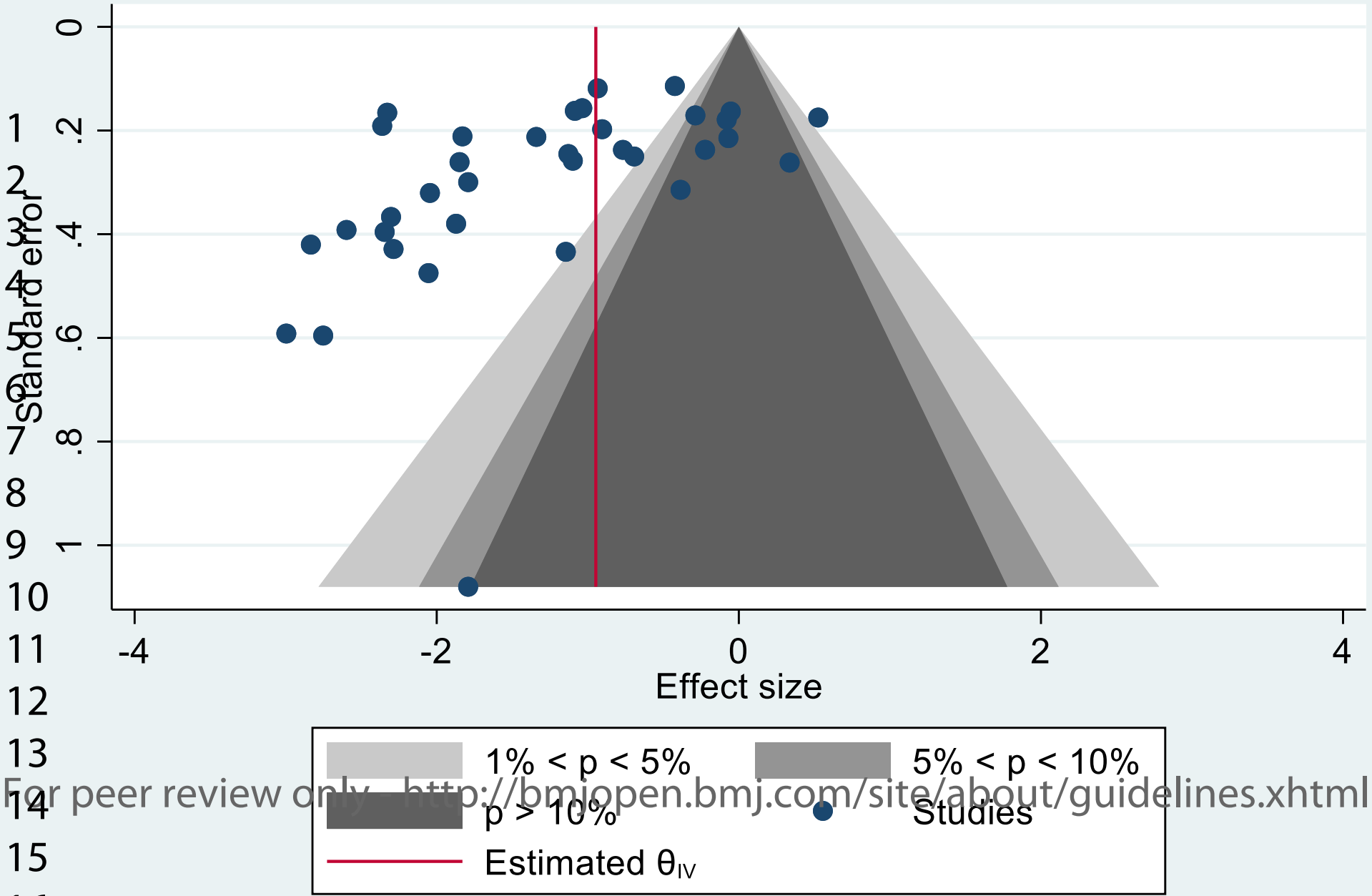
	Attrition rate effect size	Dropout rate **effect size**	Loss to follow-up **effect size**
Placebo Control Trials*	-0.17 (-0.66 to 0.32)	-0.24 (-0.86 to 0.37)	0.17 (-0.59 to 0.93)
Longest follow-up	0.0002 (-0.0004 to 0.0007)	-0.0003 (-0.0010 to 0.0004)	0.0002 (-0.0008 to 0.0011)
Female rate	-0.69 (-1.61 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	







Authors

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.)

References

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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 - change in the non-operative control group /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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Assistant/Associate Professor Adriane Lewin. South West Sydney Clinical School, UNSW

Dr Juuso Heikkinen. Department of Orthopaedics and Traumatology, Oulu University Hospital, Finland

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

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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. preanesthetic$.tw.
52. post$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 trail 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. spasmotic 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. 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$.tw.
18. prospective study/
19. or/1-18
20. case study/
21. case report.tw.
22. abstract report/ or letter/
23. or/20-22
24. 19 NOT 23
33. exp Spine/
34. (spine or spinal or vertebra$).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)

PRISMA 2020 for Abstracts Checklist

Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a systematic review.	No
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	No
Synthesis of results	6	Specify the methods used to present and synthesise results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Yes
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	Yes
Registration	12	Provide the register name and registration number.	Yes

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	N/A
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	-
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 6, Lines 123-133
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 6, Lines 136 – 139
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 7, Lines 155-155
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 7-8, Lines 162-172
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 7-8, Lines 162-172, Appendix 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 7-8, Lines 162-172
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 7-8, Lines 162-172
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 8, Lines 174-179
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 8, Lines 174-179
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Reference 12
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 8, Lines 181-193
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 8-9, Lines 195-214
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 8-9, Lines 195-214
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Figures 1, 2
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 8-9, Lines 195-207

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 9, Lines 213-214
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 9, Lines 209-211
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Reference 12
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 9, Line 213
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 9, Lines 217-219
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 10, Line 224
Study characteristics	17	Cite each included study and present its characteristics.	Appendix 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Reference 12
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Appendix 3
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Appendix 1, Reference 12
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 10-12, Line 231-279
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 11, Lines 257-261
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Page 11, Lines 249-253
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Reference 12
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page 12, Lines 276-279
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 12, Lines 288-341
	23b	Discuss any limitations of the evidence included in the review.	Page 14 Lines 336-341
	23c	Discuss any limitations of the review processes used.	Page 15 Lines 348-351

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
	23d	Discuss implications of the results for practice, policy, and future research.	Page 15, Lines 353-363
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that this review was not registered.	Page 2, Lines 30-31, Supplementary Files 1, 2
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Supplementary File 1
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Supplementary File 2
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 2, Lines 33-35
Competing interests	26	Declare any competing interests of review authors.	Page 2, Lines 37-41
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Page 2, Lines 43-44

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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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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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Randomised controlled trials, attrition, recruitment, surgery, placebo.

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 CENTRAL from their inception date to 21st 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. 25730 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, drop out 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 (IRR 1.8 [95% CI 1.1-3.0] p=0.032). The incorporation of one additional follow-up time point (regardless of follow-up duration) was associated with reduced attrition in placebo control surgical trials (IRR [95% CI] 0.64 [0.52-0.79], 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 given follow-up duration to mitigate losses to follow and dropout.

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, 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 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.

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 drop-out 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 (Supplementary File 1 and 2)

(CRD42019117364). 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, e.g. 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, that lacks the key surgical element(s) (11).

This study used the search strategy and eligibility criteria from an associated publication by Karjalainen et al (2022) (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 (2022) (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 (2014) (1) as well as an extension of its search until 21st 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 to March 13 to March 15, 2019. Where no relevant Cochrane review was identified, a search algorithm was devised and applied to the Cochrane Central Register of Controlled Trials (CENTRAL), 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 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 studies 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 vs. non-operative control trials, stratified by trial groups.

Due to the nature of the data (with varying follow-up duration), a Generalized Linear Latent and Mixed (GLLAM) Model(13) was employed for random effect Poisson regression to examine Incidents Rate Ratio (IRR) for intervention type (placebo or non-operative control). While controlling 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 (2022) (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) identified. 99 studies were included in the quantitative analysis (1 placebo control trial excluded due to unavailable full text at search date (14)). Detailed data on these included studies has been included in 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 (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% to 100%.

The random effect pooled rate was similar between placebo and non-operative control trials (rate [95% CI]: 76.9% [95% CI 71.1%-82.7%] vs 77.6% [95% CI 66.7%-88.4%], respectively, p=0.915). This included 10/36 (27.8%) 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%-78.1%] in the placebo and 74.1% [58.6%-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 to 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% - 25.2%]) and non-operative (23.7% [18.8% - 28.6%]) controlled studies (p=0.811). This was also true for discrete components of attrition including loss to follow-up, drop-out and cross-over rates (Appendix 4, 5, 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) were 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 to non-operative control trials (IRR 1.8 [95% CI 1.1-3.0], 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 1.04-6.3], p=0.042) and higher dropout (IRR 3.5 [95% CI 1.1-11.3], p=0.037) as seen in Figure 1.

The incorporation of just one additional follow-up timepoint point (regardless of length of follow up i.e. increased frequency of visits) is associated with a reduction in attrition (IRR

[95% CI] of 0.64 [0.52-0.79], p<0.001) in placebo control surgical trials, largely driven by fewer losses to follow-up (IRR [95% CI] of 0.68 [0.52-0.89], 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 (Appendix 7). Publication bias was greater in placebo control trials compared to trials of non-operative trials (Appendix 8, 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 to non-operative control trials. This was primarily driven by participant follow-up losses and drop-outs.

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 (e.g., infection) (18, 19). Previous trials such as Hare *et al.* (4), which reported 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 two-fold higher attrition rate (when considering cross-overs, drop-outs and follow-up losses) compared to 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). Metanalysis by Hróbjartsson et al., found nonblinded control groups suffer from 79% higher risk of drop-outs and 55% higher risk of co-intervention use when compared to 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 to other-control trials. Included trials in the present meta-analysis were published prior to development of the 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 drop-out. 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, whilst 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 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, pre-planned, 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 upon 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 to 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.

Figure Legends

Figure 1. Poisson Regression of Median Attrition Rates (Drop-out, Loss to Follow-up, Death, Overall Attrition) between placebo and non-operative controls.

Appendix Legends

Appendix 1. Search Strategy.

Appendix 2. Detailed data on included studies.

Appendix 3. Meta-regression for covariates including female proportion of study participants, number enrolled and number of follow-up points.

Appendix 4: Pooled (random effects) recruitment and attrition rates for studies with attrition > 0% and recruitment < 100%.

Appendix 5. Forest plot of overall follow-up rate.

Appendix 6. Forest plot of overall cross-over rate.

Appendix 7 Funnel Plot for All Included Trials. Effect sizes: 0 = 50%, +2 = ~88% and -2 = ~12 % attrition rate.

Appendix 8. Funnel Plot for Placebo Control Surgery Trials. Effect sizes: 0 = 50%, +2 = ~88% and -2 = ~12 % attrition rate.

Appendix 9. Funnel Plot for Non-Operative Control Surgery Trials. Effect sizes: 0 = 50%, +2 = ~88% and -2 = ~12 % attrition rate.

Contributorship Statement: PN and SM contributed equally to this work and share first authorship. Conception and design: SA; Administrative support: SA; Provision of study material or patients: SA; Collection and assembly of data: PN, SM, LH, MM, TK; Data analysis and interpretation: All authors; Manuscript writing: All authors; Final approval of manuscript: All authors.

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Data Sharing: Dataset included as Appendix 2. Additional relevant data available on reasonable request.

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

Protocol Registration: PROSPERO CRD42019117364. Original study protocol has been included as Supplementary File 1, and PROSPERO registration as Supplementary File 2.

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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 [1]	48 ± 8, (n=3)	47.8 ± 5.8, (n=4)	0.807
Gender of study cohorts (mean + SD)			
% 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

*number of follow-up points was not available for 5 studies (1 non-operative control and 4 placebo);

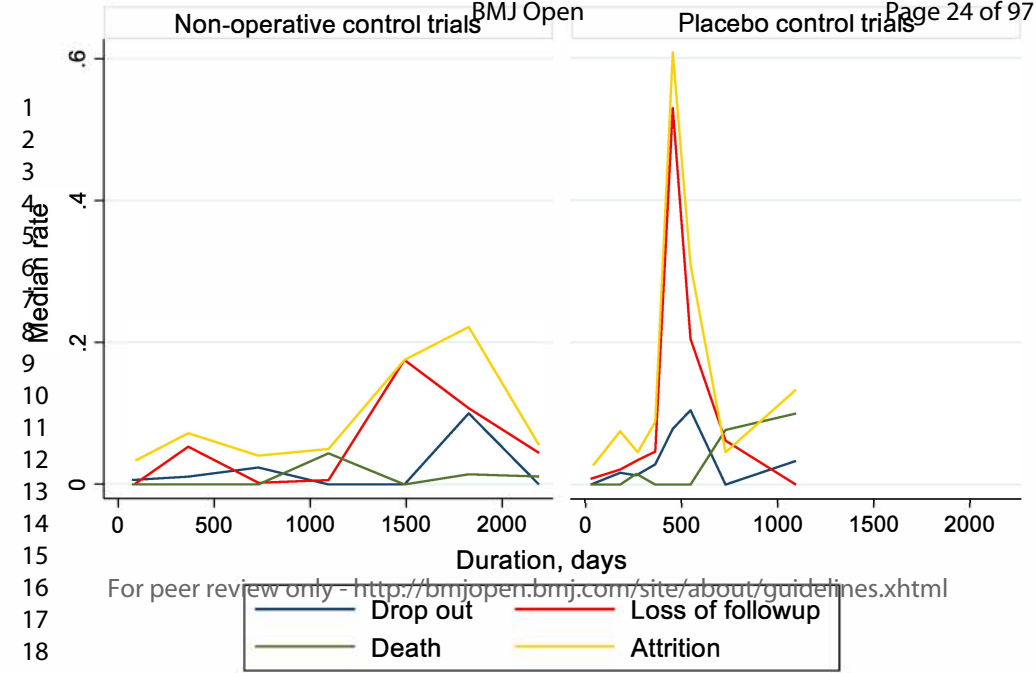
[1]Other group only applicable to trials incorporating 3 treatment arms;

SD = standard deviation, n = number of studies.

Table 2: Association between attrition rates and type of control group (placebo or non-operative) in surgical trials. Incident rate ratios (IRR) expressed for placebo control trials as a ratio of incident rates for non-operative control trials.

	Incident Rate Ratio (IRR)	95% Confidence Interval		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
Drop out	3.5	1.1	11.3	0.037

* Poisson regression analysis using a Generalized Linear Latent and Mixed Model (GLLAMM) to examine Incidents Rate Ratio (IRR), while controlling for participant gender, follow-up duration and number of follow-up timepoints.



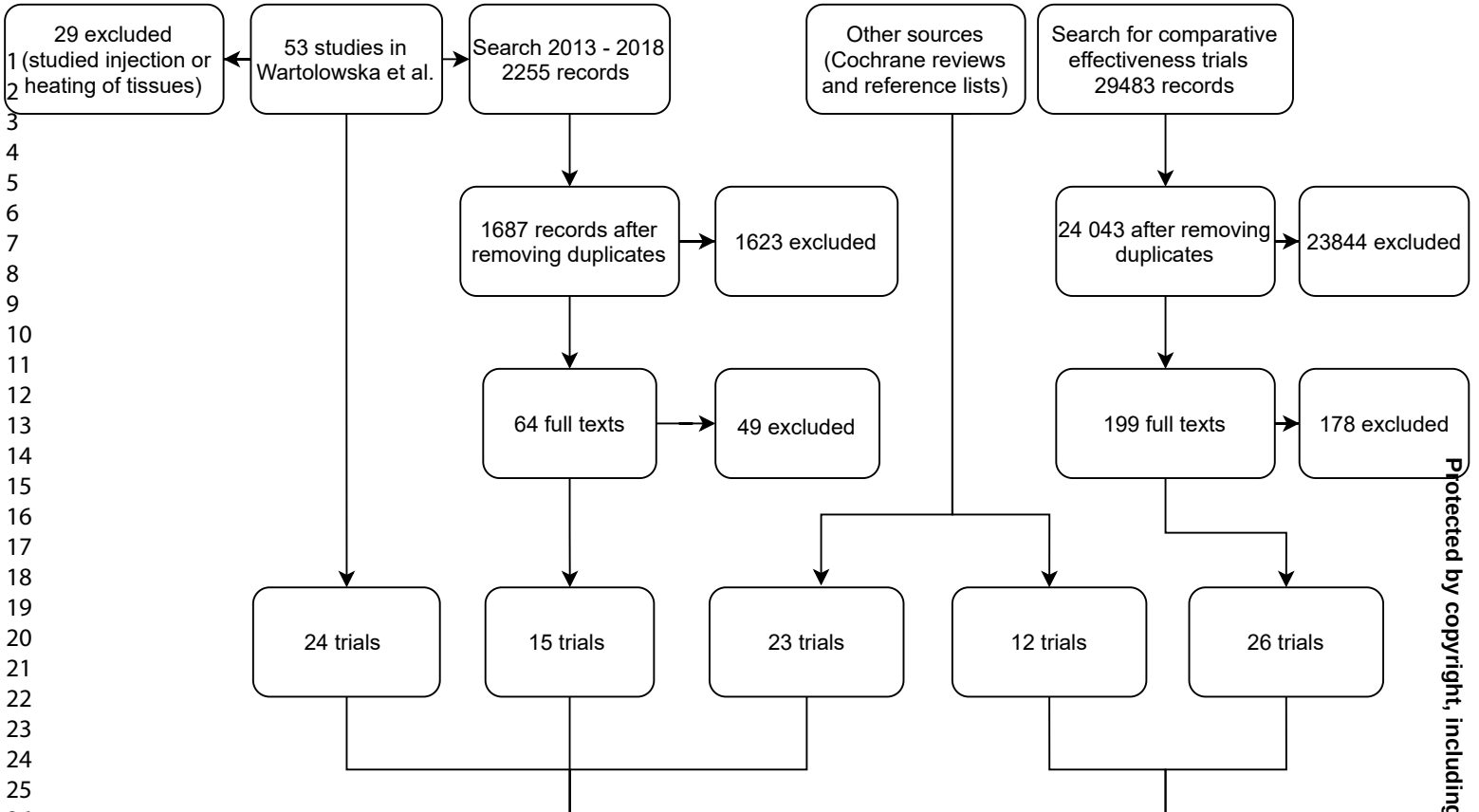


Figure 1. PRISMA flowchart of study selection

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. preanesthetic$.tw.
52. post$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 trail 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. spasmotic 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

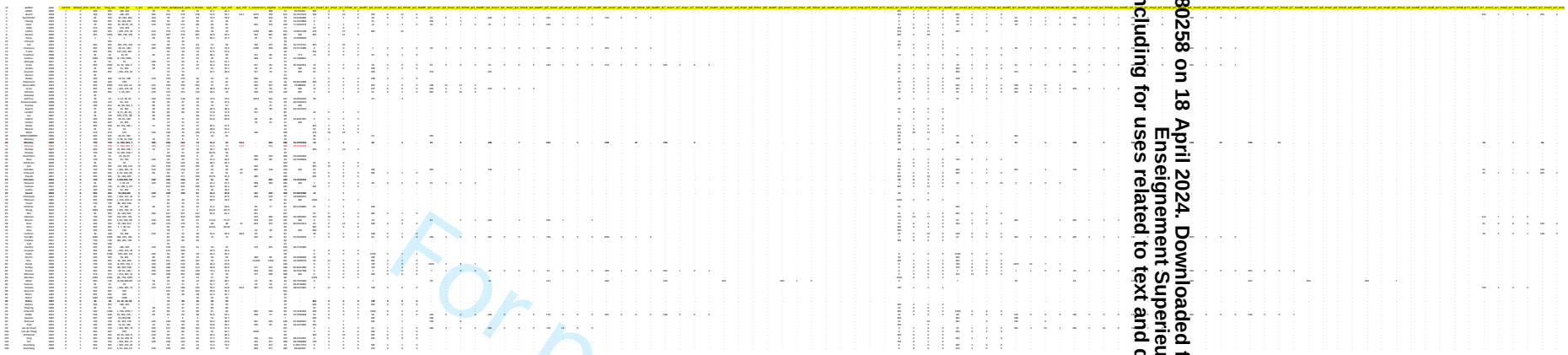
1. Clinical Trial/
2. Randomized Controlled Trial/
3. exp randomization/
4. Single Blind Procedure/
5. Double Blind Procedure/
6. Crossover Procedure/
7. Placebo/

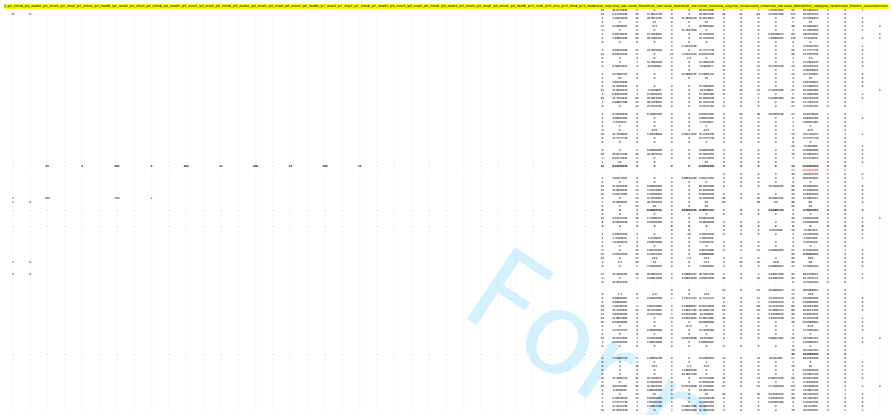
8. Randomi?ed controlled trial$.tw.
9. Rct.tw.
10. random allocation.tw.
11. randomly allocated.tw.
12. allocated randomly.tw.
13. (allocated adj2 random).tw.
14. Single blind$.tw.
15. Double blind$.tw.
16. ((treble or triple) adj blind$).tw.
17. placebo$.tw.
18. prospective study/
19. or/1-18
20. case study/
21. case report.tw.
22. abstract report/ or letter/
23. or/20-22
24. 19 NOT 23
33. exp Spine/
34. (spine or spinal or vertebra$).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)



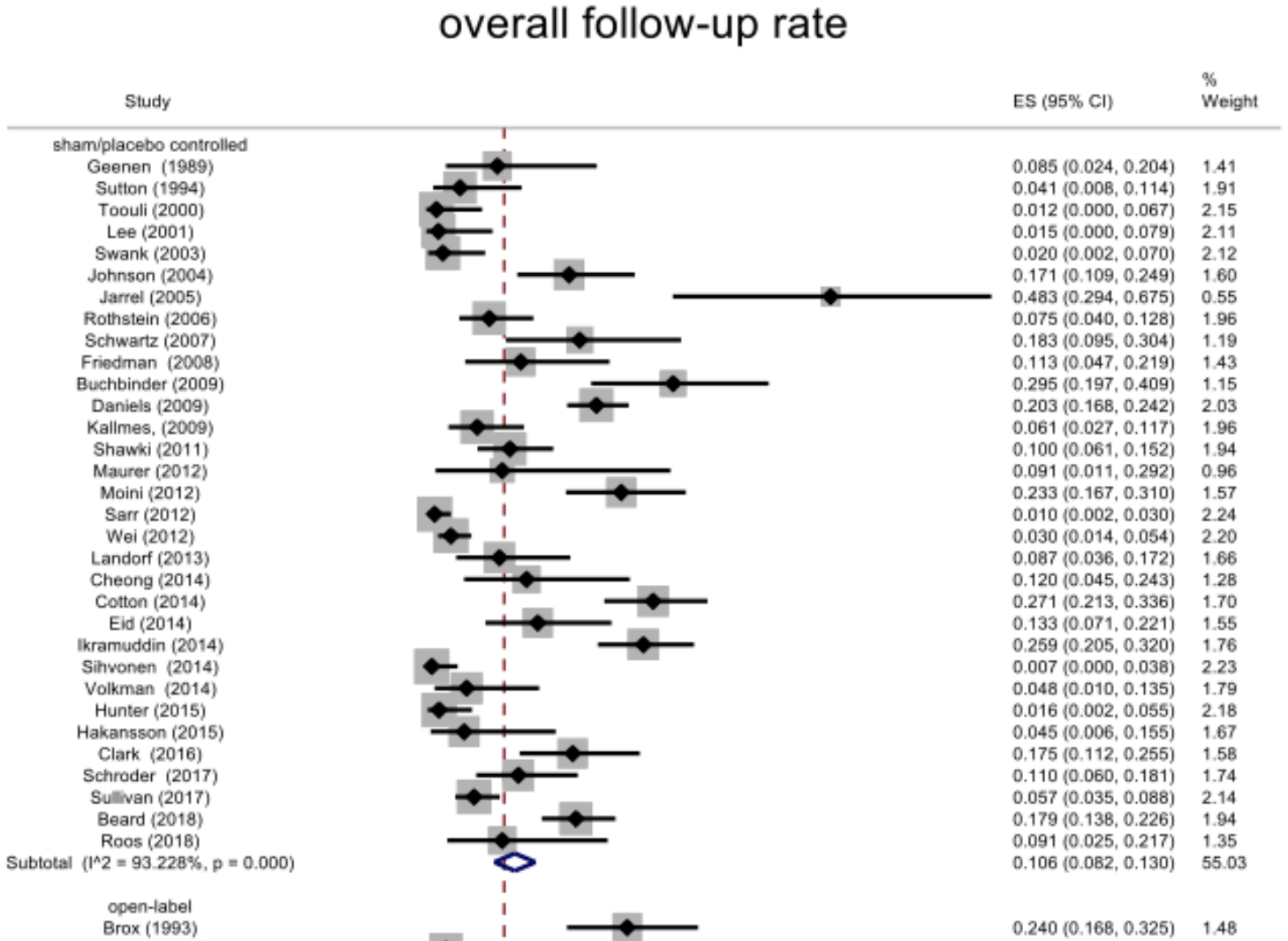


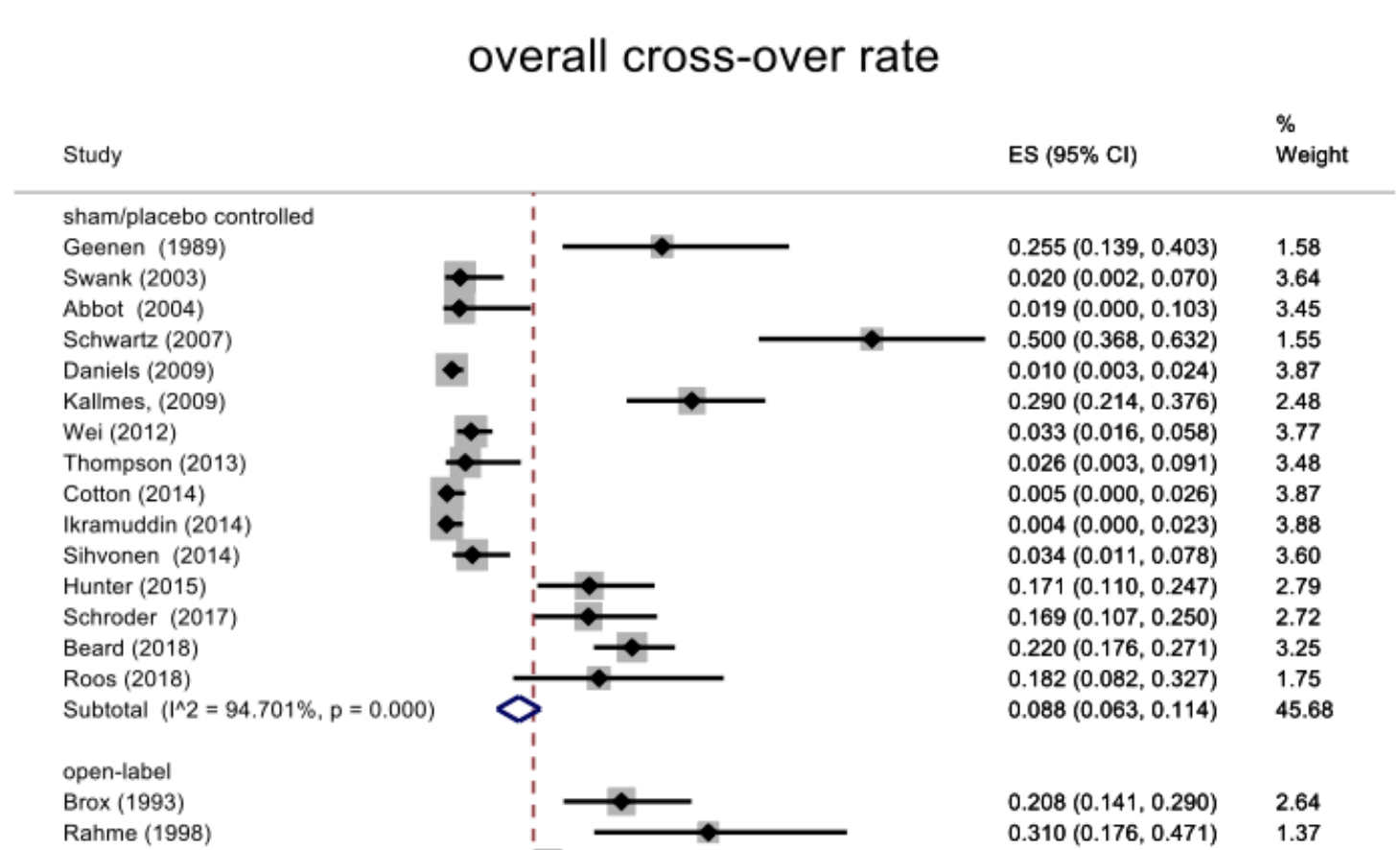
Appendix 2. Meta-regression for confounders including female proportion of study participants, number enrolled and number of follow-up points

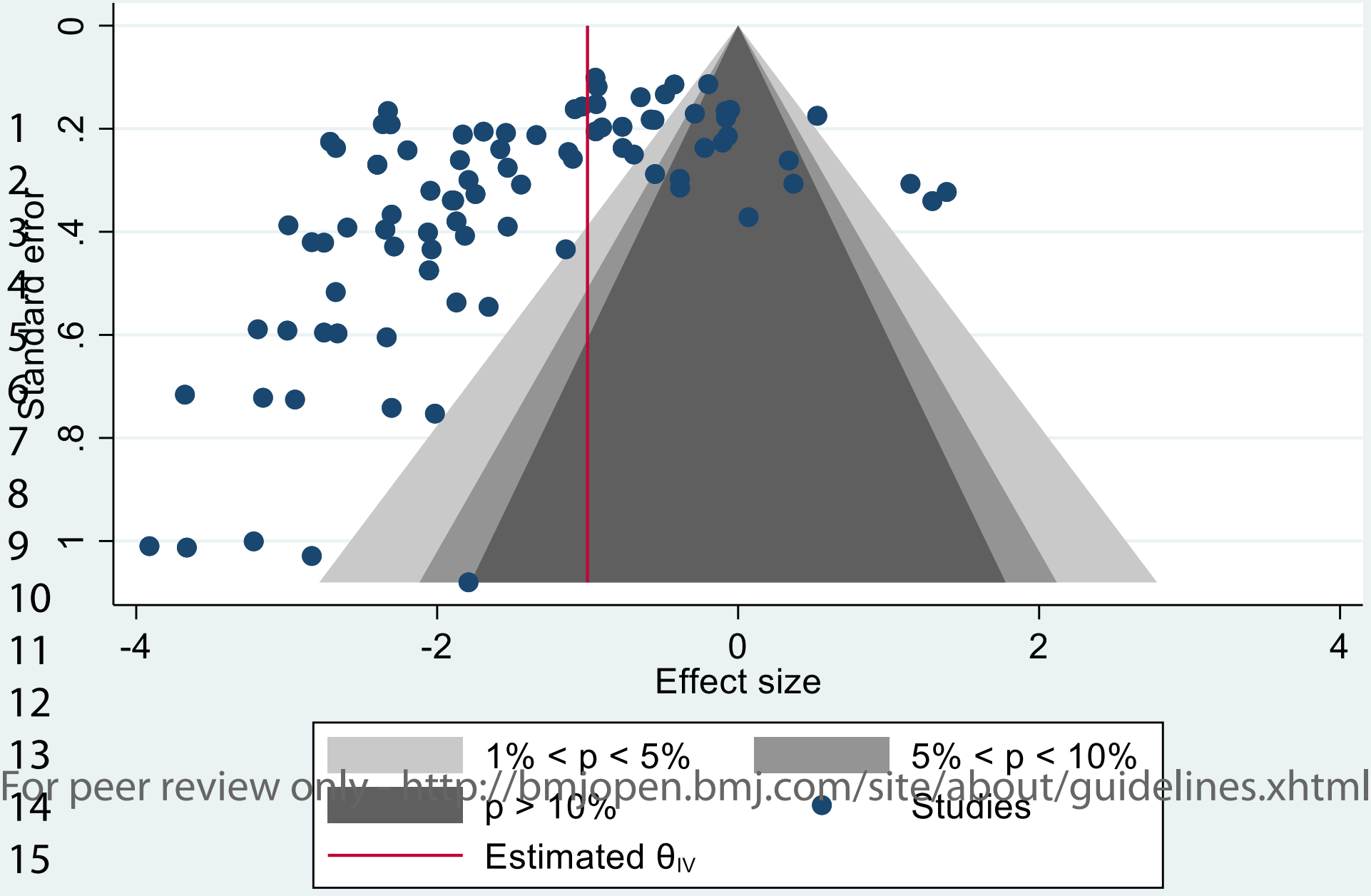
	Attrition rate effect size	Dropout rate **effect size**	Loss to follow-up **effect size**
Placebo Control Trials*	-0.17 (-0.66 to 0.32)	-0.24 (-0.86 to 0.37)	0.17 (-0.59 to 0.93)
Longest follow-up	0.0002 (-0.0004 to 0.0007)	-0.0003 (-0.0010 to 0.0004)	0.0002 (-0.0008 to 0.0011)
Female rate	-0.69 (-1.61 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			

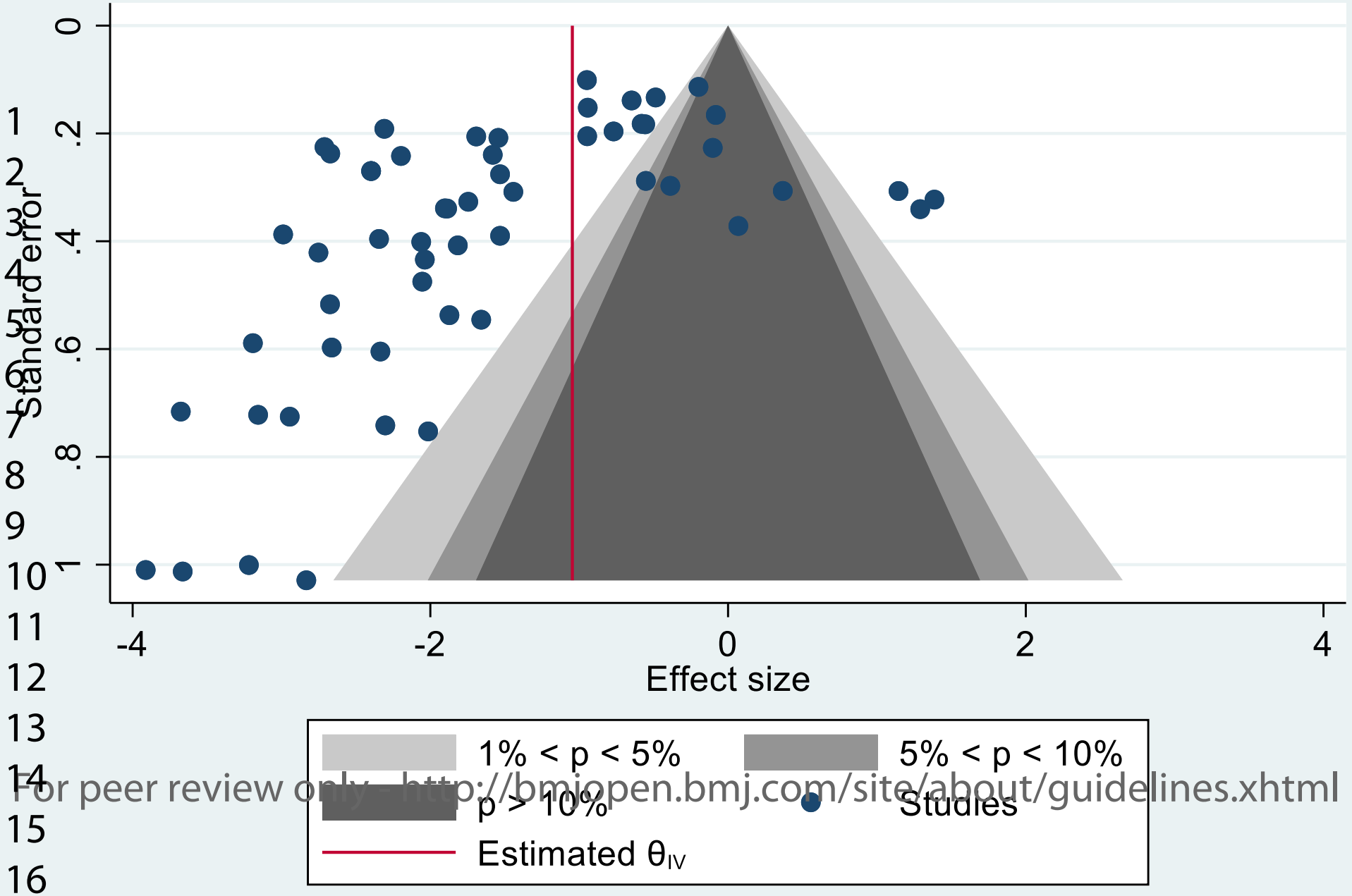
Appendix 3: Pooled (random effects) recruitment and attrition rates for studies with attrition > 0% and recruitment < 100%.

	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	

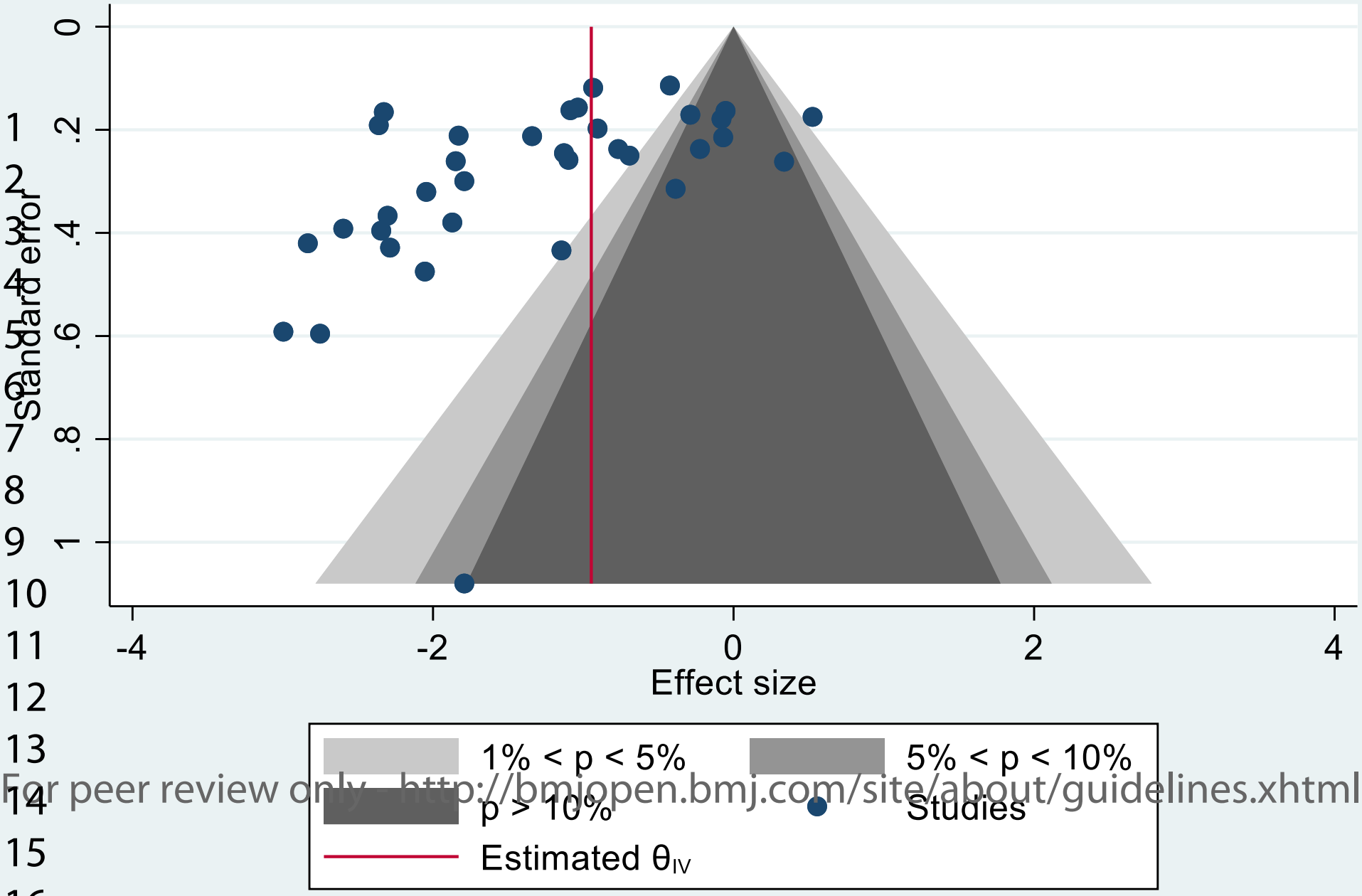








Contour-enhanced funnel plot



Authors

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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 - change in the non-operative control group /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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Unit of Hand Surgery, Departmen of Surgery, Central Finland Central Hospital

Review team members and their organisational affiliations [1 change]

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Dr Juuso Heikkinen. Department of Orthopaedics and Traumatology, Oulu University Hospital, Finland

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

PRISMA 2020 for Abstracts Checklist

Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a systematic review.	No
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	No
Synthesis of results	6	Specify the methods used to present and synthesise results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	Yes
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	Yes
Registration	12	Provide the register name and registration number.	Yes

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	N/A
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	-
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 6, Lines 123-133
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 6, Lines 136 – 139
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 7, Lines 155-155
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 7-8, Lines 162-172
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 7-8, Lines 162-172, Appendix 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 7-8, Lines 162-172
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 7-8, Lines 162-172
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 8, Lines 174-179
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 8, Lines 174-179
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Reference 12
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 8, Lines 181-193
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 8-9, Lines 195-214
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 8-9, Lines 195-214
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Figures 1, 2
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 8-9, Lines 195-207

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 9, Lines 213-214
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 9, Lines 209-211
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Reference 12
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 9, Line 213
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 9, Lines 217-219
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 10, Line 224
Study characteristics	17	Cite each included study and present its characteristics.	Appendix 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Reference 12
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Appendix 3
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Appendix 1, Reference 12
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Page 10-12, Line 231-279
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 11, Lines 257-261
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Page 11, Lines 249-253
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Reference 12
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page 12, Lines 276-279
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 12, Lines 288-341
	23b	Discuss any limitations of the evidence included in the review.	Page 14 Lines 336-341
	23c	Discuss any limitations of the review processes used.	Page 15 Lines 348-351

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
	23d	Discuss implications of the results for practice, policy, and future research.	Page 15, Lines 353-363
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that this review was not registered.	Page 2, Lines 30-31, Supplementary Files 1, 2
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Supplementary File 1
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Supplementary File 2
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 2, Lines 33-35
Competing interests	26	Declare any competing interests of review authors.	Page 2, Lines 37-41
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Page 2, Lines 43-44

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