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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

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2023-080258
Article Type:	Original research
Date Submitted by the Author:	25-Sep-2023
Complete List of Authors:	Natarajan, Pragadeesh; University of New South Wales - Saint George Campus Menounos, Spiro; University of New South Wales - Saint George Campus Harris, Laura; University of New South Wales - Saint George Campus; St George and Sutherland Centre for Clinical Orthopaedic Research Limited Monuja, Masiath; University of New South Wales - Kensington Campus; St George and Sutherland Centre for Clinical Orthopaedic Research Limited Gorelik, Alex; Monash University School of Public Health and Preventive Medicine, Department of Medicine, Royal Melbourne Hospital Karjalainen, Teemu; Monash-Cabrini Department of Musculoskeletal Health and Clinical Epidemiology, Hand and Microsurgery; Tampere University Hospital Department of Musculoskeletal Diseases, Buchbinder, Rachelle; Monash University School of Public Health and Preventive Medicine, Dept of Epidemiology and Preventive Medicine Harris, Ian; Ingham Institute, Applied Medical Research - School of Clinical Medicine Naylor, Justine; Ingham Institute, Applied Medical Research - School of Clinical Medicine Adie, Sam; University of New South Wales - Saint George Campus, South West Sydney Clinical School; St George and Sutherland Centre for Clinical Orthopaedic Research Limited, Department of Orthopaedics
Keywords:	Randomized Controlled Trial, SURGERY, Follow-Up Studies

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2 **1 Participant recruitment and attrition in**
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4 **2 surgical randomised trials with placebo-**
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6
7 **3 controls versus non-operative controls: a meta-**
8
9 **4 epidemiological study and meta-analysis**

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10 27

11 28 **Running Head:** Participant recruitment and attrition in surgical randomised trials

12 29

13 30 **Protocol Registration:** PROSPERO CRD42019117364. Original study protocol has been
14 31 included as Supplementary File 1, and PROSPERO registration as Supplementary File 2.

15 32

16 33 **Funding:** This research received no specific grant from any funding agency in the public,
17 34 commercial or not-for-profit sectors. RB is funded by an Australian National Health and
18 35 Medical Research Council Investigator Fellowship.

19 36

20 37 **Competing Interests:** RB has received royalties from UpToDate for authoring a chapter
21 38 unrelated to this paper (Plantar Fasciitis). SA has received grants and/or research contracts
22 39 from National Health and Medical Research Council, Avant Foundation and ANZ
23 40 Musculoskeletal Clinical Trial Network (ANZMUSC) as part of Sydney Partnership for
24 41 Health, Education, Research and Enterprise (SPHERE).

25 42

26 43 **Data Sharing:** Dataset included as Appendix 1. Additional relevant data available on
27 44 reasonable request.

28 45

29 46 **Word count (Abstract, Body):** 316, 2405

30 47

1
2
3 48 **Figures and Tables:** 4
4
5 49

6
7 50 **Author Statement:** Conception and design: SA; Administrative support: SA; Provision of
8 study material or patients: SA; Collection and assembly of data: PN, SM, LH, MM, TK; Data
9 analysis and interpretation: All authors; Manuscript writing: All authors; Final approval of
10 manuscript: All authors.
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18 55 **Transparency declaration:** Authors affirms that this manuscript is an honest, accurate, and
19 transparent account of the study being reported; that no important aspects of the study have
20 been omitted; and that any discrepancies from the study as planned (and, if relevant,
21 registered) have been explained.
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30 60 **Keywords**
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33 61 Randomised controlled trials, attrition, recruitment, surgery, placebo.
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Key Points

74 Question

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

78

79 Findings

80 The unadjusted pooled recruitment and attrition rates were similar between placebo and non-
81 operative control trials. After adjusting for covariates (follow-up duration and number of
82 timepoints) the attrition rate of placebo control trials was almost twice as high compared with
83 non-operative controlled trials (IRR 1.8 [95% CI 1.1-3.0] p=0.032).

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85 Meaning

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

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Abstract

98
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100 Objective

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

104

105 Design

106 Meta-Epidemiological Study.

107

108 Data Sources

109 Randomised controlled trials were identified from an electronic search of MEDLINE,
110 EMBASE and CENTRAL from their inception date to 21st November 2018.

111

112 Study Selection

113 Placebo control trials evaluating efficacy of any surgical intervention, and non-operative
114 control trials of the same surgical intervention were included in this study. 25730 records
115 were retrieved from our systemic search, identifying 61 placebo control and 38 non-operative
116 control trials for inclusion in analysis.

117

118 Outcome measures

119 Primary outcome measures were recruitment and attrition. These were assessed in terms of
120 recruitment rate (number of participants enrolled, as a proportion of those eligible) and
121 overall attrition rate (composite of dropout, loss to follow-up and cross-overs, expressed as

1
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3 122 proportion of total sample size). Secondary outcome measures included participant cross-over
4
5 123 rate, drop out and loss to follow-up.

6 124

7 125 **Results**

8 126 Unadjusted pooled recruitment and attrition rates were similar between placebo and non-
9
10 127 operative control trials. Study characteristics were not significantly different apart from time
11
12 128 to primary timepoint which was shorter in studies with placebo controls (365 vs 274 days,
13
14 129 p=0.006). After adjusting for covariates (follow-up duration and number of timepoints) the
15
16 130 attrition rate of placebo control trials was almost twice as high compared with non-operative
17
18 131 controlled-trials (IRR 1.8 [95% CI 1.1-3.0] p=0.032). The incorporation of one additional
19
20 132 follow-up time point (regardless of follow-up duration) was associated with reduced attrition
21
22 133 in placebo control surgical trials (IRR [95% CI] 0.64 [0.52-0.79], p<0.001).

23 134

24 135 **Conclusions**

25 136 Placebo control trials of surgery have similar recruitment issues but higher attrition compared
26
27 137 with non-operative (non-placebo) control trials. Study design should incorporate strategies
28
29 138 such as increased timepoints for given follow-up duration to mitigate losses to follow and
30
31 139 dropout.

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3 **144 Strengths and limitations of this study**

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5 **145** • The difficulties of participant recruitment and high attrition experienced by placebo
6
7 **146** control trials evaluating efficacy of any surgical intervention has not been empirically
8
9 **147** explored previously.
10
11 **148** • This is the first study to quantify the difficulties of conducting placebo controlled
12
13 **149** trials of surgery, and offer strategies to mitigate these issues in future trials.
14
15 **150** • To minimise bias, data was extracted independently by pairs of investigators and
16
17 **151** arbitrated by a third investigator if necessary.
18
19 **152** • Findings limited by missing data and non-reporting of recruitment (N=42 studies) or
20
21 **153** attrition (N=4 studies) data.
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23 **154** • The relatively small amount of placebo-controlled surgical trials published in the
24
25 **155** literature, limit the certainty of our evaluations.
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161 **Introduction**

162 Placebo control trials are the gold standard for determining the true therapeutic effect of
163 interventions¹. However, placebo trials commonly face difficulties in participant recruitment
164 due to a lack of willingness to participate especially in surgical placebo trials due to its
165 inherently invasive nature and higher risks of anaesthetic adverse events and infection²⁻⁴.

166

167 Invasive and lengthy procedural processes in surgical trials may also lead to participant
168 attrition⁵⁻⁷. Attrition refers to losses in participant information either due to drop-out or
169 missing data over the duration of a longitudinal study⁸. These losses can create imbalances in
170 study groups introducing bias and reduced statistical power secondary to a smaller sample
171 size^{8,9}.

172

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

178

179 **Methods**

180 *Design*

181 We performed a meta-epidemiological study and registered the protocol in the PROSPERO
182 International Prospective Register of Systematic Reviews (CRD42019117364). We followed
183 the reporting guidance of Preferred Reporting Items for Systematic Reviews and Meta-
184 Analyses (PRISMA)¹⁰.

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6 187 *Inclusion criteria and eligible study identification*

7 188 This study included randomised controlled trials incorporating a placebo control to evaluate
8
9 189 the efficacy of any surgical intervention, and randomised trials comparing the effectiveness
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11 190 of the same surgical intervention with non-operative controls. The latter may comprise either
12
13 191 standard care or no treatment. Trials were excluded if they were not evaluating the same
14
15 192 surgical effect as the corresponding placebo control trial, e.g. the non-operative control group
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17 193 received co-interventions not provided to the surgical group.

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24 195 Surgery was defined as any invasive procedure that allows access to internal anatomy for
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26 196 example through a skin incision. The surgical placebo is ill-defined and can vary in fidelity
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28 197 but was defined as any “imitation procedure” differentiated by the patient, that lacks the key
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30 198 surgical element(s)¹¹.

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35 200 This study involves the search strategy and eligibility criteria from a related publication by
36
37 201 Karjalainen et al (2022)¹². Detailed data on the search strategy and eligibility criteria
38
39 202 (including the PRISMA diagram of included studies) are available via the supplementary files
40
41 203 of Karjalainen et al (2022)¹².

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47 205 Our search included eligible placebo control trials from a published systematic review by
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49 206 Wartolowska et al (2014)¹ as well as an extension of its search until 21st November 2018.
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51 207 We also searched the reference lists of included studies for additional eligible studies. To
52
53 208 identify relevant effectiveness trials (incorporating non-blinded non-operative controls),
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55 209 relevant Cochrane reviews assessing the index surgical procedure were identified and their
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57 210 literature searches were also extended to March 13 to March 15, 2019. Where no relevant
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3 211 Cochrane review was identified, a search algorithm was devised and applied to the Cochrane
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5 212 Central Register of Controlled Trials (CENTRAL), MEDLINE and Embase from their
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7 213 inception until the same date of search. To determine eligibility, pairs of authors
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9 214 independently completed title/abstract screening (TK, SA) followed by full-text review (PN,
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11 215 SM, LH, MM, SA).

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15 217 *Data extraction*

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17 218 All data were extracted independently by pairs of investigators (PN, SM, LH, MM), and
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19 219 arbitrated by a third investigator (SA) if necessary. Extracted data from included trials
20
21 220 included year of publication, participant characteristics (age, sex), sample size, condition,
22
23 221 intervention type (open or minimally invasive/percutaneous surgery), planned length of
24
25 222 follow-up and number of follow up timepoints.

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29 224 *Primary and secondary outcome measures*

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31 225 Primary outcomes were participant recruitment and attrition. These outcomes were assessed
32
33 226 in terms of *recruitment rate* (number of participants enrolled, as a proportion of those
34
35 227 eligible) and *overall attrition rate* (composite of dropout, loss to follow-up and cross-overs,
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37 228 expressed as proportion of total sample size).

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41 230 Secondary measures included the *participant cross-over rate*, defined as an unplanned
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43 231 protocol violation resulting in participants in the control group receiving the intervention, and
44
45 232 vice versa; and *participant dropout*, defined as an inability for the participant to progress
46
47 233 further with the study. These were both reported as a proportion of total number recruited.
48
49 234 Finally we also included *participant loss to follow-up*, defined as the inability of investigators

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2 235 to obtain information at planned timepoints for reasons other than participant dropout. Where
3 236 available, these components of attrition were characterised at each follow-up timepoint.
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10 238 *Statistical Analyses*
11
12 239 The extracted data were tested for heterogeneity and random effect meta-analysis was used to
13 summarise attrition rates (overall, dropout, loss to follow up, and cross over) in placebo vs.
14
15 240 non-operative control trials, stratified by trial groups. Due to the nature of the data (with
16 varying follow-up duration), a Generalized Linear Latent and Mixed (GLLAM) Model was
17
18 242 employed for random effect Poisson regression to examine Incidents Rate Ratio (IRR) and
19 Incident Rate Differences, while controlling for potential covariates: participant gender,
20 intervention type (placebo or non-operative control), follow-up duration and number of
21
22 243 follow-up timepoints. Descriptive statistics were used to summarise key aspect of the selected
23 studies. The 'metaprop' command in Stata 16 was used to estimate pooled recruitment and
24 attrition rates, stratified by study type (placebo vs non-operative control). Overall recruitment
25 and attrition rates were the primary outcomes used for this analysis. To account for between
26 studies heterogeneity all analyses were based on the random effect model.
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28 251
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30 252 All trials with attrition and recruitment data were included in analyses. However, reporting
31 biases were suspected in studies with 0% attrition and 100% recruitment and therefore
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33 253 sensitivity analyses excluding these studies were performed.
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35 255
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37 256 Funnel plot and Egger's test were used to assess publication bias, while meta regression was
38 used to examine for the effect of covariates. Risk of bias was assessed according to Cochrane
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40 257 Risk of Bias Tool v. 1.0. and detailed in a related publication by Karjalainen et al (2022)¹².
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Results

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261 A total of 62 placebo control trials and 38 trials with non-operative controls (100 trials
262 overall) identified. 99 studies were included in the quantitative analysis (1 placebo control
263 trial excluded due to unavailable full text at search date¹³). Detailed data on these included
264 studies has been included in Appendix 1. Study cohorts were comparable between placebo
265 and non-operative control trials, however, time to the primary outcome was shorter in studies
266 with placebo controls (365 vs 274 days, p=0.006) (Table 1). No significant covariates were
267 identified in meta-regression analyses (Appendix 2).

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269

Participant Recruitment

270 Recruitment rate was available for 57 out of 99 included studies (36 (59.0%) placebo and 21
271 (55.3%) non-operative controls, respectively) and ranged between 9.3% to 100%.

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273 The random effect pooled rate was similar between placebo and non-operative control trials
274 (rate [95% CI]: 76.9% [95% CI 71.1%-82.7%] vs 77.6% [95% CI 66.7%-88.4%],
275 respectively, p=0.915). This included 10/36 (27.8%) placebo and 3/21 (14.3%) non-operative
276 control studies with 100% recruitment rates. When these studies were excluded, the adjusted
277 recruitment rates decreased to 68.7% [59.3%-78.1%] in the placebo and 74.1% [58.6%-
278 89.5%] in the non-operative controlled studies respectively, with no between-group
279 heterogeneity ($I^2=95\%$, p=0.562).

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Participant Attrition

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

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3 285 Median (IQR) attrition rates were lower in placebo trials (12.4% [6.1-29.8%]) compared to
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5 286 non-operative control trials (20.7% [9.1-33.3%]) however these did not reach statistical
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7 287 significance. These results also comprised 5/59 (8.5%) sham/placebo arm studies and 2/36
8
9 288 (5.6%) of open-label studies with no participant attrition. For studies with attrition, the
10
11 289 random effect pooled overall attrition (rate [95% CI]) did not differ significantly between
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13 290 placebo (21.2% [17.2% - 25.2%]) and non-operative (23.7% [18.8% - 28.6%]) controlled
14
15 291 studies ($p=0.811$). This was also true for discrete components of attrition including loss to
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17 292 follow-up, drop-out and cross-over rates (Appendix 3).
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26 294 *Poisson Analysis*
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28 295 The median (IQR) number of follow up timepoints (4 [3-5.5] and 3.5 [2-6], $p=0.748$) were
29
30 296 similar between non-operative and placebo control trials respectively. Longest follow-up
31
32 297 timepoint was also similar (365 [319.5-730] and 365 [183-456] days, $p=0.143$) However, the
33
34 298 follow-up time to the primary endpoint was significantly longer in non-operative control
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36 299 trials (365 [183-730] vs 274 [91-365] days, $p=0.06$).
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41 301 Following correction for covariates especially the varied study durations, Poisson regression
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43 302 analyses showed significant between-group differences in the rates of dropouts, loss to
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45 303 follow-up and attrition (Table 2). Poisson regression demonstrated a higher attrition rate in
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47 304 placebo trials compared to non-operative control trials (IRR 1.8 [95% CI 1.1-3.0], $p=0.032$)
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49 305 and was predominantly seen in the medium term (500 days). The higher attrition rate in
50
51 306 placebo trials was due to higher loss to follow-up (IRR 2.6 [95% CI 1.04-6.3], $p=0.042$) and
52
53 307 higher dropout (IRR 3.5 [95% CI 1.1-11.3], $p=0.037$) as seen in Figure 1.
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3 309 The incorporation of just one additional follow-up timepoint point (regardless of length of
4 follow up i.e. increased frequency of visits) is associated with a reduction in attrition (IRR
5 [95% CI] of 0.64 [0.52-0.79], p<0.001) in placebo control surgical trials, largely driven by
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7 311 [95% CI] of 0.68 [0.52-0.89], p=0.004).
8
9 312 fewer losses to follow-up (IRR [95% CI] of 0.68 [0.52-0.89], p=0.004).
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11 313
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14 314 *Publication Bias*
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16
17 315 Egger test (p< 0.001) indicated the presence of publication bias with the majority of included
18 studies having low attrition rates (Appendix 4). Publication bias was greater in placebo
19 control trials compared to trials of non-operative trials (Appendix 5, 6).
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22 317
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27 319 **Discussion**
28
29 320 This review demonstrates key differences in participant recruitment and retainment when
30 comparing placebo-control and non-operative (non-placebo) control randomised trials of
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32 surgery. After adjustment for the number of follow-up timepoints and study duration, attrition
33 losses were almost twice as high in placebo control compared to non-operative control trials.
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35 323
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37 324 This was primarily driven by participant follow-up losses and drop-outs.
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43 326 *Participant Recruitment*
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45
46 327 Surgical randomised controlled trials can face recruitment rates as low as 8% ¹⁴, due to
47 patients frequently failing to meet eligibility criteria for a small and specific target
48 populations ^{3,15}. Addition of a placebo component further exacerbates this problem by
49 undermining willingness to participate ^{4,16,17}. Participant surveys suggest this unwillingness
50 stems from common perceptions that invasive surgical placebos are associated with greater
51 risks (e.g., infection) ^{17,18}. Previous trials such as Hare *et al.* ⁴, which reported participant
52 concerns regarding the possibility of receiving placebo surgery being the most common
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3 334 reason (38%) for non-participation despite eligibility. Contrary to these expectations, our
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5 335 results demonstrated no significant difference in recruitment rate between placebo control
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7 336 and non-operative control trials. Our findings may be biased by sampling from published
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9 literature, with the non-representation of placebo control surgery trials that experienced
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11 337 stoppage and/or early-termination due to recruitment failure.
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17 340 *Participant Attrition*

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19 341 Our findings suggest placebo control surgery trials experience a two-fold higher attrition rate
20
21 342 (when considering cross-overs, drop-outs and follow-up losses) compared to non-operative
22
23 343 control surgery trials, after adjusting for the duration and number of follow-up timepoints.
24
25 344 One possible cause for higher attrition rates in placebo control trials could be early
26
27 345 unblinding. It is well-known that rigorous blinding is required to maintain equipoise (and
28
29 346 fidelity) in placebo control surgery trials to ensure participant retention^{11,19,20}. Metanalysis by
30
31 347 Hróbjartsson et al., found nonblinded control groups suffer from 79% higher risk of drop-outs
32
33 348 and 55% higher risk of co-intervention use when compared to blinded control groups²¹. The
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35 349 difficulties of appropriate blinding (and maintaining fidelity), especially in the context of not
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37 350 receiving treatment with persisting symptoms, likely account for the higher rates of attrition
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39 351 in placebo control surgery trials when compared to other-control trials. Included trials in the
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41 352 present meta-analysis were published prior to development of the ASPIRE guidelines for
42
43 353 acceptable surgical placebos, and therefore did not report on the fidelity and blinding of their
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45 354 surgical placebos¹¹.

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50 356 Higher attrition rates in placebo control surgical trials were primarily driven by higher losses
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52 357 to follow-up and participant drop-out. With the inherent nature of surgical interventions being
53
54 a “one-time” irreversible change²², loss to follow-up and participant withdrawals may be
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3 359 higher when there is a long follow-up period with no concomitant treatments²³. This is
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5 360 typical of placebo surgery trials, whilst non-operative trials tend to involve comparators that
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7 361 require ongoing intervention (therefore facilitating parallel follow-up).
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12 363 We also found that differences in attrition rates between placebo and non-operative control
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14 364 trials of surgery arise primarily in the medium term (~500 days), suggestive of a 'participant
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16 365 demotivation' phenomenon that develops over moderate to longer-term study participation²⁴
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18 366²⁸. Participant demotivation seems to be accelerated in placebo control trials, with the
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20 presence of additional uncertainty regarding potential allocation of a 'surgical placebo'. This
21
22 367 demotivation likely peaks following the short-term optimism initially present at enrolment
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24 368 into a placebo control surgery trial. Moreover, the finding of additional follow-up timepoints
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26 369 correlating with a reduction in attrition suggests frequent follow-up timepoints may enable
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28 370 ongoing contact and thus participant retention, as positive relationships between participants
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30 371 and trial staff are fostered^{27,29}.
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35 373
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38 374 *Publication Bias*
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40 375 Trial discontinuation and non-publication is common and occurs more frequently in surgical
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42 376 than medical trials³⁰⁻³⁴. Publication bias, or the selective submission or acceptance of a study
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44 377 into literature as such^{35,36}, is a likely limitation of the present findings. The majority of
45
46 378 included studies had a small attrition rates overall, indicating non-publication of both placebo
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48 379 and non-operative control surgical trials with high attrition rates⁸.
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55 381 *Strengths and Weaknesses*
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57 382 This study has several major strengths including a protocol driven, pre-planned, meta-
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59 383 epidemiological design that included all published surgical placebo trials until November
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3 384 2018. Given our research question did not assess intervention effectiveness but rather
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5 385 described overall data from a methodological perspective, it is unlikely additional trials will
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7 386 change our conclusion. However, our findings are limited by missing data and non-reporting
8
9 387 of recruitment (N=42) or attrition data (N=4) in some trials. Thus, our findings may be an
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11 388 underestimation of the true difference in attrition rates between placebo surgery trials non-
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13 389 operative trials.
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19 391 *Implications and Future Research*
20
21 392 There is a need to investigate reasons why participant attrition occurs at a higher rate when
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23 393 placebo controls are employed in randomised trials of surgery. Future studies build upon
24
25 394 existing ASPIRE guidelines to explore the relationship between varying levels of placebo
26
27 395 fidelity and rates of attrition¹¹. Patient education and greater transparency may promote
28
29 396 confidence and willingness among eligible patients to participate. As such, future studies may
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31 397 also explore patient perceptions and attitudes towards placebo surgical procedures. Strategies
32
33 398 to maximise continuous patient engagement may include guaranteeing placebo-exposed
34
35 399 patients the surgical intervention if a statistically significant benefit is observed. This study
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37 400 also demonstrated that additional follow up timepoints are associated with less attrition, thus
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39 401 closer follow up is recommended in placebo control trials.
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47 403 **Conclusion**
48
49 404 Placebo control trials of surgery have higher attrition rates when compared to trials with non-
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51 405 operative (non-placebo) controls. Our findings suggest that the design of surgical placebo
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53 406 trials should incorporate strategies with one key strategy being more frequent follow-up (for a
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55 407 given duration of follow-up) to mitigate losses to follow and dropout.
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3 **409 Figure Legends**

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6 **410 Figure 1.** Poisson Regression of Median Attrition Rates (Drop-out, Loss to Follow-up,
7
8 Death, Overall Attrition) between placebo and non-operative controls.
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11 **412**

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13 **413 Appendix Legends**

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15 **414 Appendix 1.** Detailed data on included studies.
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18 **415**
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20 **416 Appendix 2.** Meta-regression for covariates including female proportion of study
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22 participants, number enrolled and number of follow-up points.
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25 **418**
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27 **419 Appendix 3:** Pooled (random effects) recruitment and attrition rates for studies with attrition
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29 > 0% and recruitment < 100%.
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32 **421**
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34 **422 Appendix 4.** Funnel Plot for All Included Trials. Effect sizes: 0 = 50%, +2 = ~88% and -2 =
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36 ~12 % attrition rate.
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39 **424**
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41 **425 Appendix 5.** Funnel Plot for Placebo Control Surgery Trials. Effect sizes: 0 = 50%, +2 =
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43 ~88% and -2 = ~12 % attrition rate.
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46 **427**
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48 **428 Appendix 6.** Funnel Plot for Non-Operative Control Surgery Trials. Effect sizes: 0 = 50%,
49
50 +2 = ~88% and -2 = ~12 % attrition rate.
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558 **Table 1: Participant and Follow-up Characteristics**

	Non-operative control	Placebo control	p-value
n	38	61	
Age of study cohorts (mean \pm 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 group¹	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);

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

SD = standard deviation, n = number of studies.

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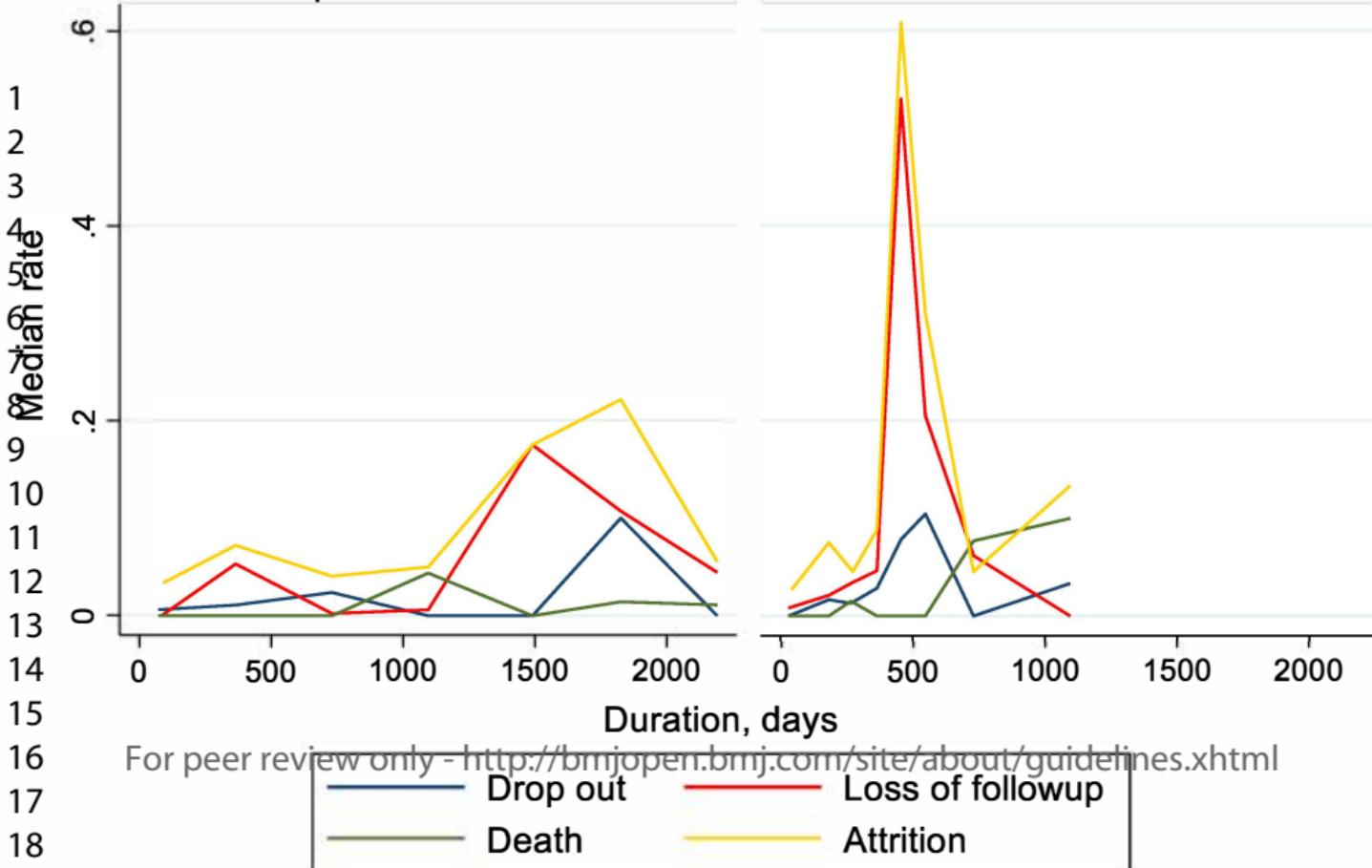
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3 575 **Table 2: Association between attrition rates and type of control group (placebo or non-**
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5 576 **operative) in surgical trials. Incident rate ratios (IRR) expressed for placebo control trials as a**
6
7 577 **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.

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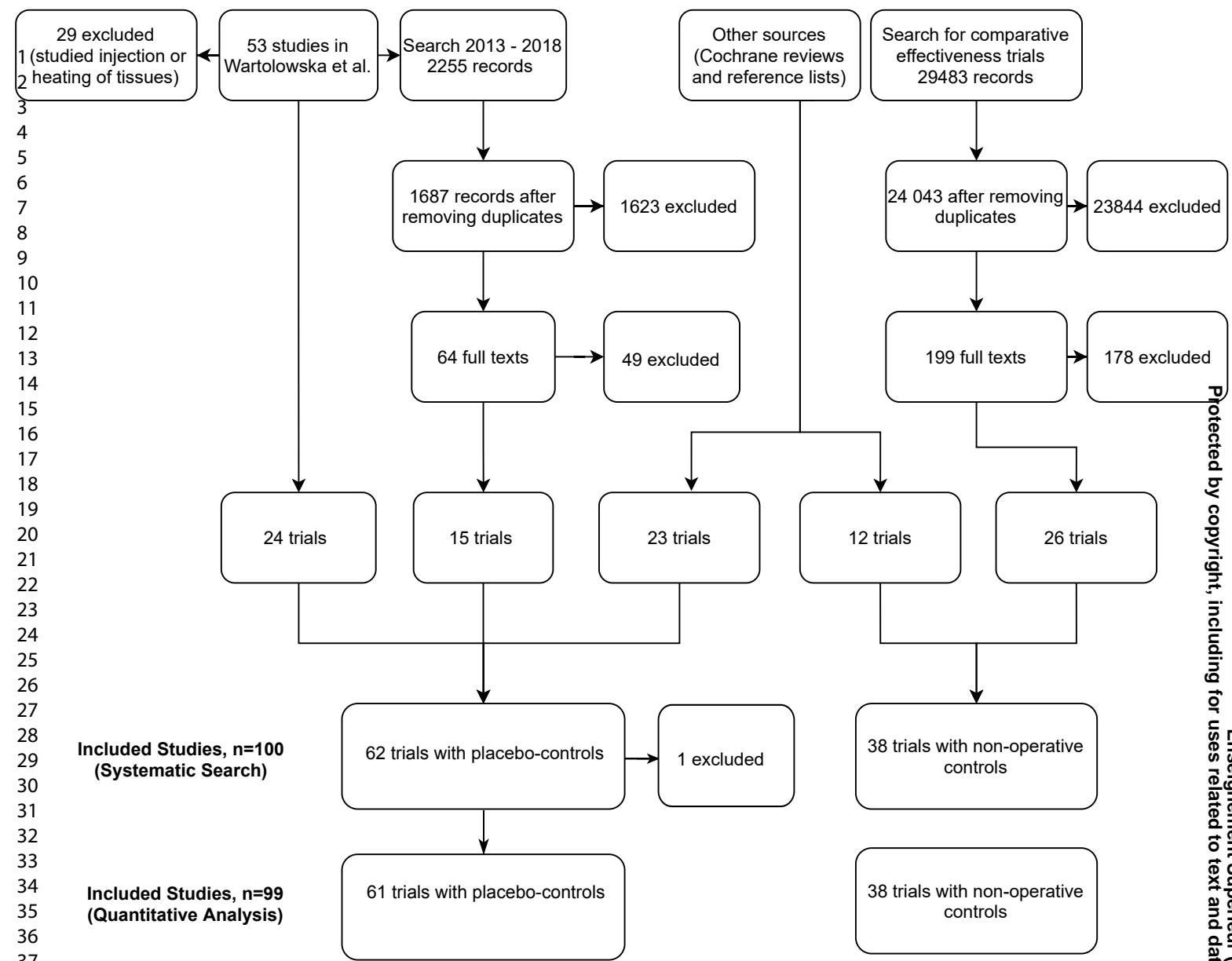


Figure 1. PRISMA flowchart of study selection

Table 1: Participant and Follow-up Characteristics

	n	Non-operative control	Placebo control	p-value
Age of study cohorts (mean \pm SD, n)				
Surgical intervention group				
		54.8 \pm 12.6, (n=34)	50.4 \pm 13.4, (n=55)	0.125
Control group				
		55.1 \pm 13.0, (n=34)	50.5 \pm 13.3, (n=55)	0.114
Other group¹				
		48 \pm 8, (n=3)	47.8 \pm 5.8, (n=4)	0.807
Gender of study cohorts (mean + SD)				
	% Female	62.7 \pm 24.8	61.8 \pm 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);

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

SD = standard deviation, n = number of studies.

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

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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.

		author	year	control	lot/lead_phase	prim_tps
1	1	Abbot	2004	1	0	183
2	2	Beard	2018	1	0	183
3	3	Buchbinder	2009	1	0	91
4	4	Cheong	2014	1	0	183
5	5	Clark	2016	1	0	14
6	6	Cobb	1959	1	0	274
7	7	Cotton	2014	1	1	365
8	8	Daniels	2009	1	0	365
9	9	Davys	2005	1	0	1
10	10	Dimond	1960	1	0	.
11	11	Eid	2014	1	0	365
12	12	Firanescu	2018	1	0	365
13	13	Freed	2001	1	0	365
14	14	Friedman	2008	1	0	91
15	15	Geenen	1989	1	0	1460
16	16	Gillespie	2011	1	0	91
17	17	Gross	2011	1	0	365
18	18	Gruber	2018	1	0	91
19	19	Guyuron	2009	1	0	365
20	20	Hansen	2016	1	0	91
21	21	Hunter	2015	1	0	183
22	22	Hakansson	2015	1	0	183
23	23	Ikramuddin	2014	1	0	365
24	24	Jarrel	2005	1	1	365
25	25	Johnson	2004	1	0	365
26	26	Kalapala	2018	1	0	91
27	27	Kallmes,	2009	1	0	30
28	28	Koutzourelakis	2008	1	0	106
29	29	Kroslak	2018	1	0	183
30	30	Kupsch	2006	1	0	91
31	31	Landorf	2013	1	0	42
32	32	Lee	2001	1	0	91
33	33	LeWitt	2011	1	1	183
34	34	Lichten	1987	1	0	365
35	35	Marks	2010	1	1	365
36	36	Maurer	2012	1	0	91
37	37	Moini	2012	1	0	274
38	38	MONTGOMERY	2006	1	0	365
39	39	Moseley	1996	1	1	183
40	40	Moseley	2002	1	1	730
41	41	Moseley	2002	1	1	730
42	42	Olanow	2015	1	1	456
43	43	Olanow	2003	1	0	730
44	44	Roehrborn	2013	1	0	91
45	45	Roos	2018	1	0	730

1	47	Rothstein	2006	1	0	91
2	48	Sarr	2012	1	0	365
3	49	Schroder	2017	1	0	730
4	50	Schwartz	2007	1	0	365
5	51	Shawki	2011	1	0	365
6	52	Sihvonen	2014	1	0	730
7	53	Steward	2008	1	0	91
8	54	Sullivan	2017	1	1	365
9	55	Sutton	1994	1	0	183
10	56	Swank	2003	1	0	365
11	57	Thompson	2013	1	1	183
12	58	Thomsen	1981	1	0	365
13	59	Toouli	2000	1	0	730
14	61	Volkman	2014	1	0	91
15	62	Wang	2016	1	0	1095
16	63	Wei	2012	1	0	91
17	64	Alkatout	2013	0	0	730
18	67	Blasco	2012	0	0	365
19	68	Brox	1993	0	1	183
20	69	Chen	2014	0	0	365
21	70	Chen	2014	0	0	183
22	71	Farfaras	2016	0	0	30
23	72	Farrokhi	2011	0	0	1095
24	73	Fuentes	2011	0	0	730
25	74	Gad	2012	0	0	548
26	75	Gauffin	2014	0	0	365
27	76	Guyuron	2004	0	1	365
28	77	Haahr	2005	0	0	365
29	78	Herrlin	2006	0	0	183
30	79	Katz	2013	0	1	183
31	80	Ketola	2009	0	0	730
32	81	Kirkley	2008	0	0	730
33	82	Klazen	2010	0	0	365
34	83	Marcoux	1997	0	0	274
35	84	Merchan	1993	0	0	1095
36	85	Miller	2016	0	0	365
37	86	Osteras	2012	0	1	91
38	87	Paavola	2018	0	0	730
39	88	Parazzini	1999	0	0	365
40	89	Peters	1992	0	0	365
41	90	Peters	1997	0	0	1460
42	90	Peters	1997	0	0	48
43	91	Rahme	1998	0	0	183
44	92	Rousing	2009	0	0	91
45	93	Schierlitz	2014	0	0	183
46	94	Siddle	2012	0	0	548

1	95	Spencer	1992	0	0	365
2	96	Stensrud	2015	0	0	730
3	97	Trad	2015	0	0	183
4	99	van de Graaf	2018	0	0	730
5	100	Van der Ploeg	2016	0	0	365
6	101	Witteman	2015	0	1	183
7	102	Yang	2016	0	0	365
8	103	Yim	2013	0	1	730
9	105	Silverberg	2002	0	1	365
10	106	Silverberg	2008	1	1	274
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	long_tps	total_tps	n_tps	plan Samp le	ndom_samp	alyse_samp	n_female
1	365	183, 365	2	50	52	39	39
2	365	183, 365	2	300	313	274	158
3	730	, 91, 183, 365	6	164	78	73	62
4	365	91, 183, 365	3	100	50	43	50
5	183	14, 30, 91, 18	5	120	120	112	88
6	456	274, 456	2	.	17	17	5
7	365	1, 183, 274, 36	4	214	214	173	197
8	1825	365, 730, 109	6	420	487	379	487
9	1	1	1	38	38	37	33
10	365	.	.	.	18	18	.
11	365	183, 213, 24	12	150	90	74	83
12	365	, 30, 91, 183,	6	180	180	176	133
13	365	122, 243, 365	3	.	40	39	19
14	91	14, 91	2	60	62	62	29
15	1460	55, 730, 1095,	5	.	47	47	45
16	91	91	1	100	51	50	8
17	1825	61, 91, 183, 2	7	68	76	67	24
18	183	91, 183	2	48	25	23	21
19	365	1, 183, 274, 36	4	.	76	75	.
20	52	46	.
21	183	14, 91, 198	3	120	129	129	66
22	183	183	1	.	44	44	20
23	1825	, 152, 183, 21	18	233	239	239	203
24	365	1, 183, 274, 36	4	100	29	16	29
25	365	1, 91, 365	3	130	123	123	123
26	13	.	.
27	91	3, 14, 30, 91	4	250	131	128	99
28	122	91, 122	.	48	49	47	19
29	913	42, 84, 183, 9	5	80	26	26	19
30	183	91, 183	2	40	40	40	13
31	42	14, 21, 28, 34,	6	80	80	80	50
32	730	183, 274, 36	8	90	68	.	68
33	183	30, 91, 183	3	40	45	37	10
34	365	91, 365	2	.	21	21	21
35	548	83, 274, 365,	7	51	58	57	15
36	91	91	1	.	22	20	22
37	274	274	1	146	146	76	146
38	365	46, 91, 365	3	.	46	43	31
39	183	5, 46, 91, 183	4	10	10	9	0
40	730	91, 183, 365, 5	7	180	180	165	13
41	730	91, 183, 365, 5	7	180	180	165	13
42	730	74, 365, 456,	9	52	51	47	16
43	730	74, 365, 456,	9	.	34	31	10
44	91	14, 30, 91	3	.	206	206	0
45	730	91, 730	2	100	44	42	21

1	548	91,183,548	3	.	7	6	3
2	730	91, 365, 730	3	140	140	140	54
3	183	14, 91, 183	3	42	63	60	33
4	730	l, 183, 365, 73	4	320	321	289	161
5	365	365	1	320	91	89	91
6	365	30, 91, 183, 3	5	120	60	57	22
7	365	30, 91, 183, 3l	5	96	135	107	69
8	730	l, 183, 365, 73	4	108	108	102	81
9	365	l, 183, 274, 36	4	.	29	23	14
10	274	0, 91, 183, 27	4	256	230	164	95
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	age_int1	age_int2	age_int3	n_screened	n_eligible	n_enrolled	recruit_rate
1	32.1	32.1	.	.	168	52	30.952381
2	52.9	53.7	53.2	2975	740	313	42.2972973
3	74.2	78.9	.	468	219	78	35.6164384
4	31	30	.	.	94	50	53.1914894
5	80	81	.	302	154	120	77.9220779
6	64	54	.	.	.	17	.
7	38	39	.	1584	286	214	74.8251748
8	30.6	30.5	.	592	487	487	100
9	60.2	57.5	.	55	51	38	74.5098039
10	18	.
11	51	50	.	763	275	90	32.7272727
12	74.7	76.9	.	1280	336	180	53.5714286
13	57.5	57.5	.	.	.	40	.
14	48.1	39	.	112	80	62	77.5
15	49	49	.	289	51	47	92.1568627
16	52.3	51.1	.	.	.	51	.
17	56.4	55.4	.	157	83	76	91.5662651
18	62	55.1	.	29	25	25	100
19	45.1	44.6	.	317	76	76	100
20	52	.
21	52	55	.	696	.	129	.
22	41	62	.	121	63	44	69.8412698
23	47	47	.	420	327	239	73.088685
24	28.9	29.4	.	36	29	29	100
25	29.5	29	.	200	123	123	100
26
27	73.4	74.3	.	1813	431	131	30.3944316
28	39	37.6	.	.	51	49	96.0784314
29	53	51	.	.	27	27	100
30	40.5	38.4	.	60	48	40	83.3333333
31	71.8	73.3	.	157	.	80	.
32	57.2	56.9	.	.	.	68	.
33	61.8	60.6	.	66	49	45	91.8367347
34	.	.	.	39	21	21	100
35	60.1	57.3	.	.	.	58	.
36	48.9	53.3	.	.	.	22	.
37	27.8	27.7	.	160	.	146	.
38	42	41	.	.	.	46	.
39	10	.
40	51.2	52	53.6	.	324	180	55.5555556
41	53.6	52	51.2	.	324	180	55.5555556
42	59.7	58.7	.	.	.	51	.
43	58.75	58	.	.	.	34	.
44	67	65	.	430	220	206	93.6363636
45	47.2	46.4	.	586	68	44	64.7058824

1	48.1	46.3	.	.	.	159	.
2	46	46	.	503	.	294	.
3	42	40	40	445	118	118	100
4	45	47	47	.	.	60	.
5	30.25	31.9	.	280	.	190	.
6	52	52	.	.	205	146	71.2195122
7	47.2	51.5	.	968	100	100	100
8	44.2	45.3	.	587	.	332	.
9	29	29.5	.	.	.	74	.
10	45.4	47.8	.	121	103	100	97.0873786
11	47.6	47.6	.	358	129	77	59.6899225
12	49.9	53.9	.	.	30	30	100
13	81	.
14	57.1	56.6	.	85	77	62	80.5194805
15	29.25	38.75	.	207	.	12	.
16	63.4	62.2	.	517	.	337	.
17	.	.	.	523	499	450	90.1803607
18	71.33	75.27	.	219	125	125	100
19	48	48	47	444	155	125	80.6451613
20	64.63	66.49	.	.	.	96	.
21	.	.	.	64	28	28	100
22	52.4	49.9	48.9	95	.	87	.
23	72	74	.	105	84	82	97.6190476
24	60	.
25	41	.
26	54	54	.	179	155	150	96.7741935
27	43.4	42.9	.	.	.	125	.
28	44.3	44.5	.	.	.	90	.
29	56	56	.	180	99	90	90.9090909
30	59	57.8	.	14,430	1330	351	26.3909774
31	46.4	47.8	.	.	.	140	.
32	58.6	60.6	.	277	219	188	85.8447489
33	75.2	75.4	.	934	434	202	46.5437788
34	31	30	.	717	348	348	100
35	57	56	.	.	.	80	.
36	38.3	38.5	.	50	49	44	89.7959184
37	52.7	47	.	29	19	17	89.4736842
38	50.5	50.8	50.4	281	213	210	98.5915493
39	30.6	30.3	.	.	.	101	.
40	35.5	35.7	.	.	.	48	.
41	56	59	.	.	.	72	.
42	56	59	.	.	.	72	.
43	42	42	.	.	.	42	.
44	80	80	.	.	.	50	.
45	67	66	.	845	146	80	54.7945205
46	55.6	55.1	.	258	71	65	91.5492958

1	52	54.7	.	.	.	7	.
2	50.2	48.9	.	341	226	140	61.9469027
3	54.8	50.1	.	196	95	63	66.3157895
4	57.6	57.3	.	.	.	321	.
5	61	63.7	.	2000	.	91	.
6	42.4	49.3	.	.	.	60	.
7	77.1	76.2	.	158	153	135	88.2352941
8	54.9	57.9	.	162	157	108	68.7898089
9	71.4	73.5	.	529	313	29	9.26517572
10	74.5	74	.	394	277	230	83.032491
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	i1_tp1_dura	i1_tp1_drop	i1_tp1_follow	i1_tp1_death	i1_tp2_dura	i1_tp2_drop	i1_tp2_follow
1	365	4	0	0	.	.	.
2	183	6	10	0	365	0	12
3	7	0	1	0	30	0	3
4	0	.	.	.	91	.	.
5	3	1	2	0	14	2	3
6	61	0	0	1	.	.	.
7	274	.	17	.	365	.	14
8	365	5	51	0	.	.	.
9
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11	365	4	10	0	.	.	.
12	0	1	0	0	1	0	0
13	243	0	0	1	.	.	.
14	14	0	0	0	91	0	2
15
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17	14	0	0	0	30	0	0
18	91	1	0	0	183	1	0
19	91	2	.	.	183	.	.
20
21	0	6	0	0	198	4	1
22	183	0	1	0	.	.	.
23	0	5	0	0	365	1	9
24	76	1	1	0	167	0	6
25	1	0	1	0	91	0	2
26
27	30	.	1	.	91	.	4
28
29
30
31	42	0	1	0	.	.	.
32
33	0	6	0	0	.	.	.
34
35	365	2	0	2	.	.	.
36	91	0	1	0	.	.	.
37	274	16	19	0	.	.	.
38	46	.	.	.	91	.	.
39	91	1
40	14	.	2	.	46	.	5
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42	456	1	14	0	.	.	.
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2	91	6	9	0	.	.	.
3	365	12	2	0	.	.	.
4	91	.	1	.	183	.	.
5	91	0	4	0	365	2	1
6	365	0	9	0	.	.	.
7
8	7	0	0	0	30	0	0
9	365	7	7	0	.	.	.
10
11	12	.	1
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13	1095	1	0	1	.	.	.
14
15	91	1	1	.	183	.	.
16
17	91	0	2	0	365	0	1
18	152	10	3	0	.	.	.
19	0	7	.	.	14	.	6
20	91	0	14	0	183	0	4
21	365	0	4	0	.	.	.
22	183
23	30	6	2	1	168	0	2
24	7	0	0	0	61	0	0
25
26	0	9	0	0	.	.	.
27	0	4	0	0	2190	0	1
28	56	.	.	.	183	.	.
29	91	12	0	1	365	4	1
30	0	1	0	0	730	2	0
31	0	2	0	0	730	1	2
32	0	2	0	0	1	0	0
33	0	5	0	0	100	9	0
34	1095	0	0	5	.	.	.
35	0	.	.	.	7	.	.
36	0
37	0	17	0	0	730	0	0
38
39
40	365	0	6	0	730	0	0
41	183	0	0	0	365	0	0
42	91	0	1	1	.	.	.
43	183	0	0	2	1490	0	6
44	42	0	0	0	84	0	0

1	183	0	.	1	365	.	.
2	91	.	7	.	365	.	7
3	183	.	1
4	0	1	0	0	91	1	2
5	0	2	0	0	365	1	3
6	183	0	10	0	365	0	5
7	0	2	0	0	365	0	8
8	730	3	1	0	.	.	.
9	0	1	0	0	365	1	1
10	0	7	0	0	274	4	0
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	i1_tp2_death	i1_tp3_dura	i1_tp3_drop	1_tp3_follow	i1_tp3_death	i1_tp4_dura	i1_tp4_drop
1
2	0	91	0	1	1	183	0
3	.	183	.	3	.	.	.
4	0	30	2	1	0	91	1
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17	0	30	0	0	0	91	1
18
19	0
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21	0
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24	0	61	0	0	0	91	0
25	0
26	0
27	.	274	.	.	.	365	.
28
29	0
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32	0	548	13	27	0	.	.
33	0	259	0	1	0	350	0
34	0	365	0	10	0	.	.
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52	.	365
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54	.	91	.	4	.	183	.
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9	0	91	0	0	0	.	.
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21	0
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24	.	61	.	2	1	183	.
25	0
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29	0
30	0	183	0	0	0	365	0
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37	1
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40	0
41	0	1825	4	8	1	.	.
42	1
43	0	7	1	0	0	30	0
44	0
45	0
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47	.	30	.	.	.	62	.
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49	0
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59	0
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61	0	126	0	0	0	183	0

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1_tp4_follow1_tp4_deathi1_tp5_dura i1_tp5_dropi1_tp5_follow1_tp5_deathi1_tp6_dura

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For peer review only

i1_tp6_drop i1_tp6_follow i1_tp6_death i1_tp7_dura i1_tp7_drop i1_tp7_follow i1_tp7_death

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44	3	0	2	365	1	0	2
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48	.	.	.	243	.	.	.
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60	0	0	0	548	0	0	0

For peer review only

1 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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For peer review only

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	i1_tp9_death	i1_tp10_dura	i1_tp10_drop	i1_tp10_follow	i1_tp10_death	i2_tp1_dura	i2_tp1_drop
1	365	1
2	183	2
3	7	0
4	0	.
5	3	0
6	243	0
7	274	.
8	365	4
9	42	.
10	365	0
11	0	3
12	14	0
13	14	0
14	91	1
15	91	.
16	0	4
17	183	3
18	0	1
19	76	0
20	30	0
21	30	1
22
23	91	2
24	42	0
25	0	2
26	365	1
27	91	0
28	274	20
29	46	.
30	91	.
31	14	.
32	456	3
33	0	0
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1		91	9
2	.	365	4
3	.	91	.
4	.	91	0
5	.	365	0
6	.	24	0
7	.	7	0
8	.	365	4
9	.	12	.
10	.	1095	0
11	.	91	.
12	.	91	0
13	.	152	14
14	.	14	.
15	.	91	0
16	.	365	0
17	.	183	.
18	.	30	0
19	.	7	0
20	.	183	8
21	.	.	.
22	.	0	2
23	.	56	.
24	.	183	5
25	.	0	1
26	.	0	8
27	.	0	1
28	.	0	4
29	.	1095	0
30	.	0	.
31	.	730	2
32	.	.	.
33	.	.	.
34	.	.	.
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56	.	.	.
57	.	183	3
58	.	91	0
59	.	183	0
60	.	42	0

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2	91	.
3	183	.
4	0	1
5	0	1
6	183	0
7	0	3
8	730	0
9	0	2
10	0	8
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	i2_tp1_follow	i2_tp1_death	i2_tp2_dura	i2_tp2_drop	i2_tp2_follow	i2_tp2_death	i2_tp3_dura
1	0	0
2	7	0	365	1	7	0	.
3	3	0	30	0	1	1	91
4	.	.	91	.	.	.	183
5	4	0	14	0	2	0	30
6	0	1
7	13	.	365	.	9	.	.
8	48	0
9
10	.	1
11	2	0
12	0	0	1	0	0	0	30
13
14
15	.	1
16	2	0
17	0	0	91	0	5	0	.
18
19	0	0	91	0	5	0	.
20
21	0	0	30	0	0	0	61
22
23
24	0	0	30	0	0	0	.
25	0	0	183	1	0	0	.
26	.	.	183	.	.	.	274
27	.	.	183
28
29	0	0	198	9	1	0	.
30	1	0
31	0	0	365	6	4	0	548
32	3	0	167	0	2	0	259
33	0	0	91	0	1	0	365
34
35	1	0	91	.	2	.	.
36
37	0	0
38	1	0
39
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41	0	0
42	1	0
43
44	0	0
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46	0	0
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48	0	0
49	1	0
50	15	0
51	.	.	91	3	.	.	365
52	0
53	.	.	46	0	3	.	91
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55	13	0
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60	2	0	730	0	2	0	.

1	.	.	365	.	.	.	548
2	.	.	365	.	9	.	730
3	10
4	2
5	0	0	91	1	2	0	181
6	0	0	365	0	5	0	.
7	0	0
8	0	0	365	2	5	0	.
9	0	0
10	0	0	365	1	0	0	.
11	1	0
12	0	0	365	2	0	0	.
13	0	0	274	2	0	4	.
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i2_tp3_drop i2_tp3_follow i2_tp3_death i2_tp4_dura i2_tp4_drop 2_tp4_follow 2_tp4_death

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31	0	0	0	365	0	2	1
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41	10	7	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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44	91	5	0	1	183	5	0
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44	0	365	0	0	4
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47	.	243	.	.	.
48	304
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60	0	548	0	0	1

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1 i2_tp8_followi2_tp8_deathi2_tp9_dura i2_tp9_dropi2_tp9_followi2_tp9_deathi2_tp10_dura
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1	i2_tp10_drop2_tp10_follov2_tp10_death i3_tp1_dura i3_tp1_drop i3_tp1_followi3_tp1_death				
2	.	.	183	7	7
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23	.	152	1	1
24	.	.	.	0
25	.	91	0	8
26	.	.	.	0
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28	.	30	5	4
29	.	.	.	1
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1 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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1 i3_tp5_followi3_tp5_death i3_tp6_dura i3_tp6_drop i3_tp6_followi3_tp6_death i3_tp7_dura
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1 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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1 i3_tp9_dura i3_tp9_drop i3_tp9_follow i3_tp9_death i3_tp10_dura i3_tp10_drop i3_tp10_follow

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	3_tp10_deat	overall_drop	drop_rate	overall_follow	follow_rate	overall_death	death_rate
1	.	18	34.6153846	0	0	0	0
2	.	16	5.11182109	56	17.8913738	0	0
3	.	2	2.56410256	23	29.4871795	12	15.3846154
4	.	1	2	6	12	0	0
5	.	11	9.16666667	21	17.5	6	5
6	.	0	0	0	0	2	11.7647059
7	.	1	0.46728972	58	27.1028037	0	0
8	.	9	1.84804928	99	20.3285421	0	0
9	.	0	0	0	0	0	0
10	1	5.55555556
11	.	4	4.44444444	12	13.3333333	0	0
12	.	15	8.33333333	0	0	13	7.22222222
13	.	0	0	0	0	1	2.5
14	.	0	0	7	11.2903226	0	0
15	.	3	6.38297872	4	8.5106383	0	0
16	0	0
17	.	5	6.57894737	0	0	5	6.57894737
18	.	4	16	0	0	0	0
19	.	3	3.94736842
20	.	6	11.5384615	0	0	0	0
21	.	23	17.8294574	2	1.5503876	0	0
22	.	3	6.81818182	2	4.54545455	0	0
23	.	28	11.7154812	62	25.9414226	0	0
24	.	1	3.44827586	14	48.2758621	0	0
25	.	0	0	21	17.0731707	0	0
26
27	.	1	0.76335878	8	6.10687023	0	0
28	.	2	4.08163265	0	0	0	0
29	.	1	3.7037037	0	0	0	0
30	.	2	5	0	0	0	0
31	.	0	0	7	8.75	0	0
32	.	10	14.7058824	1	1.47058824	2	2.94117647
33	.	8	17.7777778	0	0	0	0
34	.	0	0	0	0	0	0
35
36	.	0	0	2	9.09090909	0	0
37	.	36	24.6575342	34	23.2876712	0	0
38	.	3	6.52173913	0	0	0	0
39	.	1	10	0	0	.	.
40	.	15	8.33333333	0	0	0	0
41
42	.	1	2.94117647	0	0	2	5.88235294
43	.	0	0	0	0	0	0
44	.	14	31.8181818	4	9.09090909	0	0

1	.	16	10.0628931	12	7.54716981	0	0
2	.	16	5.44217687	3	1.02040816	0	0
3	.	0	0	13	11.0169492	0	0
4	.	7	11.6666667	11	18.3333333	0	0
5	.	0	0	19	10	0	0
6	.	0	0	1	0.68493151	1	0.68493151
7	.	0	0	0	0	0	0
8	.	11	3.31325301	19	5.72289157	0	0
9	.	8	10.8108108	3	4.05405405	0	0
10	.	2	2	2	2	0	0
11	0	0
12	.	1	3.33333333	0	0	3	10
13	.	1	1.2345679	1	1.2345679	0	0
14	.	1	1.61290323	3	4.83870968	0	0
15	.	0	0	0	0	0	0
16	.	0	0	10	2.96735905	0	0
17	.	25	5.55555556	15	3.33333333	0	0
18	.	10	8	17	13.6	9	7.2
19	.	4	3.2	30	24	0	0
20	.	0	0	7	7.29166667	0	0
21
22	.	11	12.6436782	26	29.8850575	2	2.29885057
23	.	0	0	3	3.65853659	3	3.65853659
24	.	8	13.3333333
25	0	0
26	.	9	7.2	8	6.4	0	0
27	.	6	6.66666667	4	4.44444444	1	1.11111111
28	.	6	6.66666667
29	.	26	7.40740741	3	0.85470085	2	0.56980057
30	.	22	15.7142857	15	10.7142857	2	1.42857143
31	.	11	5.85106383	8	4.25531915	1	0.53191489
32	.	24	11.8811881	0	0	11	5.44554455
33	.	30	8.62068966	0	0	0	0
34	.	0	0	0	0	7	8.75
35	.	1	2.27272727	4	9.09090909	0	0
36	.	0	0	0	0	0	0
37	.	22	10.4761905	1	0.47619048	1	0.47619048
38	.	5	4.95049505	2	1.98019802	0	0
39	.	0	0	0	0	0	0
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42	.	3	7.14285714	1	2.38095238	0	0
43	.	0	0	1	2	2	4
44	.	0	0	18	22.5	2	2.5
45	.	0	0	0	0	1	1.53846154

1	.	0	0	0	0	1	14.2857143
2	.	16	11.4285714	31	22.1428571	0	0
3	.	0	0	3	4.76190476	0	0
4	.	31	9.65732087	40	12.4610592	1	0.31152648
5	.	4	4.3956044	9	9.89010989	0	0
6	.	0	0	15	25	0	0
7	.	7	5.18518519	13	9.62962963	0	0
8	.	3	2.77777778	2	1.85185185	0	0
9	.	5	17.2413793	1	3.44827586	1	3.44827586
10	.	72	31.3043478	0	0	7	3.04347826
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	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	

1	17.6100629	28	17.6100629
2	6.46258503	0	0	0	0	19	6.46258503
3	11.0169492	20	0	20	16.9491525	33	27.9661017
4	30	30	.	30	50	48	80
5	10	19	10
6	0.68493151	5	0	5	3.42465753	7	4.79452055
7	0	0	0	0	0	0	0
8	9.03614458	30	9.03614458
9	14.8648649	0	0	0	0	11	14.8648649
10	4	2	0	2	2	6	6
11	.	0	2	2	2.5974026	10	12.987013
12	3.33333333	0	0	0	0	4	13.3333333
13	2.4691358	2	2.4691358
14	6.4516129	0	0	0	0	4	6.4516129
15	0	0	0	0	0	0	0
16	2.96735905	9	2	11	3.26409496	21	6.23145401
17	8.88888889	40	8.88888889
18	21.6	0	0	0	0	36	28.8
19	27.2	0	26	26	20.8	60	48
20	7.29166667	4	0	4	4.16666667	11	11.4583333
21
22	42.5287356	3	0	3	3.44827586	42	48.2758621
23	3.65853659	20	0	20	24.3902439	26	31.7073171
24	8	13.3333333
25
26	.	16	9	25	16.6666667	73	48.6666667
27	13.6	17	13.6
28	11.1111111	11	0	11	12.2222222	22	24.4444444
29	.	3	0	3	3.33333333	9	9.09090909
30	8.26210826	59	9	68	19.3732194	99	28.2051282
31	26.4285714	18	12	30	21.4285714	88	62.8571429
32	10.106383	0	6	6	3.19148936	26	13.8297872
33	11.8811881	10	6	16	7.92079208	51	25.2475248
34	8.62068966	0	0	0	0	30	8.62068966
35	0	0	0	0	0	7	8.75
36	11.3636364	0	0	0	0	5	11.3636364
37	0	0	0	0	0	0	0
38	10.952381	8	0	8	3.80952381	55	26.1904762
39	6.93069307	7	6.93069307
40	0	0	0	0	0	0	0
41	24	33.3333333
42	32	44.4444444
43	9.52380952	13	0	13	30.952381	17	40.4761905
44	2	0	0	0	0	3	6
45	22.5	0	0	0	0	20	25
46	0	0	0	0	0	6	9.23076923

1	0	0	0	0	0	1	14.2857143
2	33.5714286	13	0	13	9.28571429	60	42.8571429
3	4.76190476	0	0	0	0	3	4.76190476
4	22.1183801	47	8	55	17.1339564	127	39.5638629
5	14.2857143	13	14.2857143
6	25	20	0	20	33.3333333	35	58.3333333
7	14.8148148	8	0	8	5.92592593	28	20.7407407
8	4.62962963	1	0	1	0.92592593	6	5.55555556
9	20.6896552	0	0	0	0	7	24.137931
10	31.3043478	0	0	0	0	79	34.3478261
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	opped_recruminated_follitrition_reasc	retainment
1	0	1
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25	0	6
26	0	6
27	0	6
28	0	3
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34	1	.
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37	1	.
38	0	0
39	0	3
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		author	year	control	lot/lead_phas	prim_tps
1	2	Abbot	2004	1	0	183
3	4	Beard	2018	1	0	183
5	6	Buchbinder	2009	1	0	91
7	8	Cheong	2014	1	0	183
9	10	Clark	2016	1	0	14
11	12	Cobb	1959	1	0	274
13	14	Cotton	2014	1	1	365
15	16	Daniels	2009	1	0	365
17	18	Davys	2005	1	0	1
19	20	Dimond	1960	1	0	.
21	22	Eid	2014	1	0	365
23	24	Firanescu	2018	1	0	365
25	26	Freed	2001	1	0	365
27	28	Friedman	2008	1	0	91
29	30	Geenen	1989	1	0	1460
31	32	Gillespie	2011	1	0	91
33	34	Gross	2011	1	0	365
35	36	Gruber	2018	1	0	91
37	38	Guyuron	2009	1	0	365
39	40	Hansen	2016	1	0	91
41	42	Hunter	2015	1	0	183
43	44	Hakansson	2015	1	0	183
45	46	Ikramuddin	2014	1	0	365
47	48	Jarrel	2005	1	1	365
49	50	Johnson	2004	1	0	365
51	52	Kalapala	2018	1	0	91
53	54	Kallmes,	2009	1	0	30
55	56	Koutzourelakis	2008	1	0	106
57	58	Kroslak	2018	1	0	183
59	60	Kupsch	2006	1	0	91
		Landorf	2013	1	0	42
		Lee	2001	1	0	91
		LeWitt	2011	1	1	183
		Lichten	1987	1	0	365
		Marks	2010	1	1	365
		Maurer	2012	1	0	91
		Moini	2012	1	0	274
		MONTGOMERY	2006	1	0	365
		Moseley	1996	1	1	183
		Moseley	2002	1	1	730
		Moseley	2002	1	1	730
		Olanow	2015	1	1	456
		Olanow	2003	1	0	730
		Roehrborn	2013	1	0	91
		Roos	2018	1	0	730

1	47	Rothstein	2006	1	0	91
2	48	Sarr	2012	1	0	365
3	49	Schroder	2017	1	0	730
4	50	Schwartz	2007	1	0	365
5	51	Shawki	2011	1	0	365
6	52	Sihvonen	2014	1	0	730
7	53	Steward	2008	1	0	91
8	54	Sullivan	2017	1	1	365
9	55	Sutton	1994	1	0	183
10	56	Swank	2003	1	0	365
11	57	Thompson	2013	1	1	183
12	58	Thomsen	1981	1	0	365
13	59	Toouli	2000	1	0	730
14	61	Volkman	2014	1	0	91
15	62	Wang	2016	1	0	1095
16	63	Wei	2012	1	0	91
17	106	Silverberg	2008	1	1	274

	long_tps	total_tps	n_tps	plan_sampi	indom_sampi	analysed_sampi	n_female
1	365	183, 365	2	50	52	39	39
2	365	183, 365	2	300	313	274	158
3	730	1, 91, 183, 365,	6	164	78	73	62
4	365	91, 183, 365	3	100	50	43	50
5	183	, 14, 30, 91, 18	5	120	120	112	88
6	456	274, 456	2	.	17	17	5
7	365	1, 183, 274, 36	4	214	214	173	197
8	1825	, 365, 730, 109	6	420	487	379	487
9	1	1	1	38	38	37	33
10	365	.	.	.	18	18	.
11	365	, 183, 213, 243	12	150	90	74	83
12	365	, 30, 91, 183, :	6	180	180	176	133
13	365	122, 243, 365	3	.	40	39	19
14	91	14, 91	2	60	62	62	29
15	1460	55, 730, 1095,	5	.	47	47	45
16	91	91	1	100	51	50	8
17	1825	61, 91, 183, 2	7	68	76	67	24
18	183	91, 183	2	48	25	23	21
19	365	1, 183, 274, 36	4	.	76	75	.
20	52	46	.
21	183	14, 91, 198	3	120	129	129	66
22	183	183	1	.	44	44	20
23	1825	, 152, 183, 21:	18	233	239	239	203
24	365	1, 183, 274, 36	4	100	29	16	29
25	365	1, 91, 365	3	130	123	123	123
26	13	.	.
27	91	3, 14, 30, 91	4	250	131	128	99
28	122	91, 122	.	48	49	47	19
29	913	, 42, 84, 183, 9	5	80	26	26	19
30	183	91, 183	2	40	40	40	13
31	42	14, 21, 28, 34,	6	80	80	80	50
32	730	183, 274, 36	8	90	68	.	68
33	183	30, 91, 183	3	40	45	37	10
34	365	91, 365	2	.	21	21	21
35	548	83, 274, 365, :	7	51	58	57	15
36	91	91	1	.	22	20	22
37	274	274	1	146	146	76	146
38	365	46, 91, 365	3	.	46	43	31
39	183	15, 46, 91, 183	4	10	10	9	0
40	730	91, 183, 365, 5	7	180	180	165	13
41	730	91, 183, 365, 5	7	180	180	165	13
42	730	74, 365, 456, !	9	52	51	47	16
43	730	74, 365, 456, !	9	.	34	31	10
44	91	14, 30, 91	3	.	206	206	0
45	730	91, 730	2	100	44	42	21

1	91	91	1	.	159	144	69
2	365	152, 183, 213	15	222	294	253	165
3	730	1, 183, 365, 73	4	120	118	118	47
4	365	10, 91, 183, 365	4	60	60	57	24
5	365	91, 183, 365	3	.	190	171	190
6	730	1,183,365, 73	4	140	146	144	57
7	91	7, 30, 91	3	100	100	100	21
8	730	91, 183, 9, 274	7	.	332	332	296
9	183	91, 183	2	.	74	63	74
10	365	91,183,365	3	120	100	100	87
11	183	1, 183, 127, 91	6	132	77	.	73
12	1095	13, 213, 243, 2	13	.	30	30	12
13	730	183, 365, 548,	5	.	81	79	73
14	183	91, 183	2	60	62	62	35
15	1095	3, 365, 730, 10	4	.	12	12	2
16	365	91, 183, 365	3	300	337	327	337
17	274	10, 91, 183, 274	4	256	230	164	95
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	age_int1	age_int2	age_int3	n_screened	n_eligible	n_enrolled	recruit_rate
1	32.1	32.1	.	.	168	52	30.952381
2	52.9	53.7	53.2	2975	740	313	42.2972973
3	74.2	78.9	.	468	219	78	35.6164384
4	31	30	.	.	94	50	53.1914894
5	80	81	.	302	154	120	77.9220779
6	64	54	.	.	.	17	.
7	38	39	.	1584	286	214	74.8251748
8	30.6	30.5	.	592	487	487	100
9	60.2	57.5	.	55	51	38	74.5098039
10	18	.
11	51	50	.	763	275	90	32.7272727
12	74.7	76.9	.	1280	336	180	53.5714286
13	57.5	57.5	.	.	.	40	.
14	48.1	39	.	112	80	62	77.5
15	49	49	.	289	51	47	92.1568627
16	52.3	51.1	.	.	.	51	.
17	56.4	55.4	.	157	83	76	91.5662651
18	62	55.1	.	29	25	25	100
19	45.1	44.6	.	317	76	76	100
20	52	.
21	52	55	.	696	.	129	.
22	41	62	.	121	63	44	69.8412698
23	47	47	.	420	327	239	73.088685
24	28.9	29.4	.	36	29	29	100
25	29.5	29	.	200	123	123	100
26
27	73.4	74.3	.	1813	431	131	30.3944316
28	39	37.6	.	.	51	49	96.0784314
29	53	51	.	.	27	27	100
30	40.5	38.4	.	60	48	40	83.3333333
31	71.8	73.3	.	157	.	80	.
32	57.2	56.9	.	.	.	68	.
33	61.8	60.6	.	66	49	45	91.8367347
34	.	.	.	39	21	21	100
35	60.1	57.3	.	.	.	58	.
36	48.9	53.3	.	.	.	22	.
37	27.8	27.7	.	160	.	146	.
38	42	41	.	.	.	46	.
39	10	.
40	51.2	52	53.6	.	324	180	55.5555556
41	53.6	52	51.2	.	324	180	55.5555556
42	59.7	58.7	.	.	.	51	.
43	58.75	58	.	.	.	34	.
44	67	65	.	430	220	206	93.6363636
45	47.2	46.4	.	586	68	44	64.7058824

1							
2	48.1	46.3	.	.	.	159	.
3	46	46	.	503	.	294	.
4	42	40	40	445	118	118	100
5	45	47	47	.	.	60	.
6	30.25	31.9	.	280	.	190	.
7	52	52	.	.	205	146	71.2195122
8							
9	47.2	51.5	.	968	100	100	100
10							
11	44.2	45.3	.	587	.	332	.
12							
13	29	29.5	.	.	.	74	.
14	45.4	47.8	.	121	103	100	97.0873786
15							
16	47.6	47.6	.	358	129	77	59.6899225
17							
18	49.9	53.9	.	.	30	30	100
19	81	.
20	57.1	56.6	.	85	77	62	80.5194805
21							
22	29.25	38.75	.	207	.	12	.
23							
24	63.4	62.2	.	517	.	337	.
25							
26	74.5	74	.	394	277	230	83.032491
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	i1_tp1_dura	i1_tp1_drop	i1_tp1_follow	i1_tp1_death	i1_tp2_dura	i1_tp2_drop	i1_tp2_follow
1	365	4	0	0	.	.	.
2	183	6	10	0	365	0	12
3	7	0	1	0	30	0	3
4	0	.	.	.	91	.	.
5	3	1	2	0	14	2	3
6	61	0	0	1	.	.	.
7	274	.	17	.	365	.	14
8	365	5	51	0	.	.	.
9
10	365	4	10	0	.	.	.
11	0	1	0	0	1	0	0
12	243	0	0	1	.	.	.
13	14	0	0	0	91	0	2
14
15
16	14	0	0	0	30	0	0
17	91	1	0	0	183	1	0
18	91	2	.	.	183	.	.
19
20	0	6	0	0	198	4	1
21	183	0	1	0	.	.	.
22	0	5	0	0	365	1	9
23	76	1	1	0	167	0	6
24	1	0	1	0	91	0	2
25
26	30	.	1	.	91	.	4
27
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29
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42	42	0	1	0	.	.	.
43
44	0	6	0	0	.	.	.
45
46	365	2	0	2	.	.	.
47	91	0	1	0	.	.	.
48	274	16	19	0	.	.	.
49	46	.	.	.	91	.	.
50	91	1
51	14	.	2	.	46	.	5
52
53	456	1	14	0	.	.	.
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2	91	6	9	0
3	365	12	2	0
4	91	.	1	.	183	.	.	.
5	91	0	4	0	365	2	1	
6	365	0	9	0
7
8	7	0	0	0	30	0	0	
9	365	7	7	0
10
11	12	.	1
12
13	1095	1	0	1
14
15	91	1	1	.	183	.	.	.
16
17	91	0	2	0	365	0	1	
18	0	7	0	0	274	4	0	
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	i1_tp2_death	i1_tp3_dura	i1_tp3_drop	i1_tp3_follow	i1_tp3_death	i1_tp4_dura	i1_tp4_drop
1
2	0	91	0	1	1	183	0
3	.	183	.	3	.	.	.
4	0	30	2	1	0	91	1
5
6
7
8
9
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11
12
13
14
15
16
17	0	30	0	0	0	91	1
18
19	0
20
21	0
22
23
24	0	61	0	0	0	91	0
25	0
26	.	274	.	.	.	365	.
27
28
29	0
30
31
32	0	548	13	27	0	.	.
33	0	259	0	1	0	350	0
34	0	365	0	10	0	.	.
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52	.	365
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54	.	91	.	4	.	183	.
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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
1
2	1	1	365	1	1	1	730
3
4
5
6	1	0	183	0	2	3	.
7
8	3	0	183	0	2	3	.
9
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13
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16
17	0	2	183	1	0	2	365
18
19
20
21
22
23	0	0	183	0	0	0	274
24
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27
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29
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31
32
33	0	0
34
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54	7	.	365	.	5	.	548
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1 i1_tp6_drop i1_tp6_follow i1_tp6_death i1_tp7_dura i1_tp7_drop i1_tp7_follow i1_tp7_death

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1 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_death	i1_tp10_dura	i1_tp10_drop	i1_tp10_follow	i1_tp10_death	i2_tp1_dura	i2_tp1_drop
1	365	1
2	183	2
3	7	0
4	0	.
5	3	0
6	243	0
7	274	.
8	365	4
9
10	42	.
11	365	0
12	0	3
13	14	0
14
15	14	0
16	91	1
17	91	.
18	4
19	183	3
20	0	1
21	76	0
22	30	0
23
24	30	1
25
26	91	1
27	91	.
28
29	0	4
30	183	3
31	0	1
32	76	0
33	30	0
34
35	30	1
36
37	91	2
38	42	0
39	0	2
40
41	0	2
42	42	0
43	0	.
44
45	365	1
46	91	0
47	274	20
48	46	.
49	91	.
50	14	.
51	456	3
52	0	.
53	0	.
54	0	.
55	0	.
56	0	.
57	0	.
58	0	.
59	0	.
60	0	.

1		91	9
2	.	365	4
3	.	91	.
4	.	91	0
5	.	365	0
6	.	24	0
7	.	7	0
8	.	365	4
9	.	12	.
10	.	.	.
11	.	1095	0
12	.	.	.
13	.	91	.
14	.	.	0
15	.	91	8
16	.	0	.
17	.	.	.
18	.	.	.
19	.	.	.
20	.	.	.
21	.	.	.
22	.	.	.
23	.	.	.
24	.	.	.
25	.	.	.
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44	.	.	.
45	.	.	.
46	.	.	.
47	.	.	.
48	.	.	.
49	.	.	.
50	.	.	.
51	.	.	.
52	.	.	.
53	.	.	.
54	.	.	.
55	.	.	.
56	.	.	.
57	.	.	.
58	.	.	.
59	.	.	.
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	i2_tp1_follow	i2_tp1_death	i2_tp2_dura	i2_tp2_drop	i2_tp2_follow	i2_tp2_death	i2_tp3_dura
1	0	0
2	0	0	365	1	7	0	.
3	0	0	30	0	1	1	91
4	0	0	91	.	.	.	183
5	0	0	14	0	2	0	30
6	0	1
7	0	0	365	.	9	.	.
8	0	0
9	0	0
10	0	0
11	0	0	1	0	0	0	30
12	0	0
13	0	0
14	0	0
15	0	0
16	0	0
17	0	0
18	0	0	1	0	0	0	30
19	0	0
20	0	0	91	0	5	0	.
21	0	0
22	0	0
23	0	0
24	0	0	30	0	0	0	61
25	0	0	183	1	0	0	.
26	0	0	183	.	.	.	274
27	0	0	183
28	0	0
29	0	0	198	9	1	0	.
30	0	0
31	1	0
32	0	0	365	6	4	0	548
33	0	0	365	6	4	0	.
34	0	0	167	0	2	0	259
35	0	0	167	0	2	0	.
36	0	0	91	0	1	0	365
37	0	0
38	0	0	91	.	2	.	.
39	0	0
40	0	0
41	0	0
42	0	0
43	1	0
44	0	0
45	0	0
46	0	0
47	0	0
48	0	0
49	0	0
50	1	0
51	15	0
52	0	0	91	3	.	.	365
53	0	0
54	0	0	46	0	3	.	91
55	0	0
56	0	0
57	13	0
58	0	0
59	0	0
60	2	0	730	0	2	0	.

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i2_tp3_drop i2_tp3_followi2_tp3_death i2_tp4_dura i2_tp4_drop i2_tp4_followi2_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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5	365	0	2	1	730	0	4
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8	183	2	0	2	.	.	.
9
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17	183	2	0	1	365	1	0
18
19
20
21
22
23	183	0	0	.	365	1	0
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1 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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1 i2_tp8_followi2_tp8_death i2_tp9_dura i2_tp9_drop i2_tp9_followi2_tp9_deathi2_tp10_dura
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1 i2_tp10_drop2_tp10_follov2_tp10_death i3_tp1_dura i3_tp1_drop i3_tp1_followi3_tp1_death
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1 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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1 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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1 i3_tp5_followi3_tp5_death i3_tp6_dura i3_tp6_drop i3_tp6_followi3_tp6_death i3_tp7_dura
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1 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 i3_tp10_follow

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	3_tp10_death	overall_drop	drop_rate	overall_follow	follow_rate	overall_death	death_rate
1	.	18	34.6153846	0	0	0	0
2	.	16	5.11182109	56	17.8913738	0	0
3	.	2	2.56410256	23	29.4871795	12	15.3846154
4	.	1	2	6	12	0	0
5	.	11	9.16666667	21	17.5	6	5
6	.	0	0	0	0	2	11.7647059
7	.	1	0.46728972	58	27.1028037	0	0
8	.	9	1.84804928	99	20.3285421	0	0
9	.	0	0	0	0	0	0
10	1	5.55555556
11	.	4	4.44444444	12	13.3333333	0	0
12	.	15	8.33333333	0	0	13	7.22222222
13	.	0	0	0	0	1	2.5
14	.	0	0	7	11.2903226	0	0
15	.	3	6.38297872	4	8.5106383	0	0
16	0	0
17	.	5	6.57894737	0	0	5	6.57894737
18	.	4	16	0	0	0	0
19	.	3	3.94736842
20	.	6	11.5384615	0	0	0	0
21	.	23	17.8294574	2	1.5503876	0	0
22	.	3	6.81818182	2	4.54545455	0	0
23	.	28	11.7154812	62	25.9414226	0	0
24	.	1	3.44827586	14	48.2758621	0	0
25	.	0	0	21	17.0731707	0	0
26
27	.	1	0.76335878	8	6.10687023	0	0
28	.	2	4.08163265	0	0	0	0
29	.	1	3.7037037	0	0	0	0
30	.	2	5	0	0	0	0
31	.	0	0	7	8.75	0	0
32	.	10	14.7058824	1	1.47058824	2	2.94117647
33	.	8	17.7777778	0	0	0	0
34	.	0	0	0	0	0	0
35
36	.	0	0	2	9.09090909	0	0
37	.	36	24.6575342	34	23.2876712	0	0
38	.	3	6.52173913	0	0	0	0
39	.	1	10	0	0	.	.
40	.	15	8.33333333	0	0	0	0
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59	.	1	2.94117647	0	0	2	5.88235294
60	.	0	0	0	0	0	0
.	14	31.8181818	4	9.09090909	0	0	0

1	.	16	10.0628931	12	7.54716981	0	0
2	.	16	5.44217687	3	1.02040816	0	0
3	.	0	0	13	11.0169492	0	0
4	.	7	11.6666667	11	18.3333333	0	0
5	.	0	0	19	10	0	0
6	.	0	0	1	0.68493151	1	0.68493151
7	.	0	0	0	0	0	0
8	.	11	3.31325301	19	5.72289157	0	0
9	.	8	10.8108108	3	4.05405405	0	0
10	.	2	2	2	2	0	0
11	0	0
12	.	1	3.3333333	0	0	3	10
13	.	1	1.2345679	1	1.2345679	0	0
14	.	1	1.61290323	3	4.83870968	0	0
15	.	0	0	0	0	0	0
16	.	0	0	10	2.96735905	0	0
17	.	72	31.3043478	0	0	7	3.04347826
18							
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	overall_loss	cross_surg	cross_nonsurg	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	

1	17.6100629	28	17.6100629
2	6.46258503	0	0	0	0	19	6.46258503
3	11.0169492	20	0	20	16.9491525	33	27.9661017
4	30	30	.	30	50	48	80
5	10	19	10
6	0.68493151	5	0	5	3.42465753	7	4.79452055
7	0	0	0	0	0	0	0
8	9.03614458	30	9.03614458
9	14.8648649	0	0	0	0	11	14.8648649
10	4	2	0	2	2	6	6
11	.	0	2	2	2.5974026	10	12.987013
12	3.33333333	0	0	0	0	4	13.3333333
13	2.4691358	2	2.4691358
14	6.4516129	0	0	0	0	4	6.4516129
15	0	0	0	0	0	0	0
16	2.96735905	9	2	11	3.26409496	21	6.23145401
17	31.3043478	0	0	0	0	79	34.3478261
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	topped_recruminated_follttrition_reaso	retainment	
1	0	1	.
2	0	.	.
3	0	1	.
4	1	6	.
5	1	1	4
6	0	1	.
7	0	1	.
8	0	1	5
9	0	1	.
10	0	1	.
11	0	1	.
12	0	6	4
13	0	.	.
14	0	1	.
15	0	1	.
16	1	6	.
17	0	1	.
18	0	1	.
19	0	1	.
20	0	6	.
21	0	4	.
22	0	1	.
23	0	1	.
24	0	6	.
25	0	6	.
26	0	6	.
27	0	3	.
28	0	2	5
29	0	5	.
30	0	2	.
31	0	5	.
32	0	2	.
33	1	5	.
34	0	1	.
35	0	1	.
36	.	1	.
37	1	0	.
38	0	0	3
39	0	0	.
40	1	0	.
41	0	0	.
42	0	0	.
43	0	1	.
44	0	0	1
45	0	0	.
46	0	1	.
47	0	0	.
48	0	0	1
49	0	0	.
50	0	6	.
51	0	3	.
52	0	5	.
53	0	6	.
54	0	0	.
55	0	0	.
56	0	0	.
57	0	5	.
58	0	1	.
59	0	1	.
60	1	4	.

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27 5 3 56
28 56 58 61
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32 8.19672131 4.91803279
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		author	year	control	lot/lead_phase	prim_tps
1	64	Alkatout	2013	0	0	730
2	67	Blasco	2012	0	0	365
3	68	Brox	1993	0	1	183
4	69	Chen	2014	0	0	365
5	70	Chen	2014	0	0	183
6	71	Farfaras	2016	0	0	30
7	72	Farrokhi	2011	0	0	1095
8	73	Fuentes	2011	0	0	730
9	74	Gad	2012	0	0	548
10	75	Gauffin	2014	0	0	365
11	76	Guyuron	2004	0	1	365
12	77	Haahr	2005	0	0	365
13	78	Herrlin	2006	0	0	183
14	79	Katz	2013	0	1	183
15	80	Ketola	2009	0	0	730
16	81	Kirkley	2008	0	0	730
17	82	Klazen	2010	0	0	365
18	83	Marcoux	1997	0	0	274
19	84	Merchan	1993	0	0	1095
20	85	Miller	2016	0	0	365
21	86	Osteras	2012	0	1	91
22	87	Paavola	2018	0	0	730
23	88	Parazzini	1999	0	0	365
24	89	Peters	1992	0	0	365
25	90	Peters	1997	0	0	1460
26	90	Peters	1997	0	0	48
27	91	Rahme	1998	0	0	183
28	92	Rousing	2009	0	0	91
29	93	Schierlitz	2014	0	0	183
30	94	Siddle	2012	0	0	548
31	95	Spencer	1992	0	0	365
32	96	Stensrud	2015	0	0	730
33	97	Trad	2015	0	0	183
34	99	van de Graaf	2018	0	0	730
35	100	Van der Ploeg	2016	0	0	365
36	101	Witteman	2015	0	1	183
37	102	Yang	2016	0	0	365
38	103	Yim	2013	0	1	730
39	105	Silverberg	2002	0	1	365

	long_tps	total_tps	n_tps	plan_sample	indom_sample	analysed_sample	n_female
1	730	152, 365, 730	3	.	450	410	450
2	365	4, 61, 183, 36	4	128	125	95	97
3	183	91, 183, 913	3	108	125	120	71
4	365	1, 7, 30, 91,	6	.	96	89	62
5	183	183	1	.	28	7	2
6	168	30, 168	2	120	87	55	28
7	1095	183, 365, 730,	6	.	82	82	60
8	730	183, 365, 730	3	.	60	60	60
9	548	.	.	.	41	.	.
10	365	183, 365	2	150	150	150	41
11	365	1, 183, 274, 36	4	.	125	108	.
12	2190	, 183, 365, 21	4	100	90	84	58
13	183	56, 183	2	80	99	90	35
14	365	91, 183, 366	3	340	351	330	187
15	144	04, 365, 730, 1	7	140	140	134	88
16	730	183, 365, 548,	5	186	188	168	112
17	365	, 30, 91, 183, :	6	200	202	163	140
18	274	2, 152, 183, 24	6	330	348	341	348
19	1095	365, 730, 1095	3	.	80	73	53
20	730	33,243,304,36	11	44	44	39	34
21	91	91	1	20	17	17	4
22	730	1, 183, 365, 73	4	210	210	186	135
23	365	365	1	.	101	96	101
24	365	365	1	.	48	48	48
25	1460	1460	1	.	72	.	26
26	48	12, 24, 36, 48	4	.	72	48	26
27	365	183, 365	2	.	42	39	23
28	91	91	1	40	50	47	41
29	1490	5, 730, 1095, :	7	62	80	74	80
30	548	26, 183, 274, :	7	64	65	64	48
31	548	91,183,548	3	.	7	6	3
32	730	91, 365, 730	3	140	140	140	54
33	183	14, 91, 183	3	42	63	60	33
34	730	1, 183, 365, 73	4	320	321	289	161
35	365	365	1	320	91	89	91
36	365	30, 91, 183, 31	5	120	60	57	22
37	365	30, 91, 183, 36	5	96	135	107	69
38	730	1, 183, 365, 73	4	108	108	102	81
39	365	1, 183, 274, 36	4	.	29	23	14

1	age_int1	age_int2	age_int3	n_screened	n_eligible	n_enrolled	recruit_rate
2	.	.	.	523	499	450	90.1803607
3	71.33	75.27	.	219	125	125	100
4	48	48	47	444	155	125	80.6451613
5	64.63	66.49	.	.	.	96	.
6	.	.	.	64	28	28	100
7	52.4	49.9	48.9	95	.	87	.
8	72	74	.	105	84	82	97.6190476
9	60	.
10	41	.
11	54	54	.	179	155	150	96.7741935
12	43.4	42.9	.	.	.	125	.
13	44.3	44.5	.	.	.	90	.
14	56	56	.	180	99	90	90.9090909
15	59	57.8	.	14,430	1330	351	26.3909774
16	46.4	47.8	.	.	.	140	.
17	58.6	60.6	.	277	219	188	85.8447489
18	75.2	75.4	.	934	434	202	46.5437788
19	31	30	.	717	348	348	100
20	57	56	.	.	.	80	.
21	38.3	38.5	.	50	49	44	89.7959184
22	52.7	47	.	29	19	17	89.4736842
23	50.5	50.8	50.4	281	213	210	98.5915493
24	30.6	30.3	.	.	.	101	.
25	35.5	35.7	.	.	.	48	.
26	56	59	.	.	.	72	.
27	56	59	.	.	.	72	.
28	42	42	.	.	.	42	.
29	80	80	.	.	.	50	.
30	67	66	.	845	146	80	54.7945205
31	55.6	55.1	.	258	71	65	91.5492958
32	52	54.7	.	.	.	7	.
33	50.2	48.9	.	341	226	140	61.9469027
34	54.8	50.1	.	196	95	63	66.3157895
35	57.6	57.3	.	.	.	321	.
36	61	63.7	.	2000	.	91	.
37	42.4	49.3	.	.	.	60	.
38	77.1	76.2	.	158	153	135	88.2352941
39	54.9	57.9	.	162	157	108	68.7898089
40	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
1	152	10	3	0	.	.	.
2	0	7	.	.	14	.	6
3	91	0	14	0	183	0	4
4	365	0	4	0	.	.	.
5	183
6	30	6	2	1	168	0	2
7	7	0	0	0	61	0	0
8
9
10	0	9	0	0	.	.	.
11	0	4	0	0	2190	0	1
12	56	.	.	.	183	.	.
13	91	12	0	1	365	4	1
14	0	1	0	0	730	2	0
15	0	2	0	0	730	1	2
16	0	2	0	0	1	0	0
17	0	5	0	0	100	9	0
18	1095	0	0	5	.	.	.
19	0	.	.	.	7	.	.
20
21	0	17	0	0	730	0	0
22
23
24
25	365	0	6	0	730	0	0
26	183	0	0	0	365	0	0
27	91	0	1	1	.	.	.
28	183	0	0	2	1490	0	6
29	42	0	0	0	84	0	0
30	183	0	.	1	365	.	.
31	91	.	7	.	365	.	7
32	183	.	1
33	0	1	0	0	91	1	2
34	0	2	0	0	365	1	3
35	183	0	10	0	365	0	5
36	0	2	0	0	365	0	8
37	730	3	1	0	.	.	.
38	0	1	0	0	365	1	1
39	55	56	57	58	59	60	

	i1_tp2_death	i1_tp3_dura	i1_tp3_drop	i1_tp3_follow	i1_tp3_death	i1_tp4_dura	i1_tp4_drop
1
2	61	.	.	2	1	183	.
3
4	0
5
6	0
7
8	0
9
10	0
11	0	183	0	0	0	365	0
12
13
14
15
16
17	1
18
19	0
20	0	1825	4	8	1	.	.
21	1
22	0	7	1	0	0	30	0
23	0
24	0	30	.	.	.	62	.
25	0
26
27
28
29
30	0
31	0
32
33
34
35
36	0
37	0
38
39
40	0
41	0	126	0	0	0	183	0
42	.	548
43	.	730	.	8	.	.	.
44	.	183	3	3	0	365	2
45
46
47	0
48	0
49	0
50	0
51	0
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53	0
54	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

4	.	365	1	.	2	.
0	2	730	0	0	0	1095
0	1	91	4	0	0	183
.	.	121	.	.	.	183
0	0	274	0	0	0	365
9	0	730	11	0	0	.

1 i1_tp6_drop i1_tp6_follow i1_tp6_death i1_tp7_dura i1_tp7_drop i1_tp7_follow i1_tp7_death

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11 0 1 0
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24 3 0 2 365 1 0 2
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41 0 0 0 548 0 0 0
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1 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_death	i1_tp10_dura	i1_tp10_drop	i1_tp10_follow	i1_tp10_death	i2_tp1_dura	i2_tp1_drop
1	152	14
2	14	.
3	91	0
4	365	0
5	183	.
6	30	0
7	7	0
8	183	8
9
10
11
12
13
14
15
16
17	0	2
18	56	.
19	183	5
20	0	1
21	0	8
22	0	1
23	0	4
24	1095	0
25	0	.
26
27	730	2
28
29
30
31
32
33
34
35
36
37	183	3
38	91	0
39	183	0
40	42	0
41	183	.
42	91	.
43	183	.
44	0	1
45	0	1
46	183	0
47	0	3
48	730	0
49	0	2
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	i2_tp1_follow	i2_tp1_death	i2_tp2_dura	i2_tp2_drop	i2_tp2_follow	i2_tp2_death	i2_tp3_dura
1	11	0
2	.	2	61	1	2	.	183
3	3	0	183	0	0	0	.
4	3	0
5
6	10	0	168	0	3	0	.
7	0	0	61	0	0	0	183
8	0	0
9
10
11	0	0	2190	0	3	0	.
12	.	.	183
13	2	1	365	5	0	0	.
14	0	0	730	4	0	0	1825
15	0	0	730	0	6	0	.
16	0	0	1	0	0	1	7
17	0	0	132	12	0	0	.
18	0	2
19	.	.	7	.	.	.	30
20
21	1	1
22
23
24
25
26
27
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29
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31	1	1
32
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35
36
37	1	0
38	0	1
39	4	0	1490	0	8	0	.
40	0	0	84	0	0	0	126
41	.	.	365	.	.	.	548
42	10	.	365	.	9	.	730
43	2
44	0	0	91	1	2	0	181
45	0	0	365	0	5	0	.
46	0	0
47	0	0	365	2	5	0	.
48	0	0
49	0	0	365
50	0	0
51	0	0	365	2	5	0	.
52	1	0
53	0	0	365	1	0	0	.
54	55	56	57	58	59	60	

i2_tp3_drop i2_tp3_follow i2_tp3_death i2_tp4_dura i2_tp4_drop i2_tp4_follow i2_tp4_death

.	.	.	2	365	1	3	2
.
.
.	0	0	0	365	0	2	1
.
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.
10	7	1
.
1	0	0	30	.	1	0	0
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.	.	.	62
.
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.
0	0	0	183	0	0	0	0
.
.	6
3	10	1	365	6	14	0	0

i2_tp5_dura i2_tp5_drop i2_tp5_follow i2_tp5_death i2_tp6_dura i2_tp6_drop i2_tp6_follow

730 0 0 0 1095 0 0

91 5 0 1 183 5 0

121 183 . .

274 0 0 0 365 0 0

730 2 0 0 . . .

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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1 i2_tp8_followi2_tp8_death i2_tp9_dura i2_tp9_drop i2_tp9_followi2_tp9_deathi2_tp10_dura
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	i2_tp10_drop	i2_tp10_follov	i2_tp10_death	i3_tp1_dura	i3_tp1_drop	i3_tp1_follow	i3_tp1_death
1	.	.	.	152	1	1	0
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3	.	.	.	91	0	8	0
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6	.	.	.	30	5	4	1
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1	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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5	183	0	1	0	.	.	.
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9	168	0	5	0	.	.	.
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1 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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For peer review only

1 i3_tp5_followi3_tp5_death i3_tp6_dura i3_tp6_drop i3_tp6_followi3_tp6_death i3_tp7_dura
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1 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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1 i3_tp9_dura i3_tp9_drop i3_tp9_follow i3_tp9_death i3_tp10_dura i3_tp10_drop i3_tp10_follow
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	3_tp10_death	overall_drop	drop_rate	overall_follow	follow_rate	overall_death	death_rate
1	.	25	5.55555556	15	3.33333333	0	0
2	.	10	8	17	13.6	9	7.2
3	.	4	3.2	30	24	0	0
4	.	0	0	7	7.29166667	0	0
5
6	.	11	12.6436782	26	29.8850575	2	2.29885057
7	.	0	0	3	3.65853659	3	3.65853659
8	.	8	13.3333333
9
10	0	0
11	.	9	7.2	8	6.4	0	0
12	.	6	6.66666667	4	4.44444444	1	1.11111111
13	.	6	6.66666667
14	.	26	7.40740741	3	0.85470085	2	0.56980057
15	.	22	15.7142857	15	10.7142857	2	1.42857143
16	.	11	5.85106383	8	4.25531915	1	0.53191489
17	.	24	11.8811881	0	0	11	5.44554455
18	.	30	8.62068966	0	0	0	0
19	.	0	0	0	0	7	8.75
20	.	1	2.27272727	4	9.09090909	0	0
21	.	0	0	0	0	0	0
22	.	22	10.4761905	1	0.47619048	1	0.47619048
23	.	5	4.95049505	2	1.98019802	0	0
24	.	0	0	0	0	0	0
25
26
27	.	3	7.14285714	1	2.38095238	0	0
28	.	0	0	1	2	2	4
29	.	0	0	18	22.5	2	2.5
30	.	0	0	0	0	1	1.53846154
31	.	0	0	0	0	1	14.2857143
32	.	16	11.4285714	31	22.1428571	0	0
33	.	0	0	3	4.76190476	0	0
34	.	31	9.65732087	40	12.4610592	1	0.31152648
35	.	4	4.3956044	9	9.89010989	0	0
36	.	0	0	15	25	0	0
37	.	7	5.18518519	13	9.62962963	0	0
38	.	3	2.77777778	2	1.85185185	0	0
39	.	5	17.2413793	1	3.44827586	1	3.44827586
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	overall_loss	cross_surg	cross_nonsurg	overall_cross	cross_rate	verall_attritio	attrition_rate
1	8.88888889	40	8.88888889
2	21.6	0	0	0	0	36	28.8
3	27.2	0	26	26	20.8	60	48
4	7.29166667	4	0	4	4.16666667	11	11.4583333
5
6	42.5287356	3	0	3	3.44827586	42	48.2758621
7	3.65853659	20	0	20	24.3902439	26	31.7073171
8	8	13.3333333
9
10	.	16	9	25	16.6666667	73	48.6666667
11	13.6	17	13.6
12	11.1111111	11	0	11	12.2222222	22	24.4444444
13	.	3	0	3	3.33333333	9	9.09090909
14	8.26210826	59	9	68	19.3732194	99	28.2051282
15	26.4285714	18	12	30	21.4285714	88	62.8571429
16	10.106383	0	6	6	3.19148936	26	13.8297872
17	11.8811881	10	6	16	7.92079208	51	25.2475248
18	8.62068966	0	0	0	0	30	8.62068966
19	0	0	0	0	0	7	8.75
20	11.3636364	0	0	0	0	5	11.3636364
21	0	0	0	0	0	0	0
22	10.952381	8	0	8	3.80952381	55	26.1904762
23	6.93069307	7	6.93069307
24	0	0	0	0	0	0	0
25	24	33.3333333
26	32	44.4444444
27	9.52380952	13	0	13	30.952381	17	40.4761905
28	2	0	0	0	0	3	6
29	22.5	0	0	0	0	20	25
30	0	0	0	0	0	6	9.23076923
31	0	0	0	0	0	1	14.2857143
32	33.5714286	13	0	13	9.28571429	60	42.8571429
33	4.76190476	0	0	0	0	3	4.76190476
34	22.1183801	47	8	55	17.1339564	127	39.5638629
35	14.2857143	13	14.2857143
36	25	20	0	20	33.3333333	35	58.3333333
37	14.8148148	8	0	8	5.92592593	28	20.7407407
38	4.62962963	1	0	1	0.92592593	6	5.55555556
39	20.6896552	0	0	0	0	7	24.137931
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	topped_recruminated_folltrition_reaso	retainment
1	0	4
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3	0	6
4	0	.
5	0	3
6	0	.
7	0	6
8	0	.
9	0	.
10	1	1
11	0	.
12	0	1
13	0	.
14	.	.
15	0	.
16	0	.
17	0	.
18	0	6
19	0	.
20	0	3
21	0	.
22	0	3
23	0	.
24	0	4
25	0	.
26	0	1
27	0	.
28	0	2
29	0	.
30	0	4
31	0	.
32	0	1
33	0	.
34	0	3
35	0	.
36	0	.
37	0	1
38	0	.
39	0	1
40	0	.
41	0	1
42	0	.
43	0	1
44	0	.
45	0	6
46	0	.
47	0	2
48	1	.
49	0	4
50	0	.
51	0	6
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53	0	2
54	0	.
55	2	2
56	2	.
57	5.26315789	5.26315789

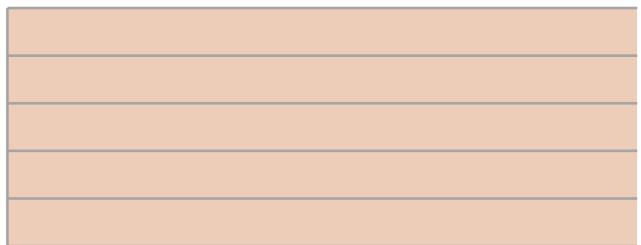
KEY

<u>Issue/Symbol</u>	<u>Explanation</u>	<u>Notes</u>
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

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

review only



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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

1	Reported Reasons for Attrition
2	Stoppage at point of recruitment (Y/N)
3	Stoppage at point of follow up (Y/N)
4	Reported Participant Retainment Strategies
5	Notes
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Variable Abbreviation (Data)

1 **id**
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5 **author**
6
7 **year**
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9 **control**
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11 **pilot/lead_phase**
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13 **prim_tps**
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15 **long_tps**
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17 **total_tps**
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19 **n_tps**
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21 **plan_sample**
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23 **randomised_sample**
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25 **analysed_sample**
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27 **n_female**
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29 **age_int1**
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31 **age_int2**
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33 **age_int3**
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37 **n_screened**
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39 **n_eligible**
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41 **n_enrolled**
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43 **recruit_rate**
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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

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2 **attrition_reason**
3 **stopped_recruit**
4 **terminated_follow**
5 **retainment**
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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 %)

Overall Attrition Losses / Randomised Sample Size

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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 feasibility

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

and 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

The number of participants that were screened via baseline assessments for commencement of treatment

The total number of potential and eligible participants invited to participate in the study

The number of participants who were assessed as eligible and commenced participation in study

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.

The number of participants that gave refusal to progress further with the study within RCT group

and aimed for sample size via statistical analysis. Includes 10% for losses - if these calculations

participants who died in RCT group at planned timepoint for primary outcomes information collection

number that dropped out (in all intervention groups) before trial completion (including follow-up

percentage 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.

int losses (either active/drop-out or passive/follow-up loss) as a proportion of randomised sam

number of participants that underwent unplanned protocol violation and received surgical interve

number of participants that underwent unplanned protocol violation and received non-surgical int

that underwent unplanned protocol violation resulting in subjects in the control group receiving

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.

1	<i>Reported reasons why participants left study.</i>
2	<i>Trial recruitment stopped early before reaching planned sample size.</i>
3	<i>Follow-up terminated earlier than planned (prior to completion of all planned follow-up timepoints).</i>
4	<i>Methods reported to be used to retain participants and actively affect attrition losses from study.</i>
5	<i>Any other comments?</i>
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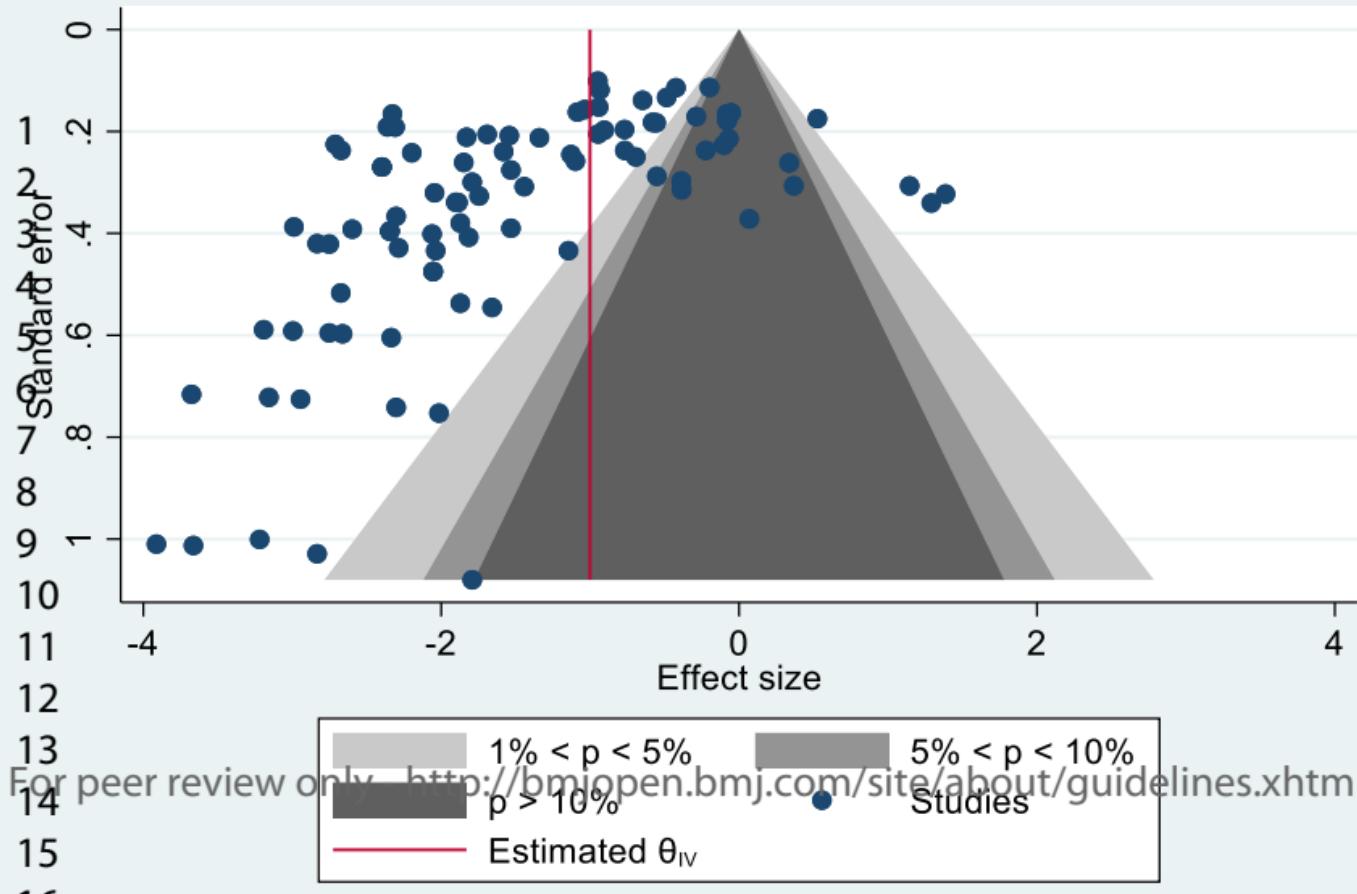
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3 **Appendix 2. Meta-regression for confounders including female proportion of study participants,**
4 **number enrolled and number of follow-up points**

	Attrition rate effect size	Dropout rate effect size	Loss to follow-up effect size
Placebo Control	-0.17	-0.24	0.17
Trials*	(-0.66 to 0.32)	(-0.86 to 0.37)	(-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)

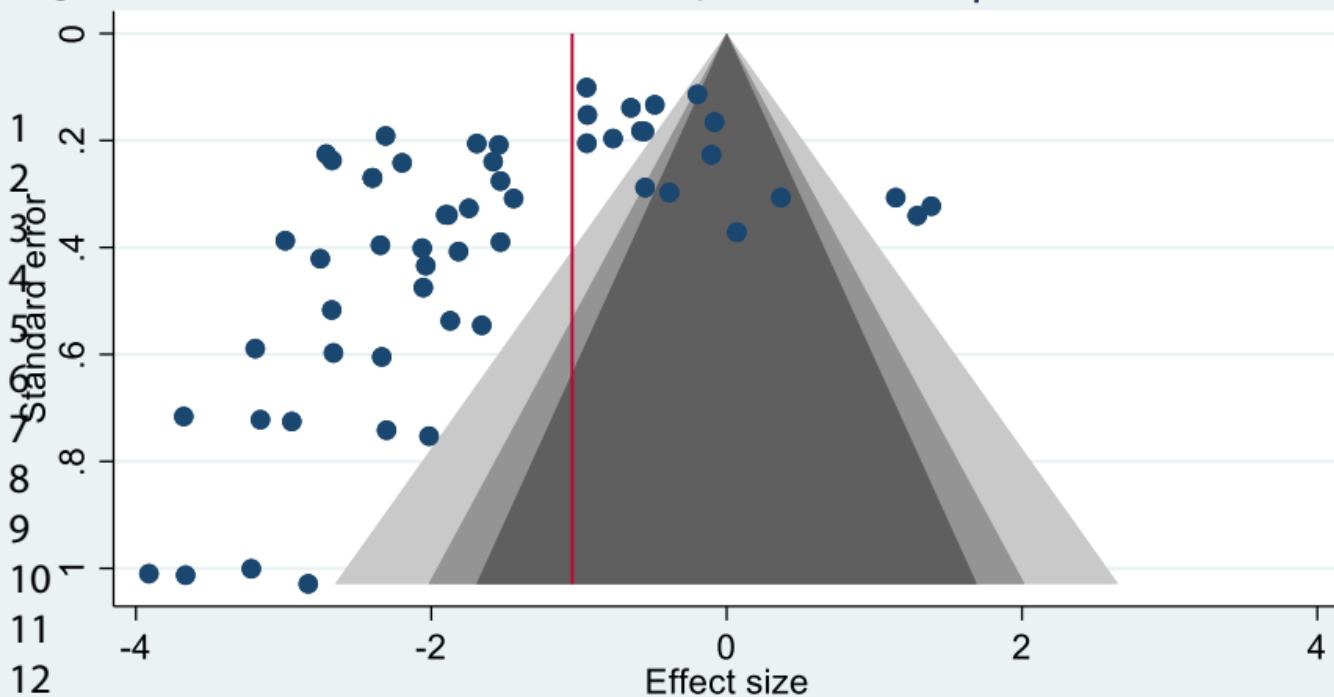
28 Note: *non-operative control trials used as a reference category

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3 **Appendix 3: Pooled (random effects) recruitment and attrition rates for studies with attrition >**
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5 **0% and recruitment < 100%.**

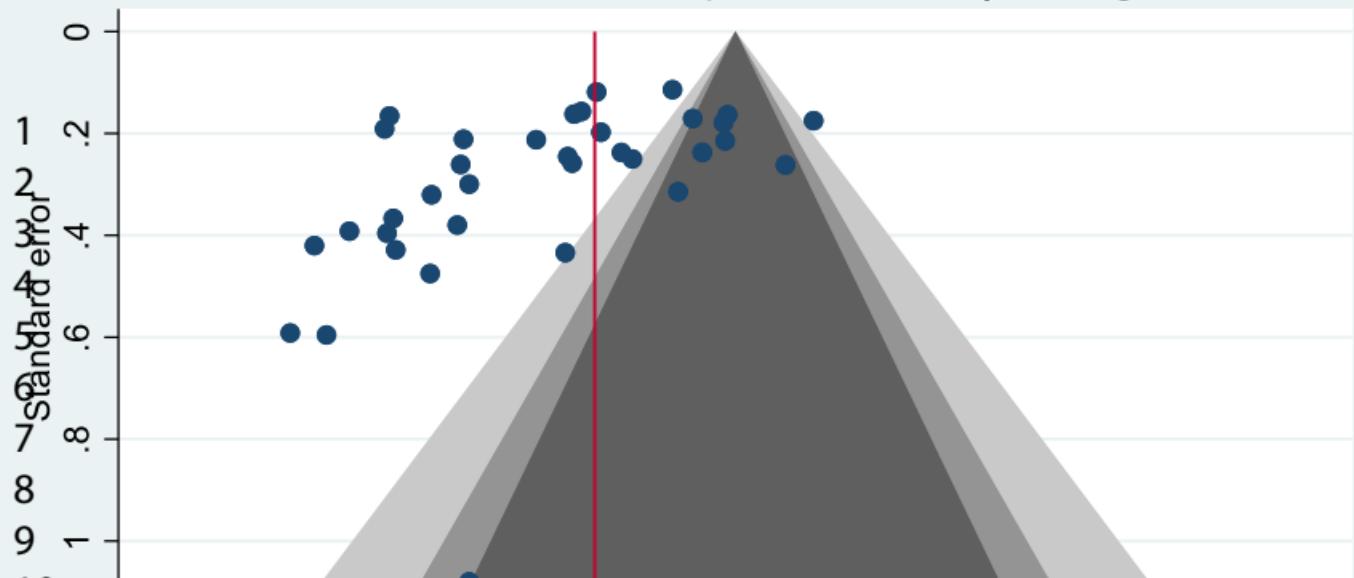
	Group	Rate (%)	95% Confidence Interval		P
			Lower (%)	Upper (%)	
Recruitment	Placebo control (n=36)	68.7	59.3	78.1	0.562
	Non-operative control (n=21)	74.1	58.6	89.5	
Attrition (Overall)	Placebo control (n= 54)	21.2	17.2	25.2	0.811
	Non-operative control (n=34)	23.7	18.8	28.6	
Cross-over	Placebo control (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-BM Open funnel plot



Contour-enhanced funnel plot



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1% < p < 5%
5% < p < 10%
p > 10%
Studies
Estimated θ_{IV}

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,

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3 we formulated our own electronic search strategies with the help of a medical librarian,
4 using a randomised trial/systematic review filter, combined with a filter specific to the
5 clinical aspects of each group of placebo-controlled RCTs. For these, we searched MEDLINE,
6 EMBASE and CENTRAL, from their inception to the present. The syntax of the search
7 strategies is contained in Appendix 1 (NEED TO COLLATE FROM DROP BOX FOLDER)
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10 Two investigators independently assessed the results of each search strategy, first screening
11 titles and abstracts, and recording the reasons for exclusion. Two independent investigators
12 conducted a full text review of papers included following the title/abstract screening. We
13 resolved any discrepancies in included studies through discussion, and if necessary, using a
14 third investigator for arbitration.
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17 Data extraction 18

19 All data will be extracted independently by two investigators, and arbitrated by a third
20 investigator if necessary. Cohen's kappa statistic and raw agreement scores will be
21 calculated to determine inter-rater reliability.
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24 General characteristics of included RCTs 25

- 26 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

42 Risk of bias 43

44 We will use the Cochrane Risk of Bias tool (11) to extract items not related to attrition.
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47 Outcome data 48

- 49 i) *Recruitment rate*, defined as the number enrolled expressed as a proportion of
those eligible for the study
- 50 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:
 - 51 a. Prior to randomisation
 - 52 b. Prior to the intervention
 - 53 c. Prior to first follow up
 - 54 d. Prior to final follow up
 - 55 e. Overall

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3 iii) *Subject loss to follow up*, defined as the inability of investigators to obtain
4 information at planned timepoints for reasons other than *subject dropout*.
5 Where available, this will be characterised at different timepoints:
6 a. Prior to first follow up
7 b. Prior to final follow up
8 c. Overall
9
10 iv) *Subject cross-over rates*, defined as an unplanned protocol violation resulting in
11 subjects in the control group receiving the intervention, and vice versa. This will
12 be reported as a proportion of the subject group, and characterised as:
13 a. Subjects crossing over into the surgical intervention
14 b. Subjects crossing over into the non-surgical intervention
15 c. Overall
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17 v) *Overall attrition of participants*, defined as a composite (or addition) of dropout,
18 loss to follow up and cross-overs, expressed as a proportion of total sample size
19
20 vi) Stoppage prior to recruitment of planned sample size. Where available, the
21 reason for stoppage will be recorded, including due to poor recruitment rates.
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24 The primary outcomes of interest will be rates of attrition (due to dropout, loss to follow up
25 and cross-over), participant recruitment rates and number of studies with unplanned
26 stoppage.
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28 **Statistical Analyses**

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

33 Due to the data nature (varying follow-up duration) mixed effect Poisson regression will be
34 used to examine Incidents Rate Ratio (IRR) and Incident Rate Difference while controlling for
35 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 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

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

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

13 Additional outcome(s) [2 changes]

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

17 Measures of effect

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

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

23 Data extraction (selection and coding)

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

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

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

36 Two authors will also extract the following study characteristics independently:

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

44 Risk of bias (quality) assessment

45 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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9 Review team members and their organisational affiliations [1 change]
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16 Ms Lucy Busija. Research Methodology, Monash University
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18 Professor Ian Harris. South West Sydney Clinical School, UNSW
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20 Professor Rachelle Buchbinder. Monash Department of Clinical Epidemiology, Cabrini Institute; Department of
21 Epidemiology and Preventive Medicine, School of Public Health & Preventive Medicine, Monash University
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Type and method of review

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

Anticipated or actual start date

22 November 2018

Anticipated completion date [3 changes]

23 August 2022

Funding sources/sponsors

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

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

Conflicts of interest

Language

English

Country

Australia, Finland

Published protocol

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

Stage of review [1 change]

Review Completed published

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

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

https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2794704

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

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

Date of registration in PROSPERO

07 January 2019

Date of first submission

20 November 2018

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

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

Revision note

Review completed. Added publication and link to the paper

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

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

Versions

07 January 2019

15 May 2020

09 November 2020

23 August 2022

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3 **Placebo-controlled randomised trials of surgical interventions**
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5 **Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)**
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2. Randomized controlled trial/
3. Randomization/
4. Rct.tw.
5. random allocation.tw.
6. Randomly allocated.tw.
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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.
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15. clinical trial.pt.
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17. or/1-16
18. PLACEBOS/
19. placebo\$.tw.
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21. immitation.tw.
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24. surgery.tw.
25. surgical.tw.
26. arthroscopy.tw.
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28. transplantation.tw.
29. \$scopy.tw.
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31. laparoscopy.tw.
32. Meta-Analysis as Topic/
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34. metaanaly\$.tw.
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36. Comment/
37. Letter/
38. Editorial/
39. animal/
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41. pre\$medication.tw.
42. an\$esthesia.tw.
43. an\$esthetic\$.tw.
44. antibiotic\$.tw.
45. steroid\$.tw.
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53. postoperative.tw.
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Ovid EMBASE

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19 5. Double blind procedure/
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21 7. Randomi?ed controlled trial\$.tw.
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50. pre\$emptive.tw.

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4 54. prevention.tw.
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7 57. scar\$.tw.
8 58. infection\$.tw.
9 59. acupressure.tw.
10 60. pre\$operative.tw.
11 61. growth factor\$.tw.
12 62. pacing.tw.
13 63. stimulation.tw.
14 64. hormon\$.tw.
15 65. case report\$.tw.
16 66. case study.tw.
17 67. or/30-66
18 68. 15 and 20
19 69. 68 and 29
20 70. 69 not 67
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22 **Cochrane Central Register of Controlled Trials**
23 http://onlinelibrary.wiley.com/o/cochrane/cochrane_clcentral_articles_fs.html

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

30
31 **ClinicalTrials.gov**

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

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3 **Non-operative controlled trials:**
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5 **Abdominal pain/adhesiolysis (2016-current)**
6

7 Before 2016: Van Beukel et al (2017) (1)
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9

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

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41 Embase
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- 45 1. Clinical Trial/
- 46 2. Randomized Controlled Trial/
- 47 3. exp randomization/
- 48 4. Single Blind Procedure/
- 49 5. Double Blind Procedure/
- 50 6. Crossover Procedure/
- 51 7. Placebo/
- 52 8. Randomi?ed controlled trial\$.tw.
- 53 9. Rct.tw.
- 54 10. random allocation.tw.
- 55 11. randomly allocated.tw.

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2
3 12. allocated randomly.tw.
4 13. (allocated adj2 random).tw.
5 14. Single blind\$.tw.
6 15. Double blind\$.tw.
7 16. ((treble or triple) adj blind\$).ti.
8 17. placebo\$.tw.
9 18. prospective study/
10 19. OR/1-18
11 20. exp abdominal pain/
12 21. exp chronic pain/
13 22. exp Tissue Adhesions/
14 23. Adhesion\$.ti.
15 24. adhesi\$.ti,ab.
16 25. OR/20-24
17 26. exp laparoscopy/
18 27. exp laparotomy/
19 28. laparoscop\$.ti,ab.
20 29. laparotomy.ti,ab.
21 30. adhesiolysis.ti,ab.
22 31. (abdomen.ti,ab. or abdominal.ti,ab. or abdomino\$.ti,ab.) AND surgery.ti,ab.
23 32. OR/26-31
24 33. AND/19,25,32
25 34. limit 33 to yr="2016-current"
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31 CENTRAL
32
33 1. (abdominal pain)
34 2. MeSH descriptor [chronic pain]) explode all trees
35 3. (Adhesion)
36 4. #1 OR #2 OR #3
37 5. MeSH descriptor [laparoscopy] explode all trees
38 6. MeSH descriptor [laparotomy] explode all trees
39 7. laparoscop\$
40 8. adhesiolysis
41 9. #5 OR #6 OR #7 OR #8
42 10. #4 AND #9
43
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46
47
48 Reference List
49
50 1. van den Beukel BA, de Ree R, van Leuven S, Bakkum EA, Strik C, van Goor H, Ten
51 Broek RP. Surgical treatment of adhesion-related chronic abdominal and pelvic pain after
52 gynaecological and general surgery: a systematic review and meta-analysis. Human
53 Reproduction Update. 2017 May 1;23(3):276-88.
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1
2
3 Benign Prostatic Hyerplasia/ Urethral Lift
4**5** Medline
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- 7**
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- 8**
1. Exp Prostatic Hyperplasia/
-
- 9**
2. prostat* adj3 hyperplasia*.tw.
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- 10**
3. Prostate* adj3 hypertroph*.tw.
-
- 11**
4. Prostat* adj3 adenoma*.tw.
-
- 12**
5. BPH or BPO or BPE.tw.
-
- 13**
6. prostat* adj3 enlarg*.tw.
-
- 14**
7. exp prostatism/
-
- 15**
8. prostatism.tw
-
- 16**
9. exp Urinary Bladder Neck Obstruction/
-
- 17**
10. Bladder* adj3 obstruct*.tw.
-
- 18**
11. BOO.tw.
-
- 19**
12. OR/1-11
-
- 20**
13. Prostatic urethral lift.tw
-
- 21**
14. prost* adj3 lift.tw.
-
- 22**
15. Urolift.tw.
-
- 23**
16. 13 or 14
-
- 24**
17. 12 and 15
-
- 25**
18. randomized controlled trial.pt.
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- 26**
19. controlled clinical trial.pt.
-
- 27**
20. randomized
-
- 28**
21. randomized
-
- 29**
22. placebo.tw
-
- 30**
23. clinical trials as topic.sh
-
- 31**
24. randomly.ab.
-
- 32**
25. trial.ti.
-
- 33**
26. groups.ti,ab.
-
- 34**
27. or/17-25
-
- 35**
28. animals not (humans and animals).sh
-
- 36**
29. 26 not 27
-
- 37**
30. 16 and 28

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46 EMBASE
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- 48**
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- 49**
- Clinical Trial/
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- 50**
- Randomized Controlled Trial/
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- 51**
- exp randomization/
-
- 52**
- Single Blind Procedure/
-
- 53**
- Double Blind Procedure/
-
- 54**
- Crossover Procedure/
-
- 55**
- Placebo/
-
- 56**
- Randomi?ed controlled trial\$.tw.
-
- 57**
- Rct.tw.
-
- 58**
- random allocation.tw.

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2
3 randomly allocated.tw.
4 allocated randomly.tw.
5 (allocated adj2 random).tw.
6 Single blind\$.tw.
7 Double blind\$.tw.
8 ((treble or triple) adj blind\$).tw.
9 placebo\$.tw.
10 prospective study/
11 or/1-18
12 case study/
13 case report.tw.
14 abstract report/ or letter/
15 or/20-22
16 19 NOT 23
17 Prostatic urethral lift.tw
18 prost\$ lift.tw.
19 Urolift.tw.
20 OR/25-27
21 Exp Prostatic Hyperplasia/
22 prostat\$ adj3 hyperplasia\$.tw.
23 Prostate\$ adj3 hypertroph\$.tw.
24 Prostat\$ adj3 adenoma\$.tw.
25 BPH or BPO or BPE.tw.
26 prostat\$ adj3 enlarg\$.tw.
27 exp prostatism/
28 prostatism.tw.
29 exp Urinary Bladder Neck Obstruction/
30 Bladder\$ adj3 obstruct\$.tw.
31 BOO.tw.
32 OR/29-39
33 and/24,28,40
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42 CENTRAL
43
44 1. MeSH description [benign prostatic hyperplasia] explode all trees
45 2. surgical procedures, operative explode all trees
46 3. surg* or surgical* or operat*:ti,ab
47 4. #2 or #3
48 5. #4 and #1
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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

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2
3 20. case study/
4 21. case report.tw.
5 22. abstract report/ or letter/
6 23. or/20-22
7 24. 19 NOT 23
8 25. Callosities/
9 26. callosities.mp.
10 27. callus.mp.
11 28. OR/25-27
12 29. Exp surgical procedures, operative/
13 30. (surg\$ or surgical\$ or operat\$).ti,ab.
14 31. debridement*.ti,ab.
15 32. OR/29-31
16 33. AND/24,28,32
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24 CENTRAL
25
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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

1
2 **Cervical dystonia**
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4

5 Medline
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8 randomized controlled trial.pt.
9 controlled clinical trial.pt.
10 randomized.ab.
11 randomised.ab.
12 placebo.tw.
13 clinical trials as topic.sh.
14 randomly.ab.
15 trial.ti.
16 (crossover or cross-over or cross over).tw.
17 or/1-9
18 exp animals/ not humans.sh.
19 10 NOT 11
20 cervical dystonia
21 Spasmodic Torticollis
22 focal dystonia
23 laterocollis or anterocollis or retrocollis):tw
24 OR/13-16
25 surgical procedures, operative/
26 (surg* or surgical* or operat*).ti,ab
27 deep brain stimulation.ti,ab
28 OR/18-20
29 and/12,17,21
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37 EMBASE
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- 40 1. Clinical Trial/
41 2. Randomized Controlled Trial/
42 3. exp randomization/
43 4. Single Blind Procedure/
44 5. Double Blind Procedure/
45 6. Crossover Procedure/
46 7. Placebo/
47 8. Randomi?ed controlled trial\$.tw.
48 9. Rct.tw.
49 10. random allocation.tw.
50 11. randomly allocated.tw.
51 12. allocated randomly.tw.
52 13. (allocated adj2 random).tw.
53 14. Single blind\$.tw.
54 15. Double blind\$.tw.
55 16. ((treble or triple) adj blind\$).tw.
56 17. placebo\$.tw.
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3 18. prospective study/
4 19. or/1-18
5 20. case study/
6 21. case report.tw.
7 22. abstract report/ or letter/
8 23. or/20-22
9 24. 19 NOT 23
10 25. cervical dystonia/
11 26. spastic torticollis.tw.
12 27. dystonia.ti,ab.
13 28. laterocollis or anterocollis or retrocollis).tw.
14 29. OR/25-28
15 30. surgical procedures, operative/
16 31. (surg* or surgical* or operat*).ti,ab
17 32. Deep brain stimulation.ti,ab.
18 33. or/30-32
19 34. and/24,29,33

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26 CENTRAL
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29 1. MeSH Term: [Torticollis] explode all trees
30 2. dystonia:kw
31 3. #1 OR #2
32 4. MeSH Term [surgical procedures, operative] explode all trees
33 5. (surg* or surgical* or operat*):ti,ab
34 6. (deep brain stimulation):kw
35 7. #4 or #5 or #6
36 8. #3 and #7
37 9. limit to trials
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3 **Endometriosis**
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6 Medline

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

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3 44. dyschezia.tw. (546)
4 45. dyspareunia.tw. (6811)
5 46. exp infertility/
6 47. or/41-46 (168951)
7 48. AND/12,40,47
8 49. limit 48 to yr="2013-current
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13 EMBASE
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15 1. Clinical Trial/
16 2. Randomized Controlled Trial/
17 3. exp randomization/
18 4. Single Blind Procedure/
19 5. Double Blind Procedure/
20 6. Crossover Procedure/
21 7. Placebo/
22 8. Randomi?ed controlled trial\$.tw.
23 9. Rct.tw.
24 10. random allocation.tw.
25 11. randomly allocated.tw.
26 12. allocated randomly.tw.
27 13. (allocated adj2 random).tw.
28 14. Single blind\$.tw.
29 15. Double blind\$.tw.
30 16. ((treble or triple) adj blind\$).tw.
31 17. placebo\$.tw.
32 18. prospective study/
33 19. or/1-18
34 20. case study/
35 21. case report.tw.
36 22. abstract report/ or letter/
37 23. or/20-22
38 24. 19 NOT 23
39 25. exp Laparoscopy/ (146878)
40 26. Laparoscop\$.tw. (183770)
41 27. celioscop\$.tw. (580)
42 28. peritoneoscop\$.tw. (1176)
43 29. exp minimally invasive surgery/ (37349)
44 30. exp laser/ (123007)
45 31. exp diathermy/ (7154)
46 32. diathermy.tw. (4955)
47 33. LUNA.tw. (1395)
48 34. presacral neurectom\$.tw. (177)
49 35. laser\$.tw. (248739)
50 36. plasmajet.tw. (75)
51 37. plasma jet.tw. (342)

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3 38. microlaparoscop\$.tw. (198)
4 39. minilaparoscop\$.tw. (342)
5 40. exp robotics/ (34612)
6 41. exp computer assisted surgery/ (11310)
7 42. Computer-Assisted Surg\$.tw. (1248)
8 43. da vinci.tw. (4710)
9 44. (keyhole adj3 surg\$).tw. (194)
10 45. Robot\$.tw. (56125)
11 46. remote surg\$.tw. (151)
12 47. microsurg\$.tw. (29971)
13 48. uterine nerve ablation\$.tw. (39)
14 49. uterosacral nerve ablation.tw. (38)
15 50. minimally invasive.tw. (84934)
16 51. (ablation or ablative).tw. (136843)
17 52. exp hand assisted laparoscopy/ (712)
18 53. or/25-53 (748344)
19 54. exp endometriosis/ (36593)
20 55. exp infertility/ (121827)
21 56. endometrio\$.tw. (42667)
22 57. dyschezia.tw. (546)
23 58. dyspareunia.tw. (6811)
24 59. or/54-58 (168951)
25 60. AND/24,53,59
26 61. limit 60 to yr=" 2013-current"
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35 CENTRAL
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37 1 exp Laparoscopy/
38 2 Laparoscop\$.ti,ab,sh.
39 3 celioscop\$.tw.
40 4 peritoneoscop\$.tw.
41 5 exp Surgical Procedures, Minimally Invasive/
42 6 Lasers/
43 7 exp Diathermy/
44 8 LUNA
45 9 presacral neurectom*
46 10 (minimal\$ adj5 surg\$).tw.
47 11 laser\$.tw.
48 12 diathermy.tw.
49 13 plasmajet.tw.
50 14 plasma jet.tw.
51 15 excision.tw.
52 16 microlaparoscop\$.tw.
53 17 minilaparoscop\$.tw.
54 18 exp Robotics/
55 19 exp Surgery, Computer-Assisted/
56 20 Computer-Assisted Surg\$.tw.
57 21 da vinci.tw.

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3 22 (keyhole near3 surg\$).tw.
4 23 Robot\$.tw.
5 24 remote surg\$.tw.
6 25 microsurg\$.tw.
7 26 minimally invasive.tw.
8 27 (ablation or ablative).tw.
9 28 or/1-27
10 29 exp Endometriosis/
11 30 endometrio\$.tw.
12 31 dyschezia.tw.
13 32 dyspareunia.tw.
14 33 infertility:kw
15 34 MeSH term infertility explode all trees
16 35 #29 or #30 or #31 or 32 #or 33
17 34 28 and 35
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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.

- 1
2
3 22. abstract report/ or letter/
4 23. or/20-22
5 24. 19 NOT 23
6 25. transoral incisionless fundoplication.mp.
7 26. EsophyX.mp.
8 27. Endocinch.mp.
9 28. transoral fundoplication.mp.
10 29. endoscopic fundoplication.mp.
11 30. or/25-29
12 31. 24 and 30
13
14
15

16 CENTRAL
17

- 18 1. EsophyX
19 2. Endocinch
20 3. (transoral fundoplication) OR (transoral plication) OR (endoscopic plication) OR
21 (endoscopic fundoplication)
22 4. TIF
23 5. #1 OR #2 OR #3 OR #4 OR #5
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IMA ligation

Embase, Medline and Central

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

For peer review only

1
2
3 Urinary Incontinence
45 Medline
6

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

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3 44. OR/38-44
4 45. AND/12,17,36 (for the sling, limit 2018 – current)
5 46. AND/12, 17, 44 (2017-current)
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8 EMBASE
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- 1 1. Clinical Trial/
2 2. Randomized Controlled Trial/
3 3. exp randomization/
4 4. Single Blind Procedure/
5 5. Double Blind Procedure/
6 6. Crossover Procedure/
7 7. Placebo/
8 8. Randomi?ed controlled trial\$.tw.
9 9. Rct.tw.
10 10. random allocation.tw.
11 11. randomly allocated.tw.
12 12. allocated randomly.tw.
13 13. (allocated adj2 random).tw.
14 14. Single blind\$.tw.
15 15. Double blind\$.tw.
16 16. ((treble or triple) adj blind\$).tw.
17 17. placebo\$.tw.
18 18. prospective study/
19 19. or/1-18
20 20. case study/
21 21. case report.tw.
22 22. abstract report/ or letter/
23 23. or/20-22
24 24. 19 NOT 23
25 25. exp Urinary Incontinence, stress/
26 26. ((stress\$ or mix\$ or urg\$ or urin\$) adj3 incontinen\$).tw.
27 27. stress urinary incontinence*.mp.
28 28. occult urinary incontinence.mp.
29 29. OR/25-28
30 30. exp surgical procedures, operative/
31 31. (surg* or surgical* or operat*).ti,ab.
32 32. suburethral sling.mp.
33 33. abdominal sling.mp.
34 34. traditional sling procedure\$*.tw.
35 35. suburethral sling procedure.tw.
36 36. mid\$urethral sling.tw.
37 37. retropubic sling procedure\$*.tw.
38 38. transobturator sling procedure\$.tw.
39 39. TVT-Secur.mp.
40 40. mini-arc or mini-arc.mp.
41 41. ajust.mp.

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2
3 42. needleless.mp.
4 43. solyx.mp.
5 44. single\$incision sling\$.mp.
6 45. mini\$sling.mp.
7 46. Ophira.mp.
8 47. Tissue Fixation System.mp.
9 48. OR/30-47
10 49. ((urethra* or periurethra* or transurethra*) adj3 (agent* or bulk* or injection* or
11 injectable*).tw.
12 50. injection therapy.tw.
13 51. injectable\$.tw.
14 52. (injectable\$ adj2 agent\$).tw.
15 53. (bulk\$ adj3 agent\$).tw.
16 54. autologous fat.mp.
17 55. Peri\$urethral injection\$.mp.
18 56. OR/38-44
19 57. AND/12,18,37 (this is for the sling, limit April 2018 – March 2019
20 58. AND/12, 18, 45 (2017-current)
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26 CENTRAL
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29 1. MeSH descriptor: [Urinary Incontinence, Stress] explode all trees
30 2. stres* near incontinent*:kw
31 3. stress near incontinence*:kw
32 4. mix* near incontinent*:kw
33 5. urg* near incontinent*:kw
34 6. stress urinary incontinence*:kw
35 7. occult urinary incontinence:kw
36 8. #1 or #2 or #3 or #4 or #5 or #6 or #7
37 9. MeSH descriptor: [Surgical Procedures, Operative] explode all trees
38 10. (surg* or surgical* or operat*):ti,ab
39 11. suburethral sling:kw
40 12. abdominal sling:kw
41 13. mid\$urethral sling:kw
42 14. retropubic sling:kw
43 15. transobturator sling:kw
44 16. "mini-arc" or "mini-arc"
45 17. ajust
46 18. needleless
47 19. solyx
48 20. single\$incision sling:kw
49 21. mini near sling:kw
50 22. Tissue Fixation System:kw
51 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
52 #20 or #21 or #22
53 24. #8 and #23
54 25. with Publication Year from 2018 to 2019, in Trials
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4 injectables
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6 1. MeSH descriptor: [Urinary Incontinence, Stress] explode all trees
7 2. stres* near incontinent*:kw
8 3. stress near incontinence*:kw
9 4. mix* near incontinent*:kw
10 5. urg* near incontinent*:kw
11 6. stress urinary incontinence*:kw
12 7. occult urinary incontinence:kw
13 8. #1 or #2 or #3 or #4 or #5 or #6 or #7
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1
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3 **Meniere's Disease**
4
56 MEDLINE
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8

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

31 EMBASE
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- 34 1. Clinical Trial/
- 35 2. Randomized Controlled Trial/
- 36 3. exp randomization/
- 37 4. Single Blind Procedure/
- 38 5. Double Blind Procedure/
- 39 6. Crossover Procedure/
- 40 7. Placebo/
- 41 8. Randomi?ed controlled trial\$.tw.
- 42 9. Rct.tw.
- 43 10. random allocation.tw.
- 44 11. randomly allocated.tw.
- 45 12. allocated randomly.tw.
- 46 13. (allocated adj2 random).tw.
- 47 14. Single blind\$.tw.
- 48 15. Double blind\$.tw.
- 49 16. ((treble or triple) adj blind\$).tw.
- 50 17. placebo\$.tw.
- 51 18. prospective study/

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2
3 19. or/1-18
4 20. case study/
5 21. case report.tw.
6 22. abstract report/ or letter/
7 23. shunt.tw.
8 24. endolymphatic sac adj3 surgery
9 25. ((endolymphatic or sac) and shunt).ti,ab.
10 26. (endolymphatic and (surg\$ or decompress\$ or drainage)).ti,ab.
11 27. OR/23-26
12 28. endolymphatic hydrops.mp.
13 29. meniere disease/
14 30. vertigo.mp.
15 31. labyrinth or aural or endolymphatic adj3 syndrome or vertigo or hydrops
16 32. OR/28-31
17
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21 CENTRAL
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23 1. surg* or decompression or drainage or shunt or operat* or surgical*
24 2. endolymphatic
25 3. #1 AND #2
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1
2 **Obesity**
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45 Medline
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- 8 1. randomized controlled trial.pt.
9 2. controlled clinical trial.pt.
10 3. randomized.ab.
11 4. randomised.ab.
12 5. placebo.tw.
13 6. clinical trials as topic.sh.
14 7. randomly.ab.
15 8. trial.ti.
16 9. (crossover or cross-over or cross over).tw.
17 10. or/1-9
18 11. exp animals/ not humans.sh.
19 12. 10 NOT 11
20 13. exp obesity/
21 14. Overweight/
22 15. over?weight.ti,ab.
23 16. over weight.ti,ab.
24 17. overeating.ti,ab.
25 18. over?eating.ti,ab.
26 19. exp Weight Loss/
27 20. weight loss.ti,ab.
28 21. weight reduc\$.ti,ab.
29 22. or/13-21
30 23. bariatric surg\$.ti,ab.
31 24. exp bariatric surgery/
32 25. (surg\$ adj5 bariatric).ti,ab.
33 26. anti?obesity surg\$.ti,ab.
34 27. antiobesity surg\$.ti,ab.
35 28. (obesity adj5 surgery).ti,ab.
36 29. (obesity adj5 surgical).ti,ab.
37 30. (gastroplasty or gastro?gastostomy or "gastric bypass" or "gastric surgery" or
38 "restrictive surgery").ti,ab.
39 31. exp gastric bypass/
40 32. gastroplasty/
41 33. ((gastric plication) or (vagal nerve stimulation) OR (vagal nerve block)).ti,ab.
42 34. stomach stapl\$.ti,ab.
43 35. obesity/su
44 36. exp Obesity, Morbid/su [Surgery]
45 37. OR/23-36
46 38. AND/12,22,37

56
57 EMBASE
58
59 1. Clinical Trial/
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3 2. Randomized Controlled Trial/
4 3. exp randomization/
5 4. Single Blind Procedure/
6 5. Double Blind Procedure/
7 6. Crossover Procedure/
8 7. Placebo/
9 8. Randomi?ed controlled trial\$.tw.
10 9. Rct.tw.
11 10. random allocation.tw.
12 11. randomly allocated.tw.
13 12. allocated randomly.tw.
14 13. (allocated adj2 random).tw.
15 14. Single blind\$.tw.
16 15. Double blind\$.tw.
17 16. ((treble or triple) adj blind\$).tw.
18 17. placebo\$.tw.
19 18. prospective study/
20 19. or/1-18
21 20. case study/
22 21. case report.tw.
23 22. abstract report/ or letter/
24 23. or/20-22
25 24. 19 NOT 23
26 25. exp OBESITY/ or exp MORBID OBESITY/
27 26. over?weight.ti,ab.
28 27. over weight.ti,ab.
29 28. overeating.ti,ab.
30 29. over?eating.ti,ab.
31 30. exp Weight Reduction/
32 31. (weight adj1 los*).ti,ab.
33 32. (weight adj1 loos*).ti,ab.
34 33. weightloss.ti,ab.
35 34. weight?loss.ti,ab.
36 35. (weight adj3 reduc*).ti,ab.
37 36. weight?reduc*.ti,ab.
38 37. or/25-36
39 38. bariatric surg*.ti,ab.
40 39. exp Bariatric Surgery/
41 40. (surg* adj5 bariatric).ti,ab.
42 41. (anti?obesity adj3 surg*).ti,ab.
43 42. (antiobesity adj3 surg*).ti,ab.
44 43. anti obesity surg*.ti,ab.
45 44. (obesity adj5 surgery).ti,ab.
46 45. (obesity adj5 surgical).ti,ab.
47 46. (gastroplasty or gastrogastrectomy or gastro?gastrostomy or gastroenterostomy or gastric
48 bypass or gastric surgery or
49 47. restrictive surgery).ti,ab.

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3 48. exp GASTROPLASTY/
4 49. ("gastric plication" or "vagal nerve stimulation" OR "vagal nerve block").ti,ab.
5 50. gastric stapl*.ti,ab.
6 51. OR/38-50
7 52. 37 AND 51
8 53. OBESITY/su [Surgery]
9 54. Morbid Obesity/su [Surgery]
10 55. 53 OR 54
11 56. 37 AND 55
12 57. 52 OR 56
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16 CENTRAL
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18
19 #1 MeSH descriptor: [Obesity] explode all trees
20 #2 MeSH descriptor: [Overweight] this term only
21 #3 MeSH descriptor: [Weight Loss] explode all trees
22 #4 (obes* or overweight or "over weight")
23 #5 #1 or #2 or #3 or #4
24
25 #6 MeSH descriptor: [Bariatric Surgery] explode all trees
26 #7 (bariatric near/5 surg*)
27 #8 (obes* near/5 surg*)
28 #9 antiobesity or anti-obesity or anti obesity near/5 (surg*))
29 #10(gastroplasty or gastrogastrostomy or gastro?gastrostomy or gastroenterostomy or "gastric
30 bypass" or "gastric surgery" or "restrictive
31 surgery")
32
33 #11 MeSH descriptor: [Gastric Bypass] explode all trees
34 #12 MeSH descriptor: [Gastropasty] explode all trees
35 #13 stomach near/5 stapl*
36 #14 gastric near/5 stapl*
37 #15 (gastric plication):ti,ab OR (vagal nerve block):ti,ab OR (vagal nerve stimulation):ti,ab
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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.

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3 18. prospective study/
4 19. or/1-18
5 20. case study/
6 21. case report.tw.
7
8 22. abstract report/ or letter/
9 23. or/20-22
10 24. 19 NOT 23
11 25. Parkinson's disease/
12 26. Parkinson's syndrome
13 27. Parkinson*.ti,ab
14 28. OR/25-27
15 29. surgical procedures, operative/
16 30. (surg* or surgical* or operat*).ti,ab
17 31. cell adj2 delivery.ti,ab.
18 32. gene adj delivery.ti,ab.
19 33. or/29-32
20 34. and/24,28,33
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25 CENTRAL
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28 1. MeSH Term: [Parkinson's disease] explode all trees
29 2. Parkinson*.ti,ab
30 3. #1 OR #2
31 4. MeSH Term [surgical procedures, operative] explode all trees
32 5. (surg* or surgical* or operat*):ti,ab
33 6. (cell adj2 delivery):ti,ab.
34 7. (gene adj delivery):ti,ab.
35 8. #4 or #5 or #6 or #7
36 9. #3 and #8
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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)

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3 23 or/20-22 (1547292)
4 24 19 not 23 (1986570)
5 25 sphincter of oddi.mp. (3272)
6 26 endoscopic sphincterotomy.mp. (5835)
7 27 exp surgical procedures, operative/ (4859006)
8 28 (surg* or surgical* or operat*).ti,ab. (3421933)
9 29 or/26-28 (6152758)
10 30 and/24-25,29 (240)
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14 CENTRAL
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17 1. sphincter of oddi
18 2. endoscopic sphincterotomy
19 3. sphincterotomy
20 4. surg* or surgical* or operative:kw
21 5. MeSH Term:[Surgical Procedures, Operative] explode all trees
22 6. #2 or #3 or #4 or #5
23 7. #1 and #6
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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/

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2
3 23. or/20-22
4 24. 19 NOT 23
5 25. (SLAP or superior labral anterior-posterior or superior labral anterior posterior).mp.
6 26. surgical procedures, operative/
7 27. (surg* or surgical* or operat*).ti,ab
8 28. (biceps tenodesis OR biceps tenotomy OR repair OR suture OR debridement).ti,ab.
9 29. OR/26-28
10 30. AND/24, 25,29
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14 CENTRAL
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16 1. SLAP
17 2. superior labral anterior-posterior or superior labral anterior posterior
18 3. #1 OR #2
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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.

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3 15. Double blind\$.tw.
4 16. ((treble or triple) adj blind\$).tw.
5 17. placebo\$.tw.
6 18. prospective study/
7 19. or/1-18
8 20. case study/
9 21. case report.tw.
10 22. abstract report/ or letter/
11 23. or/20-22
12 24. 19 NOT 23
13 25. palate/
14 26. palatal OR palate.mp.
15 27. 25 OR 26
16 28. implant*.mp.
17 29. 27 and 28
18 30. exp septumplasty/
19 31. nasal surgery/
20 32. nasal adj3 surgery.ti,ab.
21 33. resection adj4 septum.tw.
22 34. OR/29-33
23 35. exp obstructive sleep apnea/
24 36. sleep apnea.ti,ab.
25 37. sleeping disorder*.ti,ab
26 38. OR/35-37
27 39. AND/24,34,38
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36 CENTRAL
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38 1. MeSH descriptor: [Palate] explode all trees
39 2. palatal or palate:kw
40 3. implant*
41 4. #1 or #2
42 5. #3 and #4
43 6. MeSH descriptor: [Nasal Surgical Procedures] explode all trees
44 7. nasal adj3 surgery:ti,ab
45 8. septum adj4 resection
46 9. #5 OR #6 OR #7 OR #8
47 10. MeSH descriptor: [Sleep Apnea, Obstructive] explode all trees
48 11. sleep apnea:ti,ab
49 12. sleep disorder*:kw
50 13. #10 or #11 or #12
51 14. #9 and #13
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1
2 **Spinal Cord Injury**
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5 **Medline**
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- 8 1. randomized controlled trial.pt.
9 2. controlled clinical trial.pt.
10 3. randomized.ab.
11 4. randomised.ab.
12 5. placebo.tw.
13 6. clinical trials as topic.sh.
14 7. randomly.ab.
15 8. trial.ti.
16 9. (crossover or cross-over or cross over).tw.
17 10. or/1-9
18 11. exp animals/ not humans.sh.
19 12. 10 NOT 11
20 13. exp Spinal Cord Injuries/
21 14. exp Central Cord Syndrome/
22 15. (myelopathy adj3 (traumatic or post-traumatic)).ab,ti.
23 16. ((spine or spinal or vertebrae) adj3 (fracture* or wound* or trauma* or injur* or
24 damag*)).ab,ti.
25 17. (spinal cord adj3 (contusion or laceration or transaction or trauma or
26 ischemia)).ab,ti.
27 18. central cord injury syndrome.ab,ti.
28 19. central spinal cord syndrome.ab,ti.
29 20. exp Paraplegia/
30 21. exp Quadriplegia/
31 22. OR/13-21
32 23. cell adj3 transplantation
33 24. Lamina Propria Transplantation
34 25. transplant*
35 26. regenerative surgery
36 27. AND/12,22,26

44 **EMBASE**
45
46

- 47 1. Clinical Trial/
48 2. Randomized Controlled Trial/
49 3. exp randomization/
50 4. Single Blind Procedure/
51 5. Double Blind Procedure/
52 6. Crossover Procedure/
53 7. Placebo/
54 8. Randomi?ed controlled trial\$.tw.
55 9. Rct.tw.
56 10. random allocation.tw.
57 11. randomly allocated.tw.
58 12. allocated randomly.tw.

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3 13. (allocated adj2 random).tw.
4 14. Single blind\$.tw.
5 15. Double blind\$.tw.
6 16. ((treble or triple) adj blind\$).tw.
7 17. placebo\$.tw.
8 18. prospective study/
9 19. or/1-18
10 20. case study/
11 21. case report.tw.
12 22. abstract report/ or letter/
13 23. or/20-22
14 24. 19 NOT 23
15 25. exp Spinal Cord Injuries/
16 26. exp Central Cord Syndrome/
17 27. (myelopathy adj3 (traumatic or post-traumatic)).ab,ti.
18 28. ((spine or spinal or vertebrae) adj3 (fracture\$ or wound\$ or trauma\$ or injur\$ or
19 damage\$)).ab,ti.
20 29. (spinal cord adj3 (contusion or laceration or transaction or trauma or
21 ischemia)).ab,ti.
22 30. central cord injury syndrome.ab,ti.
23 31. central spinal cord syndrome.ab,ti.
24 32. exp Paraplegia/
25 33. exp Quadriplegia/
26 34. OR/25-33
27 35. cell adj3 transplantation
28 36. Lamina Propria/
29 37. transplant\$
30 38. regenerative surgery
31 39. OR/35-38
32 40. AND/24,34,39
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40 CENTRAL
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42 1. MeSH descriptor: [Spinal Cord Injuries] explode all trees
43 2. MeSH descriptor: [Central Cord Syndrome] explode all trees
44 3. myelopathy near3 (traumatic or post-traumatic)
45 4. (spine or spinal or vertebrae) near3 (fracture* or wound* or trauma* or injur* or damag*)
46 5. (spinal cord) near3 (contusion or laceration or transaction or trauma or ischemia)
47 6. central cord injury syndrome
48 7. central spinal cord syndrome
49 8. paraplegi* or quadriplegi* or tetraplegi*
50 9. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
51 10. transplant*:kw
52 11. cell near3 transplantation
53 12. regenerative surgery
54 13. MeSH descriptor: [Mucous Membrane] explode all trees
55 14. lamina propria transplant*:kw
56 15. #10 or #11 or #12 #13 or #14

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3 16. #9 and #15 (in trials)
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For peer review only

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

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EMBASE38

- 40 1. Clinical Trial/
- 41 2. Randomized Controlled Trial/
- 42 3. exp randomization/
- 43 4. Single Blind Procedure/
- 44 5. Double Blind Procedure/
- 45 6. Crossover Procedure/
- 46 7. Placebo/
- 47 8. Randomi?ed controlled trial\$.tw.
- 48 9. Rct.tw.
- 49 10. random allocation.tw.
- 50 11. randomly allocated.tw.
- 51 12. allocated randomly.tw.
- 52 13. (allocated adj2 random).tw.
- 53 14. Single blind\$.tw.
- 54 15. Double blind\$.tw.
- 55 16. ((treble or triple) adj blind\$).tw.
- 56 17. placebo\$.tw.

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2
3 18. prospective study/
4 19. or/1-18
5 20. case study/
6 21. case report.tw.
7
8 22. abstract report/ or letter/
9 23. or/20-22
10 24. 19 NOT 23
11 25. surgical procedure/
12 26. (surger\$ OR surgical\$ or operat\$).tw.
13
14 27. OR/25-27
15 28. Headache/ OR exp Headache and facial pain/
16 29. exp Migraine/
17 30. (headach* OR migrain* OR cephalgi* OR cephalalgi*).ti
18
19 31. OR/29-31
20 32. AND/24,27,31
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22
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24
25 CENTRAL
26
27 MeSH descriptor Headache/ OR MeSH descriptor Headache Disorders explode all trees
28 MeSH descriptor Migraine Disorders explode all trees
29 (headach* OR migrain* OR cephalgi* OR cephalalgi*):ti,ab,kw.
30 #1 OR #2 OR #3
31 surgical procedures, operative/
32 (surg* OR surgical* or operat*):kw,ab,ti
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2
3 **Tardive dystonia**
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56 MEDLINE
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- 9 1. randomized controlled trial.pt.
- 10 2. controlled clinical trial.pt.
- 11 3. randomized.ab.
- 12 4. randomised.ab.
- 13 5. placebo.tw.
- 14 6. clinical trials as topic.sh.
- 15 7. randomly.ab.
- 16 8. trial.ti.
- 17 9. (crossover or cross-over or cross over).tw.
- 18 10. or/1-9
- 19 11. exp animals/ not humans.sh.
- 20 12. 10 NOT 11
- 21 13. dystonia/
- 22 14. tardive dystonia.ti,ab.
- 23 15. OR/13-14
- 24 16. surgical procedures, operative/
- 25 17. (surg* or surgical* or operat*).ti,ab
- 26 18. deep brain stimulation.ti,ab
- 27 19. OR/16-18
- 28 20. AND/12,15,19

34
35 EMBASE
36
37

38 Clinical Trial/
39 Randomized Controlled Trial/
40 exp randomization/
41 Single Blind Procedure/
42 Double Blind Procedure/
43 Crossover Procedure/
44 Placebo/
45 Randomi?ed controlled trial\$.tw.
46 Rct.tw.
47 random allocation.tw.
48 randomly allocated.tw.
49 allocated randomly.tw.
50 (allocated adj2 random).tw.
51 Single blind\$.tw.
52 Double blind\$.tw.
53 ((treble or triple) adj blind\$).tw.
54 placebo\$.tw.
55 prospective study/

1
2
3 or/1-18
4 case study/
5 case report.tw.
6 abstract report/ or letter/
7 or/20-22
8 19 NOT 23
9 Exp dystonia/
10 tardive dystonia.ti,ab.
11 OR/25-26
12 surgical procedures, operative/
13 (surg* or surgical* or operat*).ti,ab
14 Deep brain stimulation.ti,ab.
15 or/28-30
16 and/24,27,31
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23 CENTRAL
24
25
26
27 1. dystonia:kw
28 2. (tardive dystonia):kw
29 3. (tarvide dyskinesia):kw
30 4. #1 OR #2 OR #3
31 5. MeSH Term [surgical procedures, operative] explode all trees
32 6. (surg* or surgical* or operat*):ti,ab
33 7. (deep brain stimulation):kw
34 8. #5 or #6 or #7
35 9. #4 and #8
36 10. limit to trials
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2 **Tennis Elbow**
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45 Medline
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- 8 1. randomized controlled trial.pt.
9 2. controlled clinical trial.pt.
10 3. randomized.ab.
11 4. randomised.ab.
12 5. placebo.tw.
13 6. clinical trials as topic.sh.
14 7. randomly.ab.
15 8. trial.ti.
16 9. (crossover or cross-over or cross over).tw.
17 10. or/1-9
18 11. exp animals/ not humans.sh.
19 12. 10 NOT 11
20 13. exp Tennis Elbow/
21 14. exp Tendinopathy/
22 15. exp Tendon Injuries/
23 16. exp Elbow Joint/
24 17. exp Pain/
25 18. 16 and 17
26 19. tennis elbow.tw.
27 20. (Tendinitis or Tendinosis or Tendonitis).tw.
28 21. (pain\$ and lateral elbow).tw.
29 22. epicondylitis.tw.
30 23. common extensor origin.tw.
31 24. epicondylalgia.tw.
32 25. or/13-15,18-24
33 26. exp Surgery/
34 27. (surgery\$ or surgeries or surgical or operat\$).tw.
35 28. (tenotomy or tendon release or ECRB release or extensor carpi radialis brevis
36 release).ti,ab.
37 29. or/26-28
38 30. AND/12,25,29

45 EMBASE
46
47

- 48 1. Clinical Trial/
49 2. Randomized Controlled Trial/
50 3. exp randomization/
51 4. Single Blind Procedure/
52 5. Double Blind Procedure/
53 6. Crossover Procedure/
54 7. Placebo/
55 8. Randomi?ed controlled trial\$.tw.
56 9. Rct.tw.
57 10. random allocation.tw.
58 11. randomly allocated.tw.

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2
3 12. allocated randomly.tw.
4 13. (allocated adj2 random).tw.
5 14. Single blind\$.tw.
6 15. Double blind\$.tw.
7 16. ((treble or triple) adj blind\$).tw.
8 17. placebo\$.tw.
9 18. prospective study/
10 19. or/1-18
11 20. case study/
12 21. case report.tw.
13 22. abstract report/ or letter/
14 23. or/20-22
15 24. 19 NOT 23
16 25. exp Tennis Elbow/
17 26. exp Tendinopathy/
18 27. exp Tendon Injuries/
19 28. exp Elbow Joint/
20 29. exp Pain/
21 30. 28 and 29
22 31. tennis elbow.tw.
23 32. (Tendinitis or Tendinosis or Tendonitis).tw.
24 33. (pain\$ and lateral elbow).tw.
25 34. epicondylitis.tw.
26 35. common extensor origin.tw.
27 36. epicondylalgia.tw.
28 37. or/25-27,30-36
29 38. exp Surgery/
30 39. (surgery\$ or surgeries or surgical or operat\$).ti,ab.
31 40. (tenotomy or tendon release or ECRB release or extensor carpi radialis brevis
32 release).ti,ab.
33 41. or/26-28
34 42. AND/12,25,29

41
42 CENTRAL
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- 44 1. MeSH descriptor: [Tennis Elbow] explode all trees
45 2. MeSH descriptor: [Elbow Tendinopathy] explode all trees
46 3. MeSH descriptor: [Tendon Injuries] explode all trees
47 4. MeSH descriptor: [Tendon Injuries] explode all trees
48 5. MeSH descriptor: [Pain] explode all trees
49 6. #4 and #5
50 7. tennis elbow:ti,ab
51 8. (Tendinitis or Tendinosis or Tendonitis):ti,ab
52 9. (pain* and “lateral elbow”):ti,ab
53 10. epicondylitis:ti,ab
54 11. “common extensor origin”:ti,ab
55 12. epicondylalgia:ti,ab
56 13. (#1 OR #2 OR #3 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12)
57 14. MeSH descriptor: [Surgical Procedures, Operative] explode all trees

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3 15. (surgery* or surgeries or surgical or operat*):ti,ab
4 16. (tenotomy or tendon release or ECRB release or extensor carpi radialis brevis release):ti,ab
5 17. #14 or #15 or #16
6 18. #13 and #17
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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
47. 2017-current

EMBASE

52. 1. Clinical Trial/
53. 2. Randomized Controlled Trial/
54. 3. exp randomization/
55. 4. Single Blind Procedure/
56. 5. Double Blind Procedure/
57. 6. Crossover Procedure/
58. 7. Placebo/

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3 8. Randomi?ed controlled trial\$.tw.
4 9. Rct.tw.
5 10. random allocation.tw.
6 11. randomly allocated.tw.
7 12. allocated randomly.tw.
8 13. (allocated adj2 random).tw.
9
10 14. Single blind\$.tw.
11 15. Double blind\$.tw.
12 16. ((treble or triple) adj blind\$).tw.
13 17. placebo\$.tw.
14 18. prospective study/
15 19. or/1-18
16 20. case study/
17 21. case report.tw.
18 22. abstract report/ or letter/
19 23. or/20-22
20 24. 19 NOT 23
21 25. exp Spine/
22 26. 34. (spine or spinal or vertebra\$).tw.
23 27. 35. exp Fractures, Bone/
24 28. 36. fractur\$.ti.
25 29. 37. 33 or 34
26 30. 38. 35 or 36
27 31. 39. 37 and 38
28 32. 40. exp Spinal Fractures/
29 33. 41. 39 or 40
30 34. 42. exp Bone Cements/
31 35. 43. exp Methylmethacrylates/
32 36. 44. methacrylate\$.tw.
33 37. 45. bone cement\$.tw.
34 38. 46. exp Fracture Fixation, Internal/
35 39. 47. exp Vertebroplasty/
36 40. 48. vertebroplast\$.tw.
37 41. 49. cementoplast\$.tw.
38 42. 50. 50. sacroplast\$.tw. (114)
39 43. 51. or/42-50
40 44. 52. and/12,41,51
41 45. 2017-current
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52 CENTRAL
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54 1 exp Spine/ (4032)
55 2 (spine or spinal or vertebra\$).tw. (20306)
56 3 exp Fractures, Bone/ (3949)
57 4 fractur\$.ti. (6791)
58 5 1 or 2 (21641)
59 6 3 or 4 (8007)

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3 7 5 and 6 (1504)
4 8 exp Spinal Fractures/ (561)
5 9 7 or 8 (1528)
6 10 exp Bone Cements/ (769)
7 11 exp Methylmethacrylates/ (389)
8 12 methacrylate\$.tw. (251)
9 13 bone cement\$.tw. (201)
10 14 exp Fracture Fixation, Internal/ (1077)
11 15 exp Vertebroplasty/ (112)
12 16 vertebroplast\$.tw. (202)
13 17 cementoplast\$.tw. (10)
14 18 sacroplast\$.tw. (2)
15 19 or/10-18 (2421)
16 20 9 and 19 (244)
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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

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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

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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 analyses, 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 bias).	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) 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 the 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

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/>

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BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2023-080258.R1
Article Type:	Original research
Date Submitted by the Author:	28-Feb-2024
Complete List of Authors:	Natarajan, Pragadeesh; University of New South Wales - Saint George Campus Menounos, Spiro; University of New South Wales - Saint George Campus Harris, Laura; University of New South Wales - Saint George Campus; St George and Sutherland Centre for Clinical Orthopaedic Research Limited Monuja, Masiath; University of New South Wales - Kensington Campus; St George and Sutherland Centre for Clinical Orthopaedic Research Limited Gorelik, Alex; Monash University School of Public Health and Preventive Medicine, Department of Medicine, Royal Melbourne Hospital Karjalainen, Teemu; Monash-Cabrini Department of Musculoskeletal Health and Clinical Epidemiology, Hand and Microsurgery; Tampere University Hospital Department of Musculoskeletal Diseases, Buchbinder, Rachelle; Monash University School of Public Health and Preventive Medicine, Dept of Epidemiology and Preventive Medicine Harris, Ian; Ingham Institute, Applied Medical Research - School of Clinical Medicine Naylor, Justine; Ingham Institute, Applied Medical Research - School of Clinical Medicine Adie, Sam; University of New South Wales - Saint George Campus, South West Sydney Clinical School; St George and Sutherland Centre for Clinical Orthopaedic Research Limited, Department of Orthopaedics
Primary Subject Heading:	Surgery
Secondary Subject Heading:	Evidence based practice, Research methods
Keywords:	Randomized Controlled Trial, SURGERY, Follow-Up Studies

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1
2 **1 Participant recruitment and attrition in**
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4 **2 surgical randomised trials with placebo-**
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7 **3 controls versus non-operative controls: a meta-**
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9 **4 epidemiological study and meta-analysis**

10 **5 Authors**

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6 27

7 28 **Running Head:** Participant recruitment and attrition in surgical randomised trials

8 29 **Word count (Abstract, Body):** 300, 2475

9 30 **Figures and Tables:** 4

10 31

11 32 **Keywords**

12 33 Randomised controlled trials, attrition, recruitment, surgery, placebo.

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Abstract

Objective

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

Design

Meta-Epidemiological Study.

Data Sources

Randomised controlled trials were identified from an electronic search of MEDLINE, EMBASE and 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

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3 67 proportion of total sample size). Secondary outcome measures included participant cross-over
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5 68 rate, drop out and loss to follow-up.

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10 70 **Results**

11
12 71 Unadjusted pooled recruitment and attrition rates were similar between placebo and non-
13
14 72 operative control trials. Study characteristics were not significantly different apart from time
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16 73 to primary timepoint which was shorter in studies with placebo controls (365 vs 274 days,
17
18 74 p=0.006). After adjusting for covariates (follow-up duration and number of timepoints) the
19
20 75 attrition rate of placebo control trials was almost twice as high compared with non-operative
21
22 76 controlled-trials (IRR 1.8 [95% CI 1.1-3.0] p=0.032). The incorporation of one additional
23
24 77 follow-up time point (regardless of follow-up duration) was associated with reduced attrition
25
26 78 in placebo control surgical trials (IRR [95% CI] 0.64 [0.52-0.79], p<0.001).

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30 80 **Conclusions**

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32 81 Placebo control trials of surgery have similar recruitment issues but higher attrition compared
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34 82 with non-operative (non-placebo) control trials. Study design should incorporate strategies
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36 83 such as increased timepoints for given follow-up duration to mitigate losses to follow and
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38 84 dropout.

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3 **89 Strengths and limitations of this study**

- 4
5 • Randomised controlled trials incorporating a placebo control to evaluate effectiveness
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7 of a surgical intervention were compared with randomised trials comparing the
8
9 effectiveness of the same surgical intervention with non-operative controls
10
11 • In addition to primary outcomes collected, secondary outcomes including participant
12
13 cross-over rate, participant dropout, participant loss to follow-up were recorded and
14
15 evaluated
16
17 • To minimise bias, data was extracted independently by pairs of investigators and
18
19 arbitrated by a third investigator if necessary.
20
21 • Findings limited by missing data and non-reporting of recruitment (N=42 studies) or
22
23 attrition (N=4 studies) data.
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25
26 • The relatively small amount of placebo-controlled surgical trials published in the
27
28 literature, limit the certainty of our evaluations.

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3 107 **Introduction**
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6 108 Placebo control trials are the gold standard for determining the true therapeutic effect of
7
8 109 interventions (1). However, placebo trials commonly face difficulties in participant
9
10 110 recruitment due to a lack of willingness to participate especially in surgical placebo trials due
11
12 111 to its inherently invasive nature and higher risks of anaesthetic adverse events and infection
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14 112 (2-4).

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18 113
19
20 114 Invasive and lengthy procedural processes in surgical trials may also lead to participant
21
22 115 attrition (5-7). Attrition refers to losses in participant information either due to drop-out or
23
24 116 missing data over the duration of a longitudinal study (8). These losses can create imbalances
25
26 117 in study groups introducing bias and reduced statistical power secondary to a smaller sample
27
28 118 size (8, 9).

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34 120 The extent of attrition and recruitment issues in placebo control trials of surgical
35
36 121 interventions have not been explored empirically. The aim of this study was therefore to
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38 122 investigate differences in participant recruitment and attrition rates between placebo and non-
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40 123 operative (non-placebo) control surgical trials testing the same surgical intervention to guide
41
42 124 future planning of placebo control studies.

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47 126 **Methods**
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52 128 *Design*
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55 129 We performed a meta-epidemiological study and registered the protocol in the PROSPERO
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57 130 International Prospective Register of Systematic Reviews (Supplementary File 1 and 2)

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3 131 (CRD42019117364). We followed the reporting guidance of Preferred Reporting Items for
4 Systematic Reviews and Meta-Analyses (PRISMA) (10).
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10 134 *Inclusion criteria and eligible study identification*
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12 135 This study included randomised controlled trials incorporating a placebo control to evaluate
13 the efficacy of any surgical intervention, and randomised trials comparing the effectiveness
14 of the same surgical intervention with non-operative controls. The latter may comprise either
15 standard care or no treatment. Trials were excluded if they were not evaluating the same
16 surgical effect as the corresponding placebo control trial, e.g. the non-operative control group
17 received co-interventions not provided to the surgical group.
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22 142 Surgery was defined as any invasive procedure that allows access to internal anatomy for
23 example through a skin incision. The surgical placebo is ill-defined and can vary in fidelity
24 but was defined as any “imitation procedure” differentiated by the patient, that lacks the key
25 surgical element(s) (11).
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30 147 This study used the search strategy and eligibility criteria from an associated publication by
31 Karjalainen et al (2022) (Appendix 1) (12). Detailed data on the search strategy and
32 eligibility criteria (including the PRISMA diagram of included studies) are available via the
33 supplementary files of Karjalainen et al (2022) (12). Based on a full text assessment, trials
34 were excluded because of two main reasons - they did not meet our definition of a surgical
35 intervention (such as the injection or heating of tissue) or they were duplicate articles. The
36 search identified 62 placebo controlled surgical trials.
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3 155 Our search included eligible placebo control trials from a published systematic review by
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5 156 Wartolowska et al (2014) (1) as well as an extension of its search until 21st November 2018.
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7 157 We also searched the reference lists of included studies for additional eligible studies. To
8
9 158 identify relevant effectiveness trials (incorporating non-blinded non-operative controls),
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11 159 relevant Cochrane reviews assessing the index surgical procedure were identified and their
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13 160 literature searches were also extended to March 13 to March 15, 2019. Where no relevant
14
15 161 Cochrane review was identified, a search algorithm was devised and applied to the Cochrane
16
17 162 Central Register of Controlled Trials (CENTRAL), MEDLINE and Embase from their
18
19 163 inception until the same date of search. To determine eligibility, pairs of authors
20
21 164 independently completed title/abstract screening (TK, SA) followed by full-text review (PN,
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23 165 SM, LH, MM, SA).
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33 167 *Data extraction*
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35 168 All data were extracted independently by pairs of investigators (PN, SM, LH, MM), and
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37 169 arbitrated by a third investigator (SA) if necessary. Extracted data from included trials
38
39 170 included year of publication, participant characteristics (age, sex), sample size, condition,
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41 171 intervention type (open or minimally invasive/percutaneous surgery), planned length of
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43 172 follow-up and number of follow up timepoints.
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49 174 *Primary and secondary outcome measures*
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51 175 Primary outcomes were participant recruitment and attrition. These outcomes were assessed
52
53 176 in terms of *recruitment rate* (number of participants enrolled, as a proportion of those
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55 177 eligible) and *overall attrition rate* (composite of dropout, loss to follow-up and cross-overs,
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57 178 expressed as proportion of total sample size).
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3 180 Secondary measures included the *participant cross-over rate*, defined as an unplanned
4 protocol violation resulting in participants in the control group receiving the intervention, and
5 vice versa; and *participant dropout*, defined as an inability for the participant to progress
6 further with the study. These were both reported as a proportion of total number recruited.
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8 183
9
10 184 Finally we also included *participant loss to follow-up*, defined as the inability of investigators
11 to obtain information at planned timepoints for reasons other than participant dropout. Where
12 available, these components of attrition were characterised at each follow-up timepoint.
13
14 187
15
16 188 *Statistical Analyses*
17
18 189 Descriptive statistics were used to summarise key aspect of the selected studies. The
19 'metaprop' command in Stata 16 was used to estimate pooled recruitment and attrition rates,
20 stratified by study type (placebo vs non-operative control). Overall recruitment and attrition
21 rates were the primary outcomes used for this analysis. To account for between studies
22 heterogeneity all analyses were based on the random effect model. Random effect meta-
23 analysis was used to summarise attrition rates (overall, dropout, loss to follow up, and cross
24 over) in placebo vs. non-operative control trials, stratified by trial groups.
25
26 196
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28 197 Due to the nature of the data (with varying follow-up duration), a Generalized Linear Latent
29 and Mixed (GLLAM) Model(13) was employed for random effect Poisson regression to
30 examine Incidents Rate Ratio (IRR) for intervention type (placebo or non-operative control).
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32 200 While controlling for participant gender, follow-up duration and number of follow-up
33 timepoints.
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37 203 All trials with attrition and recruitment data were included in analyses. However, reporting
38 biases were suspected in studies with 0% attrition and 100% recruitment and therefore
39 sensitivity analyses excluding these studies were performed.
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5 207 Funnel plot and Egger's test were used to assess publication bias, while meta regression was
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7 208 used to examine for the effect of covariates. Risk of bias was assessed according to Cochrane
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9 209 Risk of Bias Tool v. 1.0. and detailed in a related publication by Karjalainen et al (2022) (12).
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14 211 *Patient and public involvement*
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17 212 As this was a meta-epidemiological study and meta-analysis, there was no patient
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19 213 involvement in study design or conduct.
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Results

6 217 A total of 62 placebo control trials and 38 trials with non-operative controls (100 trials
7 overall) identified. 99 studies were included in the quantitative analysis (1 placebo control
8 trial excluded due to unavailable full text at search date (14)). Detailed data on these included
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10 219 studies has been included in Appendix 2. Study cohorts were comparable between placebo
11 and non-operative control trials, however, time to the primary outcome was shorter in studies
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13 220 with placebo controls (365 vs 274 days, $p=0.006$) (Table 1). No significant covariates were
14
15 221 identified in meta-regression analyses (Appendix 3).
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26 225 *Participant Recruitment*
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28 226 Recruitment rate was available for 57 out of 99 included studies (36 (59.0%) placebo and 21
29 (55.3%) non-operative controls, respectively) and ranged between 9.3% to 100%.
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34 229 The random effect pooled rate was similar between placebo and non-operative control trials
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36 230 (rate [95% CI]: 76.9% [95% CI 71.1%-82.7%] vs 77.6% [95% CI 66.7%-88.4%],
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38 231 respectively, $p=0.915$). This included 10/36 (27.8%) placebo and 3/21 (14.3%) non-operative
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40 232 control studies with 100% recruitment rates. When these studies were excluded, the
41
42 233 recruitment rates decreased to 68.7% [59.3%-78.1%] in the placebo and 74.1% [58.6%-
43
44 234 89.5%] in the non-operative controlled studies respectively, with no between-group
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46 235 heterogeneity ($I^2=95\%$, $p=0.562$).
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52 237 *Participant Attrition*
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54 238 Overall attrition rate was not available for 4 studies (2/61 placebo arms and 2/38 non-
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56 239 operative controls) and ranged from 0% to 80.0% in trials with available data.
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3 241 Median (IQR) attrition rates were lower in placebo trials (12.4% [6.1-29.8%]) compared to
4 non-operative control trials (20.7% [9.1-33.3%]) however these did not reach statistical
5 significance. These results also comprised 5/59 (8.5%) placebo arm studies and 2/36 (5.6%)
6 of non-operative control studies with no participant attrition. For studies with attrition, the
7 244 random effect pooled overall attrition (rate [95% CI]) did not differ significantly between
8 placebo (21.2% [17.2% - 25.2%]) and non-operative (23.7% [18.8% - 28.6%]) controlled
9 studies ($p=0.811$). This was also true for discrete components of attrition including loss to
10 follow-up, drop-out and cross-over rates (Appendix 4, 5, 6).
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24 250 *Random effect Poisson regression*
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26 251 The median (IQR) number of follow up timepoints (4 [3-5.5] and 3.5 [2-6], $p=0.748$) were
27 similar between non-operative and placebo control trials respectively. Longest follow-up
28 timepoint (365 [319.5-730] and 365 [183-456] days, $p=0.143$) was also similar between non-
29 operative and placebo control trials respectively.
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37 256 Following correction for covariates especially the varied study durations, Poisson regression
38 analyses showed significant between-group differences in the rates of dropouts, loss to
39 follow-up and attrition (Table 2). Poisson regression demonstrated a higher attrition rate in
40 placebo trials compared to non-operative control trials (IRR 1.8 [95% CI 1.1-3.0], $p=0.032$)
41 and was predominantly seen in the medium term (500 days). The higher attrition rate in
42 placebo trials was due to higher loss to follow-up (IRR 2.6 [95% CI 1.04-6.3], $p=0.042$) and
43 higher dropout (IRR 3.5 [95% CI 1.1-11.3], $p=0.037$) as seen in Figure 1.
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56 264 The incorporation of just one additional follow-up timepoint point (regardless of length of
57 follow up i.e. increased frequency of visits) is associated with a reduction in attrition (IRR
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3 266 [95% CI] of 0.64 [0.52-0.79], p<0.001) in placebo control surgical trials, largely driven by
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5 267 fewer losses to follow-up (IRR [95% CI] of 0.68 [0.52-0.89], p=0.004).
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10 269 *Publication Bias*
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12 270 Egger test (p< 0.001) indicated the presence of publication bias with the majority of included
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14 271 studies having low attrition rates (Appendix 7). Publication bias was greater in placebo
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16 272 control trials compared to trials of non-operative trials (Appendix 8, 9).
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Discussion

22 275 This review demonstrates key differences in participant recruitment and retainment when
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24 276 comparing placebo-control and non-operative (non-placebo) control randomised trials of
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26 surgery. After adjustment for the number of follow-up timepoints and study duration, attrition
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28 277 losses were almost twice as high in placebo control compared to non-operative control trials.
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30 278 This was primarily driven by participant follow-up losses and drop-outs.
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32 279
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34 280

35 281 *Participant Recruitment*
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37 282 Surgical randomised controlled trials can face recruitment rates as low as 8% (15), due to
38
39 283 patients frequently failing to meet eligibility criteria for a small and specific target
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41 284 populations (3, 16). Addition of a placebo component further exacerbates this problem by
42
43 285 undermining willingness to participate (4, 17, 18). Participant surveys suggest this
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45 286 unwillingness stems from common perceptions that invasive surgical placebos are associated
46
47 287 with greater risks (e.g., infection) (18, 19). Previous trials such as Hare *et al.* (4), which
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49 288 reported participant concerns regarding the possibility of receiving placebo surgery being the
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51 289 most common reason (38%) for non-participation despite eligibility. Contrary to these
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53 290 expectations, our results demonstrated no significant difference in recruitment rate between
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3 291 placebo control and non-operative control trials. Our findings may be biased by sampling
4 from published literature, with the non-representation of placebo control surgery trials that
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6 292 experienced stoppage and/or early-termination due to recruitment failure.
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12 295 *Participant Attrition*
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14 296 Our findings suggest placebo control surgery trials experience a two-fold higher attrition rate
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16 297 (when considering cross-overs, drop-outs and follow-up losses) compared to non-operative
17
18 298 control surgery trials, after adjusting for the duration and number of follow-up timepoints.
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21 299 One possible cause for higher attrition rates in placebo control trials could be early
22
23 300 unblinding. It is well-known that rigorous blinding is required to maintain equipoise (and
24
25 301 fidelity) in placebo control surgery trials to ensure participant retention (11, 20, 21).
26
27
28 302 Metanalysis by Hróbjartsson et al., found nonblinded control groups suffer from 79% higher
29
30 303 risk of drop-outs and 55% higher risk of co-intervention use when compared to blinded
31
32 304 control groups (22). The difficulties of appropriate blinding (and maintaining fidelity),
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34 305 especially in the context of not receiving treatment with persisting symptoms, likely account
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36 306 for the higher rates of attrition in placebo control surgery trials when compared to other-
37
38 307 control trials. Included trials in the present meta-analysis were published prior to
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40 development of the ASPIRE guidelines for acceptable surgical placebos, and therefore did
41
42 308 not report on the fidelity and blinding of their surgical placebos (11).
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49 311 Higher attrition rates in placebo control surgical trials were primarily driven by higher losses
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51 312 to follow-up and participant drop-out. With the inherent nature of surgical interventions being
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53 313 a “one-time” irreversible change (23), loss to follow-up and participant withdrawals may be
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55 314 higher when there is a long follow-up period with no concomitant treatments (24). This is
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3 315 typical of placebo surgery trials, whilst non-operative trials tend to involve comparators that
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5 316 require ongoing intervention (therefore facilitating parallel follow-up).
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11 318 We also found that differences in attrition rates between placebo and non-operative control
12 trials of surgery arise primarily in the medium term (~500 days), suggestive of a 'participant
13
14 320 demotivation' phenomenon that develops over moderate to longer-term study participation
15
16 321 (25-29). Participant demotivation seems to be accelerated in placebo control trials, with the
17
18 322 presence of additional uncertainty regarding potential allocation of a 'surgical placebo'. This
19
20 323 demotivation likely peaks following the short-term optimism initially present at enrolment
21
22 324 into a placebo control surgery trial. Moreover, the finding of additional follow-up timepoints
23
24 325 correlating with a reduction in attrition suggests frequent follow-up timepoints may enable
25
26 326 ongoing contact and thus participant retention, as positive relationships between participants
27
28 327 and trial staff are fostered (28, 30).
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33

329 *Publication Bias*

330 Trial discontinuation and non-publication is common and occurs more frequently in surgical
331 than medical trials (31-35). Publication bias, or the selective submission or acceptance of a
332 study into literature as such (36, 37), is a likely limitation of the present findings. The
333 majority of included studies had low attrition rates overall, indicating less publication of both
334 placebo and non-operative control surgical trials with high attrition rates (8).
335
336

336 *Strengths and Weaknesses*

337 This study has several major strengths including a protocol driven, pre-planned, meta-
338 epidemiological design that included all published surgical placebo trials until November
339 2018. Given our research question did not assess intervention effectiveness but rather

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3 340 described overall data from a methodological perspective, it is unlikely additional trials will
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5 341 change our conclusion. However, our findings are limited by missing data and non-reporting
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7 342 of recruitment (N=42) or attrition data (N=4) in some trials. Thus, our findings may be an
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9 343 underestimation of the true difference in attrition rates between placebo surgery trials and
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11 344 non-operative trials, as unfavourable attrition/recruitment data is less likely to be published.

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15 346 *Implications and Future Research*

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17 347 There is a need to investigate reasons why participant attrition occurs at a higher rate when
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19 348 placebo controls are employed in randomised trials of surgery. Future studies build upon
20
21 349 existing ASPIRE guidelines to explore the relationship between varying levels of placebo
22
23 350 fidelity and rates of attrition (11). Patient education and greater transparency may promote
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25 351 confidence and willingness among eligible patients to participate. As such, future studies may
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27 352 also explore patient perceptions and attitudes towards placebo surgical procedures. Strategies
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29 353 to maximise continuous patient engagement may include guaranteeing placebo-exposed
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31 354 patients the surgical intervention if a statistically significant benefit is observed. This study
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33 355 also demonstrated that additional follow up timepoints are associated with less attrition, thus
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35 356 closer follow up is recommended in placebo control trials.

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39 358 **Conclusion**

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41 359 Placebo control trials of surgery have higher attrition rates when compared to trials with non-
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43 360 operative (non-placebo) controls. Our findings suggest that the design of surgical placebo
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45 361 trials should incorporate strategies with one key strategy being more frequent follow-up (for a
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47 362 given duration of follow-up) to mitigate losses to follow and dropout.

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3 365 **Figure Legends**
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6 366 **Figure 1.** Poisson Regression of Median Attrition Rates (Drop-out, Loss to Follow-up,
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8 Death, Overall Attrition) between placebo and non-operative controls.
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13 369 **Appendix Legends**
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16 370 **Appendix 1.** Search Strategy.
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18 371 **Appendix 2.** Detailed data on included studies.
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20 372 **Appendix 3.** Meta-regression for covariates including female proportion of study
21
22 participants, number enrolled and number of follow-up points.
23
24 374 **Appendix 4:** Pooled (random effects) recruitment and attrition rates for studies with attrition
25
26
27 375 > 0% and recruitment < 100%.
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29 376 **Appendix 5.** Forest plot of overall follow-up rate.
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31 377 **Appendix 6.** Forest plot of overall cross-over rate.
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34 378 **Appendix 7** Funnel Plot for All Included Trials. Effect sizes: 0 = 50%, +2 = ~88% and -2 =
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36
37 379 ~12 % attrition rate.
38
39 380 **Appendix 8.** Funnel Plot for Placebo Control Surgery Trials. Effect sizes: 0 = 50%, +2 =
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41
42 381 ~88% and -2 = ~12 % attrition rate.
43
44 382 **Appendix 9.** Funnel Plot for Non-Operative Control Surgery Trials. Effect sizes: 0 = 50%,
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47 383 +2 = ~88% and -2 = ~12 % attrition rate.
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3 387 **Contributorship Statement:** PN and SM contributed equally to this work and share first
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5 388 authorship. Conception and design: SA; Administrative support: SA; Provision of study
6
7 389 material or patients: SA; Collection and assembly of data: PN, SM, LH, MM, TK; Data
8
9 390 analysis and interpretation: All authors; Manuscript writing: All authors; Final approval of
10
11 391 manuscript: All authors.

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15 392
16 393 **Competing Interests:** RB has received royalties from UpToDate for authoring a chapter
17
18 394 unrelated to this paper (Plantar Fasciitis). SA has received grants and/or research contracts
19
20 395 from National Health and Medical Research Council, Avant Foundation and ANZ
21
22 396 Musculoskeletal Clinical Trial Network (ANZMUSC) as part of Sydney Partnership for
23
24 397 Health, Education, Research and Enterprise (SPHERE).

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26 398
27 399 **Funding:** This research received no specific grant from any funding agency in the public,
28
29
30 400 commercial or not-for-profit sectors. RB is funded by an Australian National Health and
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32 401 Medical Research Council Investigator Fellowship.

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34 402
35 403 **Data Sharing:** Dataset included as Appendix 2. Additional relevant data available on
36
37 404 reasonable request.

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41 406 **Transparency and Ethical declaration:** Authors affirms that this manuscript is an honest,
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44 407 accurate, and transparent account of the study being reported; that no important aspects of the
45
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47 408 study have been omitted; and that any discrepancies from the study as planned (and, if
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50 409 relevant, registered) have been explained.

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54 411 **Protocol Registration:** PROSPERO CRD42019117364. Original study protocol has been
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57 412 included as Supplementary File 1, and PROSPERO registration as Supplementary File 2.

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8 510 511
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11 512 **Table 1: Participant and Follow-up Characteristics**

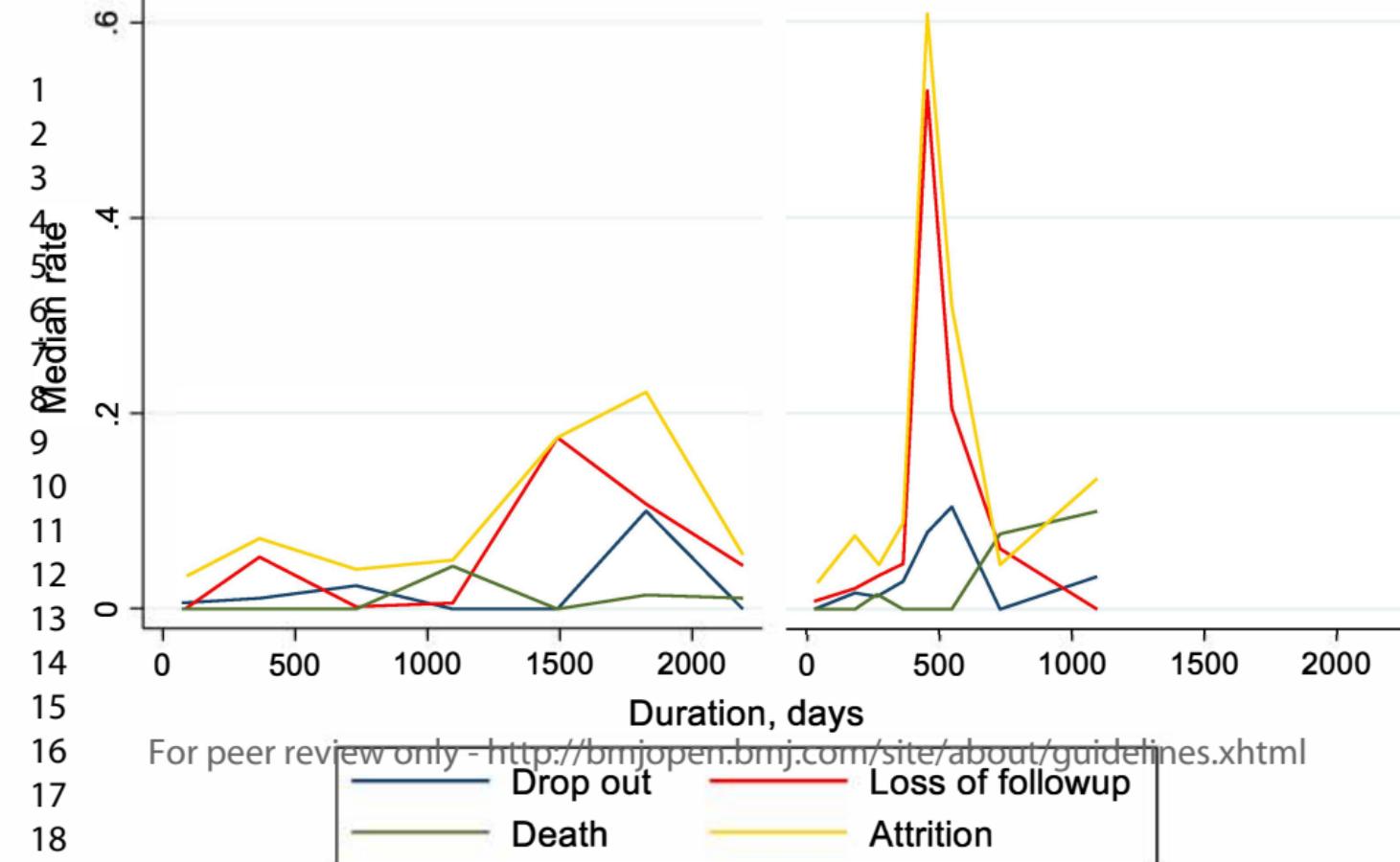
	Non-operative control	Placebo control	p-value
n	38	61	
Age of study cohorts (mean \pm SD, n)			
Surgical intervention group	54.8 \pm 12.6, (n=34)	50.4 \pm 13.4, (n=55)	0.125
Control group	55.1 \pm 13.0, (n=34)	50.5 \pm 13.3, (n=55)	0.114
Other group ¹	48 \pm 8, (n=3)	47.8 \pm 5.8, (n=4)	0.807
Gender of study cohorts (mean + SD)			
% Female	62.7 \pm 24.8	61.8 \pm 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

31 513
32 514 *number of follow-up points was not available for 5 studies (1 non-operative control and 4 placebo);
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34 515 ¹Other group only applicable to trials incorporating 3 treatment arms;
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36 516 SD = standard deviation, n = number of studies.
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3 522 **Table 2: Association between attrition rates and type of control group (placebo or non-**
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5 523 **operative) in surgical trials. Incident rate ratios (IRR) expressed for placebo control trials as a**
6
7 524 **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

19 525
20 526 * Poisson regression analysis using a Generalized Linear Latent and Mixed Model (GLLAMM) to
21
22 527 examine Incidents Rate Ratio (IRR), while controlling for participant gender, follow-up duration and
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24 528 number of follow-up timepoints.
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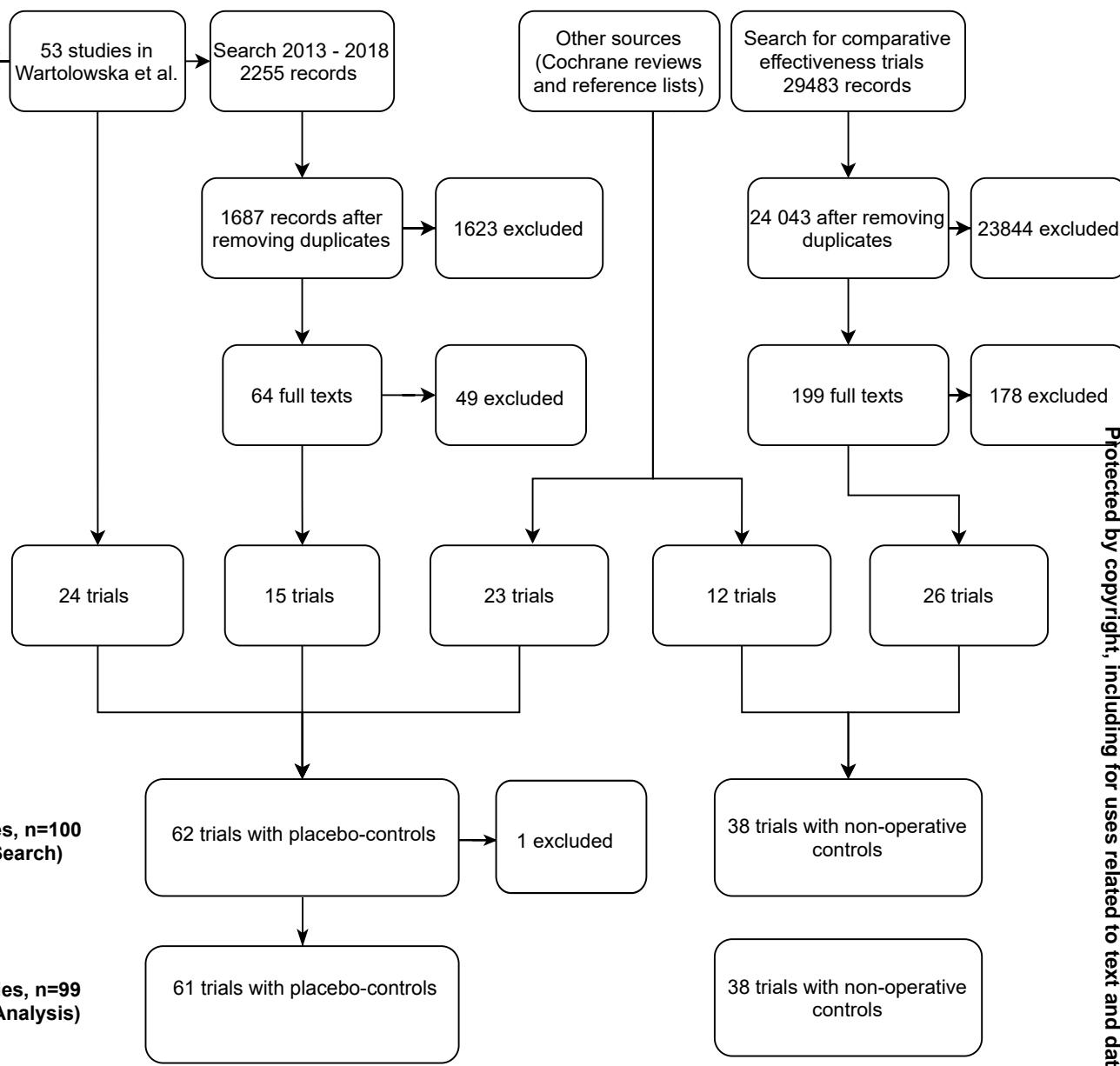


Figure 1. PRISMA flowchart of study selection

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.
1 62. post\$surgical.tw.
2 63. pre\$surgical.tw.
3 64. case report.tw.
4 65. case study.tw.
5 66. pacing.tw.
6 67. stimulation.tw.
7 68. growth factor\$.tw.
8 69. hormon\$.tw.
9 70. or/24-31
10 71. or/32-69
11 72. 17 and 23
12 73. 72 and 70
13 74. 73 not 71

14 **Ovid EMBASE**

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

1 51. pre\$an\$esthetic\$.tw.
2 52. post\$operative.tw.
3 53. prophylaxis.tw.
4 54. prevention.tw.
5 55. acupuncture.tw.
6 56. accupressure.tw.
7 57. scar\$.tw.
8 58. infection\$.tw.
9 59. acupressure.tw.
10 60. pre\$operative.tw.
11 61. growth factor\$.tw.
12 62. pacing.tw.
13 63. stimulation.tw.
14 64. hormon\$.tw.
15 65. case report\$.tw.
16 66. case study.tw.
17 67. or/30-66
18 68. 15 and 20
19 69. 68 and 29
20 70. 69 not 67
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22

Cochrane Central Register of Controlled Trials

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

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

ClinicalTrials.gov

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

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2 **Non-operative controlled trials:**
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5 **Abdominal pain/adhesiolysis (2016-current)**
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8 Before 2016: Van Beukel et al (2017) (1)
9
10 MEDLINE
11
12 1. randomized controlled trial.pt.
13 2. controlled clinical trial.pt.
14 3. randomized.ab.
15 4. randomised.ab.
16 5. placebo.tw.
17 6. clinical trials as topic.sh.
18 7. randomly.ab.
19 8. trial.ti.
20 9. groups.tiab.
21 10. OR/1-9
22 11. exp animals/ not humans.sh.
23 12. 10 NOT 11
24 13. exp abdominal pain/
25 14. exp chronic pain/
26 15. exp Tissue Adhesions/
27 16. Adhesion\$.tw.
28 17. adhesi*.tiab.
29 18. OR/12-17
30 19. exp laparotomy
31 20. exp laparoscopy
32 21. laparoscop*.ti,ab.
33 22. laparotomy.ti,ab.
34 23. adhesiolysis.ti,ab.
35 24. ((abdomen or abdominal or abdomino*) and surgery).ti,ab.
36 25. OR/18-24
37 26. AND/11,18,25
38 27. limit 26 to yr="2016-Current"
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46 Embase
47
48 1. Clinical Trial/
49 2. Randomized Controlled Trial/
50 3. exp randomization/
51 4. Single Blind Procedure/
52 5. Double Blind Procedure/
53 6. Crossover Procedure/
54 7. Placebo/
55 8. Randomi?ed controlled trial\$.tw.
56 9. Rct.tw.
57 10. random allocation.tw.
58 11. randomly allocated.tw.
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3 12. allocated randomly.tw.
4 13. (allocated adj2 random).tw.
5 14. Single blind\$.tw.
6 15. Double blind\$.tw.
7 16. ((treble or triple) adj blind\$).ti.
8 17. placebo\$.tw.
9 18. prospective study/
10 19. OR/1-18
11 20. exp abdominal pain/
12 21. exp chronic pain/
13 22. exp Tissue Adhesions/
14 23. Adhesion\$.ti.
15 24. adhesi\$.ti,ab.
16 25. OR/20-24
17 26. exp laparoscopy/
18 27. exp laparotomy/
19 28. laparoscop\$.ti,ab.
20 29. laparotomy.ti,ab.
21 30. adhesiolysis.ti,ab.
22 31. (abdomen.ti,ab. or abdominal.ti,ab. or abdomino\$.ti,ab.) AND surgery.ti,ab.
23 32. OR/26-31
24 33. AND/19,25,32
25 34. limit 33 to yr="2016-current"
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31 CENTRAL
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33 1. (abdominal pain)
34 2. MeSH descriptor [chronic pain]) explode all trees
35 3. (Adhesion)
36 4. #1 OR #2 OR #3
37 5. MeSH descriptor [laparoscopy] explode all trees
38 6. MeSH descriptor [laparotomy] explode all trees
39 7. laparoscop\$
40 8. adhesiolysis
41 9. #5 OR #6 OR #7 OR #8
42 10. #4 AND #9
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48 Reference List
49
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52 gynaecological and general surgery: a systematic review and meta-analysis. Human
53 Reproduction Update. 2017 May 1;23(3):276-88.
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1
2
3 **Benign Prostatic Hyerplasia/ Urethral Lift**
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5

6 Medline

- 7
8 1. Exp Prostatic Hyperplasia/
9 2. prostat* adj3 hyperplasia*.tw.
10 3. Prostate* adj3 hypertroph*.tw.
11 4. Prostat* adj3 adenoma*.tw.
12 5. BPH or BPO or BPE.tw.
13 6. prostat* adj3 enlarg*.tw.
14 7. exp prostatism/
15 8. prostatism.tw
16 9. exp Urinary Bladder Neck Obstruction/
17 10. Bladder* adj3 obstruct*.tw.
18 11. BOO.tw.
19 12. OR/1-11
20 13. Prostatic urethral lift.tw
21 14. prost* adj3 lift.tw.
22 15. Urolift.tw.
23 16. 13 or 14
24 17. 12 and 15
25 18. randomized controlled trial.pt.
26 19. controlled clinical trial.pt.
27 20. randomized
28 21. randomized
29 22. placebo.tw
30 23. clinical trials as topic.sh
31 24. randomly.ab.
32 25. trial.ti.
33 26. groups.ti,ab.
34 27. or/17-25
35 28. animals not (humans and animals).sh
36 29. 26 not 27
37 30. 16 and 28

46 EMBASE

- 47
48 Clinical Trial/
49 Randomized Controlled Trial/
50 exp randomization/
51 Single Blind Procedure/
52 Double Blind Procedure/
53 Crossover Procedure/
54 Placebo/
55 Randomi?ed controlled trial\$.tw.
56 Rct.tw.
57 random allocation.tw.

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3 randomly allocated.tw.
4 allocated randomly.tw.
5 (allocated adj2 random).tw.
6 Single blind\$.tw.
7 Double blind\$.tw.
8 ((treble or triple) adj blind\$).tw.
9 placebo\$.tw.
10 prospective study/
11 or/1-18
12 case study/
13 case report.tw.
14 abstract report/ or letter/
15 or/20-22
16 19 NOT 23
17 Prostatic urethral lift.tw
18 prost\$ lift.tw.
19 Urolift.tw.
20 OR/25-27
21 Exp Prostatic Hyperplasia/
22 prostat\$ adj3 hyperplasia\$.tw.
23 Prostate\$ adj3 hypertroph\$.tw.
24 Prostat\$ adj3 adenoma\$.tw.
25 BPH or BPO or BPE.tw.
26 prostat\$ adj3 enlarg\$.tw.
27 exp prostatism/
28 prostatism.tw.
29 exp Urinary Bladder Neck Obstruction/
30 Bladder\$ adj3 obstruct\$.tw.
31 BOO.tw.
32 OR/29-39
33 and/24,28,40
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42 CENTRAL
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45 1. MeSH description [benign prostatic hyperplasia] explode all trees
46 2. surgical procedures, operative explode all trees
47 3. surg* or surgical* or operat*:ti,ab
48 4. #2 or #3
49 5. #4 and #1
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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

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3 20. case study/
4 21. case report.tw.
5 22. abstract report/ or letter/
6 23. or/20-22
7 24. 19 NOT 23
8 25. Callosities/
9 26. callosities.mp.
10 27. callus.mp.
11 28. OR/25-27
12 29. Exp surgical procedures, operative/
13 30. (surg\$ or surgical\$ or operat\$).ti,ab.
14 31. debridement*.ti,ab.
15 32. OR/29-31
16 33. AND/24,28,32
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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

1
2
3 **Cervical dystonia**
4
5

6 Medline

7 randomized controlled trial.pt.
8 controlled clinical trial.pt.
9 randomized.ab.
10 randomised.ab.
11 placebo.tw.
12 clinical trials as topic.sh.
13 randomly.ab.
14 trial.ti.
15 (crossover or cross-over or cross over).tw.
16 or/1-9
17 exp animals/ not humans.sh.
18 10 NOT 11
19 cervical dystonia
20 Spasmodic Torticollis
21 focal dystonia
22 laterocollis or anterocollis or retrocollis):tw
23 OR/13-16
24 surgical procedures, operative/
25 (surg* or surgical* or operat*).ti,ab
26 deep brain stimulation.ti,ab
27 OR/18-20
28 and/12,17,21
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37 EMBASE
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40 1. Clinical Trial/
41 2. Randomized Controlled Trial/
42 3. exp randomization/
43 4. Single Blind Procedure/
44 5. Double Blind Procedure/
45 6. Crossover Procedure/
46 7. Placebo/
47 8. Randomi?ed controlled trial\$.tw.
48 9. Rct.tw.
49 10. random allocation.tw.
50 11. randomly allocated.tw.
51 12. allocated randomly.tw.
52 13. (allocated adj2 random).tw.
53 14. Single blind\$.tw.
54 15. Double blind\$.tw.
55 16. ((treble or triple) adj blind\$).tw.
56 17. placebo\$.tw.
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3 18. prospective study/
4 19. or/1-18
5 20. case study/
6 21. case report.tw.
7 22. abstract report/ or letter/
8 23. or/20-22
9 24. 19 NOT 23
10 25. cervical dystonia/
11 26. spastic torticollis.tw.
12 27. dystonia.ti,ab.
13 28. laterocollis or anterocollis or retrocollis).tw.
14 29. OR/25-28
15 30. surgical procedures, operative/
16 31. (surg* or surgical* or operat*).ti,ab
17 32. Deep brain stimulation.ti,ab.
18 33. or/30-32
19 34. and/24,29,33
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26 CENTRAL
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28 1. MeSH Term: [Torticollis] explode all trees
29 2. dystonia:kw
30 3. #1 OR #2
31 4. MeSH Term [surgical procedures, operative] explode all trees
32 5. (surg* or surgical* or operat*):ti,ab
33 6. (deep brain stimulation):kw
34 7. #4 or #5 or #6
35 8. #3 and #7
36 9. limit to trials
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2 **Endometriosis**
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45 Medline
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- 8 1. randomized controlled trial.pt.
9 2. controlled clinical trial.pt.
10 3. randomized.ab.
11 4. randomised.ab.
12 5. placebo.tw.
13 6. clinical trials as topic.sh.
14 7. randomly.ab.
15 8. trial.ti.
16 9. (crossover or cross-over or cross over).tw.
17 10. or/1-9
18 11. exp animals/ not humans.sh.
19 12. 10 NOT 11
20 13. exp Laparoscopy/ (146878)
21 14. Laparoscop\$.tw. (183770)
22 15. celioscop\$.tw. (580)
23 16. peritoneoscop\$.tw. (1176)
24 17. exp minimally invasive surgery/ (37349)
25 18. exp laser/ (123007)
26 19. exp diathermy/ (7154)
27 20. diathermy.tw. (4955)
28 21. LUNA.tw. (1395)
29 22. presacral neurectom\$.tw. (177)
30 23. laser\$.tw. (248739)
31 24. plasmajet.tw. (75)
32 25. plasma jet.tw. (342)
33 26. microlaparoscop\$.tw. (198)
34 27. minilaparoscop\$.tw. (342)
35 28. exp robotics/ (34612)
36 29. exp computer assisted surgery/ (11310)
37 30. Computer-Assisted Surg\$.tw. (1248)
38 31. da vinci.tw. (4710)
39 32. (keyhole adj3 surg\$).tw. (194)
40 33. Robot\$.tw. (56125)
41 34. remote surg\$.tw. (151)
42 35. microsurg\$.tw. (29971)
43 36. uterine nerve ablation\$.tw. (39)
44 37. uterosacral nerve ablation.tw. (38)
45 38. minimally invasive.tw. (84934)
46 39. (ablation or ablative).tw. (136843)
47 40. or/13-39 (748344)
48 41. exp endometriosis/ (36593)
49 42. exp infertility/ (121827)
50 43. endometrio\$.tw. (42667)

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3 44. dyschezia.tw. (546)
4 45. dyspareunia.tw. (6811)
5 46. exp infertility/
6 47. or/41-46 (168951)
7 48. AND/12,40,47
8 49. limit 48 to yr="2013-current
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13 EMBASE
14

15 1. Clinical Trial/
16 2. Randomized Controlled Trial/
17 3. exp randomization/
18 4. Single Blind Procedure/
19 5. Double Blind Procedure/
20 6. Crossover Procedure/
21 7. Placebo/
22 8. Randomi?ed controlled trial\$.tw.
23 9. Rct.tw.
24 10. random allocation.tw.
25 11. randomly allocated.tw.
26 12. allocated randomly.tw.
27 13. (allocated adj2 random).tw.
28 14. Single blind\$.tw.
29 15. Double blind\$.tw.
30 16. ((treble or triple) adj blind\$).tw.
31 17. placebo\$.tw.
32 18. prospective study/
33 19. or/1-18
34 20. case study/
35 21. case report.tw.
36 22. abstract report/ or letter/
37 23. or/20-22
38 24. 19 NOT 23
39 25. exp Laparoscopy/ (146878)
40 26. Laparoscop\$.tw. (183770)
41 27. celioscop\$.tw. (580)
42 28. peritoneoscop\$.tw. (1176)
43 29. exp minimally invasive surgery/ (37349)
44 30. exp laser/ (123007)
45 31. exp diathermy/ (7154)
46 32. diathermy.tw. (4955)
47 33. LUNA.tw. (1395)
48 34. presacral neurectom\$.tw. (177)
49 35. laser\$.tw. (248739)
50 36. plasmajet.tw. (75)
51 37. plasma jet.tw. (342)

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3 38. microlaparoscop\$.tw. (198)
4 39. minilaparoscop\$.tw. (342)
5 40. exp robotics/ (34612)
6 41. exp computer assisted surgery/ (11310)
7 42. Computer-Assisted Surg\$.tw. (1248)
8 43. da vinci.tw. (4710)
9 44. (keyhole adj3 surg\$).tw. (194)
10 45. Robot\$.tw. (56125)
11 46. remote surg\$.tw. (151)
12 47. microsurg\$.tw. (29971)
13 48. uterine nerve ablation\$.tw. (39)
14 49. uterosacral nerve ablation.tw. (38)
15 50. minimally invasive.tw. (84934)
16 51. (ablation or ablative).tw. (136843)
17 52. exp hand assisted laparoscopy/ (712)
18 53. or/25-53 (748344)
19 54. exp endometriosis/ (36593)
20 55. exp infertility/ (121827)
21 56. endometrio\$.tw. (42667)
22 57. dyschezia.tw. (546)
23 58. dyspareunia.tw. (6811)
24 59. or/54-58 (168951)
25 60. AND/24,53,59
26 61. limit 60 to yr=" 2013-current"
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35 CENTRAL
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37 1 exp Laparoscopy/
38 2 Laparoscop\$.ti,ab,sh.
39 3 celioscop\$.tw.
40 4 peritoneoscop\$.tw.
41 5 exp Surgical Procedures, Minimally Invasive/
42 6 Lasers/
43 7 exp Diathermy/
44 8 LUNA
45 9 presacral neurectom*
46 10 (minimal\$ adj5 surg\$).tw.
47 11 laser\$.tw.
48 12 diathermy.tw.
49 13 plasmajet.tw.
50 14 plasma jet.tw.
51 15 excision.tw.
52 16 microlaparoscop\$.tw.
53 17 minilaparoscop\$.tw.
54 18 exp Robotics/
55 19 exp Surgery, Computer-Assisted/
56 20 Computer-Assisted Surg\$.tw.
57 21 da vinci.tw.

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3 22 (keyhole near3 surg\$).tw.
4 23 Robot\$.tw.
5 24 remote surg\$.tw.
6 25 microsurg\$.tw.
7 26 minimally invasive.tw.
8 27 (ablation or ablative).tw.
9 28 or/1-27
10 29 exp Endometriosis/
11 30 endometrio\$.tw.
12 31 dyschezia.tw.
13 32 dyspareunia.tw.
14 33 infertility:kw
15 34 MeSH term infertility explode all trees
16 35 #29 or #30 or #31 or 32 #or 33
17 34 28 and 35
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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.

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3 22. abstract report/ or letter/
4 23. or/20-22
5 24. 19 NOT 23
6 25. transoral incisionless fundoplication.mp.
7 26. EsophyX.mp.
8 27. Endocinch.mp.
9 28. transoral fundoplication.mp.
10 29. endoscopic fundoplication.mp.
11 30. or/25-29
12 31. 24 and 30
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16 CENTRAL
17

- 18 1. EsophyX
19 2. Endocinch
20 3. (transoral fundoplication) OR (transoral plication) OR (endoscopic plication) OR
21 (endoscopic fundoplication)
22 4. TIF
23 5. #1 OR #2 OR #3 OR #4 OR #5
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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 incontinent\$).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.

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2
3 44. OR/38-44
4 45. AND/12,17,36 (for the sling, limit 2018 – current)
5 46. AND/12, 17, 44 (2017-current)
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8 EMBASE
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- 1 1. Clinical Trial/
2 2. Randomized Controlled Trial/
3 3. exp randomization/
4 4. Single Blind Procedure/
5 5. Double Blind Procedure/
6 6. Crossover Procedure/
7 7. Placebo/
8 8. Randomi?ed controlled trial\$.tw.
9 9. Rct.tw.
10 10. random allocation.tw.
11 11. randomly allocated.tw.
12 12. allocated randomly.tw.
13 13. (allocated adj2 random).tw.
14 14. Single blind\$.tw.
15 15. Double blind\$.tw.
16 16. ((treble or triple) adj blind\$).tw.
17 17. placebo\$.tw.
18 18. prospective study/
19 19. or/1-18
20 20. case study/
21 21. case report.tw.
22 22. abstract report/ or letter/
23 23. or/20-22
24 24. 19 NOT 23
25 25. exp Urinary Incontinence, stress/
26 26. ((stress\$ or mix\$ or urg\$ or urin\$) adj3 incontinen\$).tw.
27 27. stress urinary incontinence*.mp.
28 28. occult urinary incontinence.mp.
29 29. OR/25-28
30 30. exp surgical procedures, operative/
31 31. (surg* or surgical* or operat*).ti,ab.
32 32. suburethral sling.mp.
33 33. abdominal sling.mp.
34 34. traditional sling procedure\$*.tw.
35 35. suburethral sling procedure.tw.
36 36. mid\$urethral sling.tw.
37 37. retropubic sling procedure\$*.tw.
38 38. transobturator sling procedure\$.tw.
39 39. TVT-Secur.mp.
40 40. mini-arc or mini-arc.mp.
41 41. ajust.mp.

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2
3 42. needleless.mp.
4 43. solyx.mp.
5 44. single\$incision sling\$.mp.
6 45. mini\$sling.mp.
7 46. Ophira.mp.
8 47. Tissue Fixation System.mp.
9 48. OR/30-47
10 49. ((urethra* or periurethra* or transurethra*) adj3 (agent* or bulk* or injection* or
11 injectable*).tw.
12 50. injection therapy.tw.
13 51. injectable\$.tw.
14 52. (injectable\$ adj2 agent\$).tw.
15 53. (bulk\$ adj3 agent\$).tw.
16 54. autologous fat.mp.
17 55. Peri\$urethral injection\$.mp.
18 56. OR/38-44
19 57. AND/12,18,37 (this is for the sling, limit April 2018 – March 2019
20 58. AND/12, 18, 45 (2017-current)
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26 CENTRAL
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29 1. MeSH descriptor: [Urinary Incontinence, Stress] explode all trees
30 2. stres* near incontinen*:kw
31 3. stress near incontinence*:kw
32 4. mix* near incontinen*:kw
33 5. urg* near incontinen*:kw
34 6. stress urinary incontinence*:kw
35 7. occult urinary incontinence:kw
36 8. #1 or #2 or #3 or #4 or #5 or #6 or #7
37 9. MeSH descriptor: [Surgical Procedures, Operative] explode all trees
38 10. (surg* or surgical* or operat*):ti,ab
39 11. suburethral sling:kw
40 12. abdominal sling:kw
41 13. mid\$urethral sling:kw
42 14. retropubic sling:kw
43 15. transobturator sling:kw
44 16. "mini-arc" or "mini-arc"
45 17. ajust
46 18. needleless
47 19. solyx
48 20. single\$incision sling:kw
49 21. mini near sling:kw
50 22. Tissue Fixation System:kw
51 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
52 #20 or #21 or #22
53 24. #8 and #23
54 25. with Publication Year from 2018 to 2019, in Trials
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4 injectables
5 1. MeSH descriptor: [Urinary Incontinence, Stress] explode all trees
6 2. stres* near incontinent*:kw
7 3. stress near incontinence*:kw
8 4. mix* near incontinent*:kw
9 5. urg* near incontinent*:kw
10 6. stress urinary incontinence*:kw
11 7. occult urinary incontinence:kw
12 8. #1 or #2 or #3 or #4 or #5 or #6 or #7
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3 Meniere's Disease
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67 MEDLINE
8

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

31 EMBASE
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- 33 1. Clinical Trial/
- 34 2. Randomized Controlled Trial/
- 35 3. exp randomization/
- 36 4. Single Blind Procedure/
- 37 5. Double Blind Procedure/
- 38 6. Crossover Procedure/
- 39 7. Placebo/
- 40 8. Randomi?ed controlled trial\$.tw.
- 41 9. Rct.tw.
- 42 10. random allocation.tw.
- 43 11. randomly allocated.tw.
- 44 12. allocated randomly.tw.
- 45 13. (allocated adj2 random).tw.
- 46 14. Single blind\$.tw.
- 47 15. Double blind\$.tw.
- 48 16. ((treble or triple) adj blind\$).tw.
- 49 17. placebo\$.tw.
- 50 18. prospective study/

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3 19. or/1-18
4 20. case study/
5 21. case report.tw.
6 22. abstract report/ or letter/
7 23. shunt.tw.
8 24. endolymphatic sac adj3 surgery
9 25. ((endolymphatic or sac) and shunt).ti,ab.
10 26. (endolymphatic and (surg\$ or decompress\$ or drainage)).ti,ab.
11 27. OR/23-26
12 28. endolymphatic hydrops.mp.
13 29. meniere disease/
14 30. vertigo.mp.
15 31. labyrinth or aural or endolymphatic adj3 syndrome or vertigo or hydrops
16 32. OR/28-31
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21 CENTRAL
22
23 1. surg* or decompression or drainage or shunt or operat* or surgical*
24 2. endolymphatic
25 3. #1 AND #2
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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/

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

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3 48. exp GASTROPLASTY/
4 49. ("gastric plication" or "vagal nerve stimulation" OR "vagal nerve block").ti,ab.
5 50. gastric stapl*.ti,ab.
6 51. OR/38-50
7 52. 37 AND 51
8 53. OBESITY/su [Surgery]
9 54. Morbid Obesity/su [Surgery]
10 55. 53 OR 54
11 56. 37 AND 55
12 57. 52 OR 56
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15
16 CENTRAL
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18
19 #1 MeSH descriptor: [Obesity] explode all trees
20 #2 MeSH descriptor: [Overweight] this term only
21 #3 MeSH descriptor: [Weight Loss] explode all trees
22 #4 (obes* or overweight or "over weight")
23 #5 #1 or #2 or #3 or #4
24
25 #6 MeSH descriptor: [Bariatric Surgery] explode all trees
26 #7 (bariatric near/5 surg*)
27 #8 (obes* near/5 surg*)
28 #9 antiobesity or anti-obesity or anti obesity near/5 (surg*))
29 #10(gastroplasty or gastrogastrostomy or gastro?gastrostomy or gastroenterostomy or "gastric
30 bypass" or "gastric surgery" or "restrictive
31 surgery")
32
33 #11 MeSH descriptor: [Gastric Bypass] explode all trees
34 #12 MeSH descriptor: [Gastropasty] explode all trees
35 #13 stomach near/5 stapl*
36 #14 gastric near/5 stapl*
37 #15 (gastric plication):ti,ab OR (vagal nerve block):ti,ab OR (vagal nerve stimulation):ti,ab
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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.

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2
3 18. prospective study/
4 19. or/1-18
5 20. case study/
6 21. case report.tw.
7
8 22. abstract report/ or letter/
9 23. or/20-22
10 24. 19 NOT 23
11 25. Parkinson's disease/
12 26. Parkinson's syndrome
13 27. Parkinson*.ti,ab
14 28. OR/25-27
15 29. surgical procedures, operative/
16 30. (surg* or surgical* or operat*).ti,ab
17 31. cell adj2 delivery.ti,ab.
18 32. gene adj delivery.ti,ab.
19 33. or/29-32
20 34. and/24,28,33
21
22
23
24
25 CENTRAL
26
27
28 1. MeSH Term: [Parkinson's disease] explode all trees
29 2. Parkinson*.ti,ab
30 3. #1 OR #2
31 4. MeSH Term [surgical procedures, operative] explode all trees
32 5. (surg* or surgical* or operat*):ti,ab
33 6. (cell adj2 delivery):ti,ab.
34 7. (gene adj delivery):ti,ab.
35 8. #4 or #5 or #6 or #7
36 9. #3 and #8
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1
2
3 **Sphincter of Oddi (Sphincterotomy)**
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6 Medline

- 7
8 1. randomized controlled trial.pt.
9 2. controlled clinical trial.pt.
10 3. randomized.ab.
11 4. randomised.ab.
12 5. placebo.tw.
13 6. clinical trials as topic.sh.
14 7. randomly.ab.
15 8. trial.ti.
16 9. (crossover or cross-over or cross over).tw.
17 10. or/1-9
18 11. exp animals/ not humans.sh.
19 12. 10 NOT 11
20 13. sphincter of oddi.mp.
21 14. endoscopic sphincterotomy.mp.
22 15. exp surgical procedures, operative/
23 16. (surg* or surgical* or operat*).ti,ab.
24 17. or/14-16
25 18. and/24-25,29 (240)
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32 EMBASE
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- 34 1 Clinical Trial/ (972204)
35 2 Randomized Controlled Trial/ (538693)
36 3 exp randomization/ (81721)
37 4 Single Blind Procedure/ (33954)
38 5 Double Blind Procedure/ (160406)
39 6 Crossover Procedure/ (58585)
40 7 Placebo/ (340669)
41 8 Randomi?ed controlled trial\$.tw. (196048)
42 9 Rct.tw. (31284)
43 10 random allocation.tw. (1931)
44 11 randomly allocated.tw. (31999)
45 12 allocated randomly.tw. (2439)
46 13 (allocated adj2 random).tw. (960)
47 14 Single blind\$.tw. (22514)
48 15 Double blind\$.tw. (200441)
49 16 ((treble or triple) adj blind\$).tw. (954)
50 17 placebo\$.tw. (290122)
51 18 prospective study/ (504017)
52 19 or/1-18 (2037125)
53 20 case study/ (68702)
54 21 case report.tw. (400876)
55 22 abstract report/ or letter/ (1086984)
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3 23 or/20-22 (1547292)
4 24 19 not 23 (1986570)
5 25 sphincter of oddi.mp. (3272)
6 26 endoscopic sphincterotomy.mp. (5835)
7 27 exp surgical procedures, operative/ (4859006)
8 28 (surg* or surgical* or operat*).ti,ab. (3421933)
9 29 or/26-28 (6152758)
10 30 and/24-25,29 (240)
11
12
13
14 CENTRAL
15
16
17 1. sphincter of oddi
18 2. endoscopic sphincterotomy
19 3. sphincterotomy
20 4. surg* or surgical* or operative:kw
21 5. MeSH Term:[Surgical Procedures, Operative] explode all trees
22 6. #2 or #3 or #4 or #5
23 7. #1 and #6
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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/

- 1
2
3 23. or/20-22
4 24. 19 NOT 23
5 25. (SLAP or superior labral anterior-posterior or superior labral anterior posterior).mp.
6 26. surgical procedures, operative/
7 27. (surg* or surgical* or operat*).ti,ab
8 28. (biceps tenodesis OR biceps tenotomy OR repair OR suture OR debridement).ti,ab.
9 29. OR/26-28
10 30. AND/24, 25,29
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12
13
14 CENTRAL
15
16 1. SLAP
17 2. superior labral anterior-posterior or superior labral anterior posterior
18 3. #1 OR #2
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1
2 **Sleep Apnea**
3
45 **Medline**
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- 8 1. randomized controlled trial.pt.
- 9 2. controlled clinical trial.pt.
- 10 3. randomized.ab.
- 11 4. randomised.ab.
- 12 5. placebo.tw.
- 13 6. clinical trials as topic.sh.
- 14 7. randomly.ab.
- 15 8. trial.ti.
- 16 9. (crossover or cross-over or cross over).tw.
- 17 10. or/1-9
- 18 11. exp animals/ not humans.sh.
- 19 12. 10 NOT 11
- 20 13. palate/
- 21 14. palatal OR palate
- 22 15. 13 OR 14
- 23 16. implant*
- 24 17. 15 AND 16
- 25 18. septumplasty/
- 26 19. nasal adj3 surgery.ti,ab.
- 27 20. resection adj4 septum.tw.
- 28 21. OR/17-20
- 29 22. obstructive sleep apnea/
- 30 23. sleep apnea.ti,ab.
- 31 24. sleeping disorder.ti,ab
- 32 25. OR/22-24
- 33 26. AND/12,21,25

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41 **EMBASE**
42
43

- 44 1. Clinical Trial/
- 45 2. Randomized Controlled Trial/
- 46 3. exp randomization/
- 47 4. Single Blind Procedure/
- 48 5. Double Blind Procedure/
- 49 6. Crossover Procedure/
- 50 7. Placebo/
- 51 8. Randomi?ed controlled trial\$.tw.
- 52 9. Rct.tw.
- 53 10. random allocation.tw.
- 54 11. randomly allocated.tw.
- 55 12. allocated randomly.tw.
- 56 13. (allocated adj2 random).tw.
- 57 14. Single blind\$.tw.

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3 15. Double blind\$.tw.
4 16. ((treble or triple) adj blind\$).tw.
5 17. placebo\$.tw.
6 18. prospective study/
7 19. or/1-18
8 20. case study/
9 21. case report.tw.
10 22. abstract report/ or letter/
11 23. or/20-22
12 24. 19 NOT 23
13 25. palate/
14 26. palatal OR palate.mp.
15 27. 25 OR 26
16 28. implant*.mp.
17 29. 27 and 28
18 30. exp septumplasty/
19 31. nasal surgery/
20 32. nasal adj3 surgery.ti,ab.
21 33. resection adj4 septum.tw.
22 34. OR/29-33
23 35. exp obstructive sleep apnea/
24 36. sleep apnea.ti,ab.
25 37. sleeping disorder*.ti,ab
26 38. OR/35-37
27 39. AND/24,34,38
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36 CENTRAL
37
38 1. MeSH descriptor: [Palate] explode all trees
39 2. palatal or palate:kw
40 3. implant*
41 4. #1 or #2
42 5. #3 and #4
43 6. MeSH descriptor: [Nasal Surgical Procedures] explode all trees
44 7. nasal adj3 surgery:ti,ab
45 8. septum adj4 resection
46 9. #5 OR #6 OR #7 OR #8
47 10. MeSH descriptor: [Sleep Apnea, Obstructive] explode all trees
48 11. sleep apnea:ti,ab
49 12. sleep disorder*:kw
50 13. #10 or #11 or #12
51 14. #9 and #13
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1
2 **Spinal Cord Injury**
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45 **Medline**
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- 8 1. randomized controlled trial.pt.
- 9 2. controlled clinical trial.pt.
- 10 3. randomized.ab.
- 11 4. randomised.ab.
- 12 5. placebo.tw.
- 13 6. clinical trials as topic.sh.
- 14 7. randomly.ab.
- 15 8. trial.ti.
- 16 9. (crossover or cross-over or cross over).tw.
- 17 10. or/1-9
- 18 11. exp animals/ not humans.sh.
- 19 12. 10 NOT 11
- 20 13. exp Spinal Cord Injuries/
- 21 14. exp Central Cord Syndrome/
- 22 15. (myelopathy adj3 (traumatic or post-traumatic)).ab,ti.
- 23 16. ((spine or spinal or vertebrae) adj3 (fracture* or wound* or trauma* or injur* or
24 damag*)).ab,ti.
- 25 17. (spinal cord adj3 (contusion or laceration or transaction or trauma or
26 ischemia)).ab,ti.
- 27 18. central cord injury syndrome.ab,ti.
- 28 19. central spinal cord syndrome.ab,ti.
- 29 20. exp Paraplegia/
- 30 21. exp Quadriplegia/
- 31 22. OR/13-21
- 32 23. cell adj3 transplantation
- 33 24. Lamina Propria Transplantation
- 34 25. transplant*
- 35 26. regenerative surgery
- 36 27. AND/12,22,26

43 **EMBASE**
44
45

- 46 1. Clinical Trial/
- 47 2. Randomized Controlled Trial/
- 48 3. exp randomization/
- 49 4. Single Blind Procedure/
- 50 5. Double Blind Procedure/
- 51 6. Crossover Procedure/
- 52 7. Placebo/
- 53 8. Randomi?ed controlled trial\$.tw.
- 54 9. Rct.tw.
- 55 10. random allocation.tw.
- 56 11. randomly allocated.tw.
- 57 12. allocated randomly.tw.

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2
3 13. (allocated adj2 random).tw.
4 14. Single blind\$.tw.
5 15. Double blind\$.tw.
6 16. ((treble or triple) adj blind\$).tw.
7 17. placebo\$.tw.
8 18. prospective study/
9 19. or/1-18
10 20. case study/
11 21. case report.tw.
12 22. abstract report/ or letter/
13 23. or/20-22
14 24. 19 NOT 23
15 25. exp Spinal Cord Injuries/
16 26. exp Central Cord Syndrome/
17 27. (myelopathy adj3 (traumatic or post-traumatic)).ab,ti.
18 28. ((spine or spinal or vertebrae) adj3 (fracture\$ or wound\$ or trauma\$ or injur\$ or
19 damage\$)).ab,ti.
20 29. (spinal cord adj3 (contusion or laceration or transaction or trauma or
21 ischemia)).ab,ti.
22 30. central cord injury syndrome.ab,ti.
23 31. central spinal cord syndrome.ab,ti.
24 32. exp Paraplegia/
25 33. exp Quadriplegia/
26 34. OR/25-33
27 35. cell adj3 transplantation
28 36. Lamina Propria/
29 37. transplant\$
30 38. regenerative surgery
31 39. OR/35-38
32 40. AND/24,34,39
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40 CENTRAL
41
42 1. MeSH descriptor: [Spinal Cord Injuries] explode all trees
43 2. MeSH descriptor: [Central Cord Syndrome] explode all trees
44 3. myelopathy near3 (traumatic or post-traumatic)
45 4. (spine or spinal or vertebrae) near3 (fracture* or wound* or trauma* or injur* or damag*)
46 5. (spinal cord) near3 (contusion or laceration or transaction or trauma or ischemia)
47 6. central cord injury syndrome
48 7. central spinal cord syndrome
49 8. paraplegi* or quadriplegi* or tetraplegi*
50 9. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
51 10. transplant*:kw
52 11. cell near3 transplantation
53 12. regenerative surgery
54 13. MeSH descriptor: [Mucous Membrane] explode all trees
55 14. lamina propria transplant*:kw
56 15. #10 or #11 or #12 #13 or #14

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3 16. #9 and #15 (in trials)
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For peer review only

1
2 **Migraine**
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6 **MEDLINE**
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8

- 9 1. randomized controlled trial.pt.
- 10 2. controlled clinical trial.pt.
- 11 3. randomized.ab.
- 12 4. randomised.ab.
- 13 5. placebo.tw.
- 14 6. clinical trials as topic.sh.
- 15 7. randomly.ab.
- 16 8. trial.ti.
- 17 9. (crossover or cross-over or cross over).tw.
- 18 10. or/1-9
- 19 11. exp animals/ not humans.sh.
- 20 12. 10 NOT 11
- 21 13. Headache/ OR exp Headache Disorders/
- 22 14. exp Migraine Disorders/
- 23 15. (headach* OR migrain* OR cephalgi* OR cephalalgi*).ti,ab.
- 24 16. OR/13-15
- 25 17. surgical procedure, operative/
- 26 18. (surger* OR surgical* or operat*).tw.
- 27 19. ((nerve decompr*) OR (surgical decompr*) OR (surgical treat*)).tw.
- 28 20. OR/17-19
- 29 21. AND/12,16,20
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38 **EMBASE**
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- 41 1. Clinical Trial/
- 42 2. Randomized Controlled Trial/
- 43 3. exp randomization/
- 44 4. Single Blind Procedure/
- 45 5. Double Blind Procedure/
- 46 6. Crossover Procedure/
- 47 7. Placebo/
- 48 8. Randomi?ed controlled trial\$.tw.
- 49 9. Rct.tw.
- 50 10. random allocation.tw.
- 51 11. randomly allocated.tw.
- 52 12. allocated randomly.tw.
- 53 13. (allocated adj2 random).tw.
- 54 14. Single blind\$.tw.
- 55 15. Double blind\$.tw.
- 56 16. ((treble or triple) adj blind\$).tw.
- 57 17. placebo\$.tw.
- 58
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3 18. prospective study/
4 19. or/1-18
5 20. case study/
6 21. case report.tw.
7
8 22. abstract report/ or letter/
9 23. or/20-22
10 24. 19 NOT 23
11 25. surgical procedure/
12 26. (surger\$ OR surgical\$ or operat\$).tw.
13
14 27. OR/25-27
15 28. Headache/ OR exp Headache and facial pain/
16 29. exp Migraine/
17 30. (headach* OR migrain* OR cephalgi* OR cephalalgi*).ti
18
19 31. OR/29-31
20 32. AND/24,27,31
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25 CENTRAL
26
27 MeSH descriptor Headache/ OR MeSH descriptor Headache Disorders explode all trees
28 MeSH descriptor Migraine Disorders explode all trees
29 (headach* OR migrain* OR cephalgi* OR cephalalgi*):ti,ab,kw.
30
31 #1 OR #2 OR #3
32 surgical procedures, operative/
33 (surg* OR surgical* or operat*):kw,ab,ti
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1
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3 **Tardive dystonia**
45 MEDLINE
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- 9 1. randomized controlled trial.pt.
- 10 2. controlled clinical trial.pt.
- 11 3. randomized.ab.
- 12 4. randomised.ab.
- 13 5. placebo.tw.
- 14 6. clinical trials as topic.sh.
- 15 7. randomly.ab.
- 16 8. trial.ti.
- 17 9. (crossover or cross-over or cross over).tw.
- 18 10. or/1-9
- 19 11. exp animals/ not humans.sh.
- 20 12. 10 NOT 11
- 21 13. dystonia/
- 22 14. tardive dystonia.ti,ab.
- 23 15. OR/13-14
- 24 16. surgical procedures, operative/
- 25 17. (surg* or surgical* or operat*).ti,ab
- 26 18. deep brain stimulation.ti,ab
- 27 19. OR/16-18
- 28 20. AND/12,15,19

34
35 EMBASE
36
37

38 Clinical Trial/
39 Randomized Controlled Trial/
40 exp randomization/
41 Single Blind Procedure/
42 Double Blind Procedure/
43 Crossover Procedure/
44 Placebo/
45 Randomi?ed controlled trial\$.tw.
46 Rct.tw.
47 random allocation.tw.
48 randomly allocated.tw.
49 allocated randomly.tw.
50 (allocated adj2 random).tw.
51 Single blind\$.tw.
52 Double blind\$.tw.
53 ((treble or triple) adj blind\$).tw.
54 placebo\$.tw.
55 prospective study/

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2
3 or/1-18
4 case study/
5 case report.tw.
6
7 abstract report/ or letter/
8 or/20-22
9 19 NOT 23
10 Exp dystonia/
11 tardive dystonia.ti,ab.
12
13 OR/25-26
14 surgical procedures, operative/
15 (surg* or surgical* or operat*).ti,ab
16 Deep brain stimulation.ti,ab.
17
18 or/28-30
19 and/24,27,31
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23 CENTRAL
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- 26 1. dystonia:kw
27 2. (tardive dystonia):kw
28 3. (tarvide dyskinesia):kw
29 4. #1 OR #2 OR #3
30
31 5. MeSH Term [surgical procedures, operative] explode all trees
32 6. (surg* or surgical* or operat*):ti,ab
33 7. (deep brain stimulation):kw
34 8. #5 or #6 or #7
35 9. #4 and #8
36 10. limit to trials
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1
2
3 **Tennis Elbow**
4
56 Medline
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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

45 EMBASE
46
47

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.

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2
3 12. allocated randomly.tw.
4 13. (allocated adj2 random).tw.
5 14. Single blind\$.tw.
6 15. Double blind\$.tw.
7 16. ((treble or triple) adj blind\$).tw.
8 17. placebo\$.tw.
9 18. prospective study/
10 19. or/1-18
11 20. case study/
12 21. case report.tw.
13 22. abstract report/ or letter/
14 23. or/20-22
15 24. 19 NOT 23
16 25. exp Tennis Elbow/
17 26. exp Tendinopathy/
18 27. exp Tendon Injuries/
19 28. exp Elbow Joint/
20 29. exp Pain/
21 30. 28 and 29
22 31. tennis elbow.tw.
23 32. (Tendinitis or Tendinosis or Tendonitis).tw.
24 33. (pain\$ and lateral elbow).tw.
25 34. epicondylitis.tw.
26 35. common extensor origin.tw.
27 36. epicondylalgia.tw.
28 37. or/25-27,30-36
29 38. exp Surgery/
30 39. (surgery\$ or surgeries or surgical or operat\$).ti,ab.
31 40. (tenotomy or tendon release or ECRB release or extensor carpi radialis brevis
32 release).ti,ab.
33 41. or/26-28
34 42. AND/12,25,29
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41
42 CENTRAL
43
44 1. MeSH descriptor: [Tennis Elbow] explode all trees
45 2. MeSH descriptor: [Elbow Tendinopathy] explode all trees
46 3. MeSH descriptor: [Tendon Injuries] explode all trees
47 4. MeSH descriptor: [Tendon Injuries] explode all trees
48 5. MeSH descriptor: [Pain] explode all trees
49 6. #4 and #5
50 7. tennis elbow:ti,ab
51 8. (Tendinitis or Tendinosis or Tendonitis):ti,ab
52 9. (pain* and “lateral elbow”):ti,ab
53 10. epicondylitis:ti,ab
54 11. “common extensor origin”:ti,ab
55 12. epicondylalgia:ti,ab
56 13. (#1 OR #2 OR #3 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12)
57 14. MeSH descriptor: [Surgical Procedures, Operative] explode all trees
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3 15. (surgery* or surgeries or surgical or operat*):ti,ab
4 16. (tenotomy or tendon release or ECRB release or extensor carpi radialis brevis release):ti,ab
5 17. #14 or #15 or #16
6 18. #13 and #17
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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
- 48
49 2017-current

EMBASE

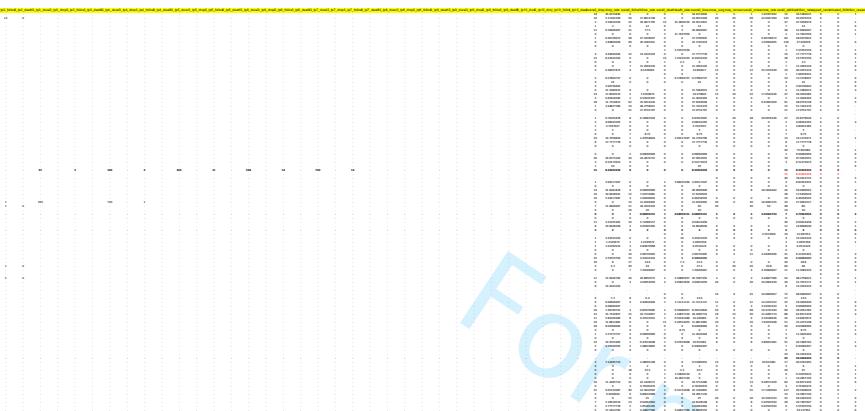
52. 1. Clinical Trial/
53. 2. Randomized Controlled Trial/
54. 3. exp randomization/
55. 4. Single Blind Procedure/
56. 5. Double Blind Procedure/
57. 6. Crossover Procedure/
58. 7. Placebo/

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3 8. Randomized controlled trial\$.tw.
4 9. Rct.tw.
5 10. random allocation.tw.
6 11. randomly allocated.tw.
7 12. allocated randomly.tw.
8 13. (allocated adj2 random).tw.
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10 14. Single blind\$.tw.
11 15. Double blind\$.tw.
12 16. ((treble or triple) adj blind\$).tw.
13 17. placebo\$.tw.
14 18. prospective study/
15 19. or/1-18
16 20. case study/
17 21. case report.tw.
18 22. abstract report/ or letter/
19 23. or/20-22
20 24. 19 NOT 23
21 25. exp Spine/
22 26. 34. (spine or spinal or vertebra\$).tw.
23 27. 35. exp Fractures, Bone/
24 28. 36. fractur\$.ti.
25 29. 37. 33 or 34
26 30. 38. 35 or 36
27 31. 39. 37 and 38
28 32. 40. exp Spinal Fractures/
29 33. 41. 39 or 40
30 34. 42. exp Bone Cements/
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32 36. 44. methacrylate\$.tw.
33 37. 45. bone cement\$.tw.
34 38. 46. exp Fracture Fixation, Internal/
35 39. 47. exp Vertebroplasty/
36 40. 48. vertebroplast\$.tw.
37 41. 49. cementoplast\$.tw.
38 42. 50. 50. sacroplast\$.tw. (114)
39 43. 51. or/42-50
40 44. 52. and/12,41,51
41 45. 2017-current
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52 CENTRAL
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54 1 exp Spine/ (4032)
55 2 (spine or spinal or vertebra\$).tw. (20306)
56 3 exp Fractures, Bone/ (3949)
57 4 fractur\$.ti. (6791)
58 5 1 or 2 (21641)
59 6 3 or 4 (8007)

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3 7 5 and 6 (1504)
4 8 exp Spinal Fractures/ (561)
5 9 7 or 8 (1528)
6 10 exp Bone Cements/ (769)
7 11 exp Methylmethacrylates/ (389)
8 12 methacrylate\$.tw. (251)
9 13 bone cement\$.tw. (201)
10 14 exp Fracture Fixation, Internal/ (1077)
11 15 exp Vertebroplasty/ (112)
12 16 vertebroplast\$.tw. (202)
13 17 cementoplast\$.tw. (10)
14 18 sacroplast\$.tw. (2)
15 19 or/10-18 (2421)
16 20 9 and 19 (244)
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3 **Appendix 2. Meta-regression for confounders including female proportion of study participants,**
4 **number enrolled and number of follow-up points**

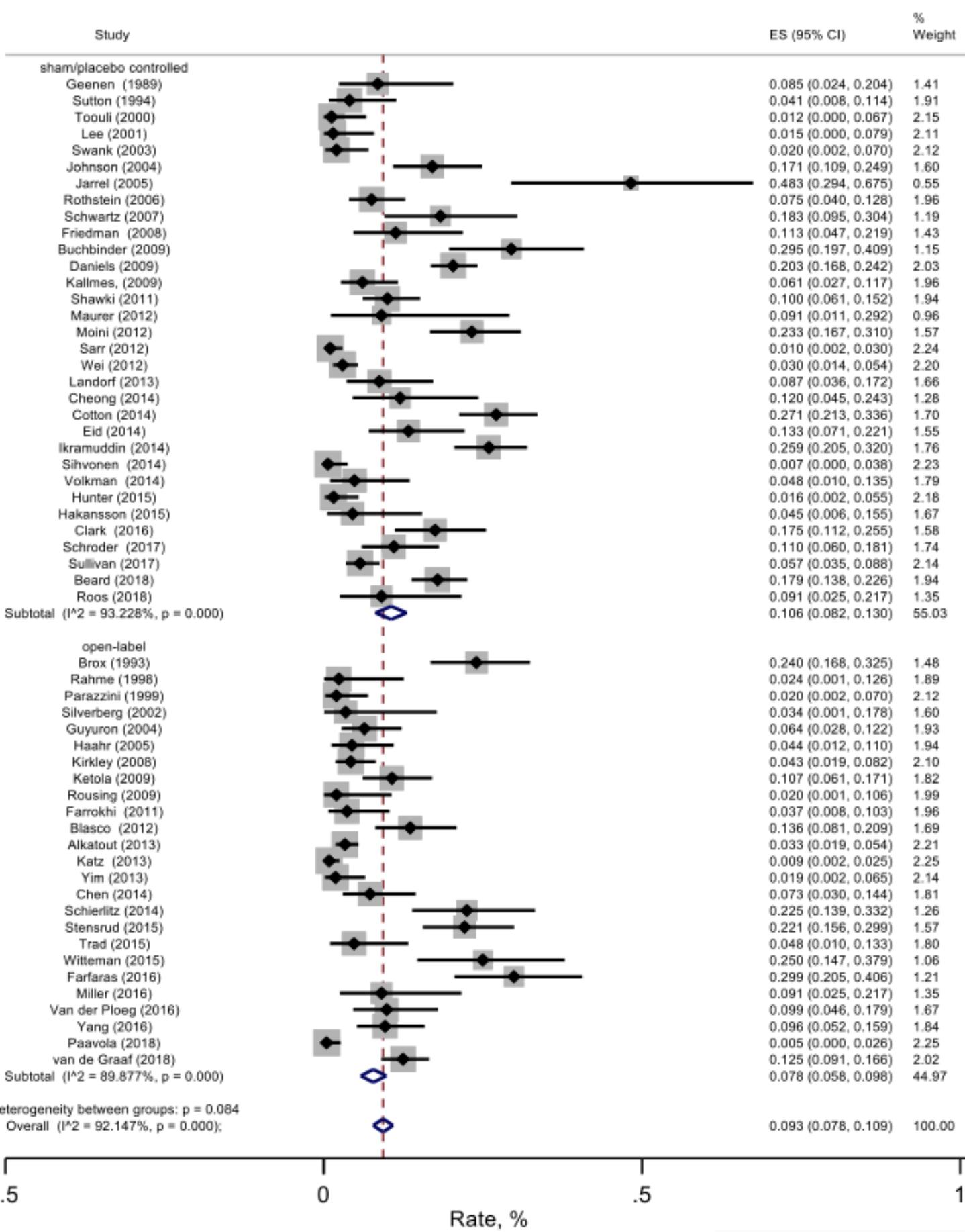
	Attrition rate effect size	Dropout rate effect size	Loss to follow-up effect size
Placebo Control Trials*	-0.17 (-0.66 to 0.32)	-0.24 (-0.86 to 0.37)	0.17 (-0.59 to 0.93)
Longest follow-up	0.0002 (-0.0004 to 0.0007)	-0.0003 (-0.0010 to 0.0004)	0.0002 (-0.0008 to 0.0011)
Female rate	-0.69 (-1.61 to 0.24)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

28 Note: *non-operative control trials used as a reference category

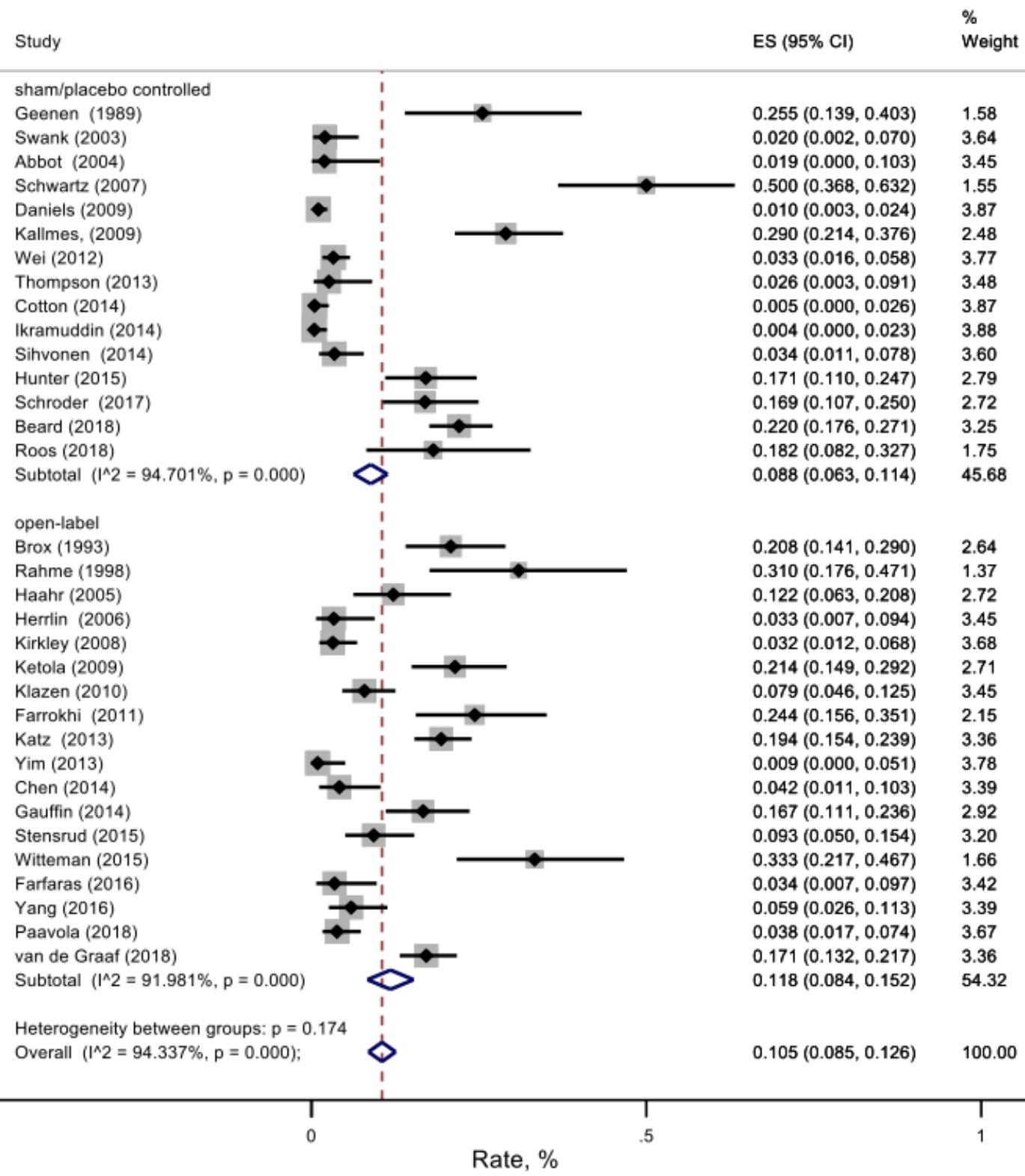
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3 Appendix 3: Pooled (random effects) recruitment and attrition rates for studies with attrition >
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5 0% and recruitment < 100%.
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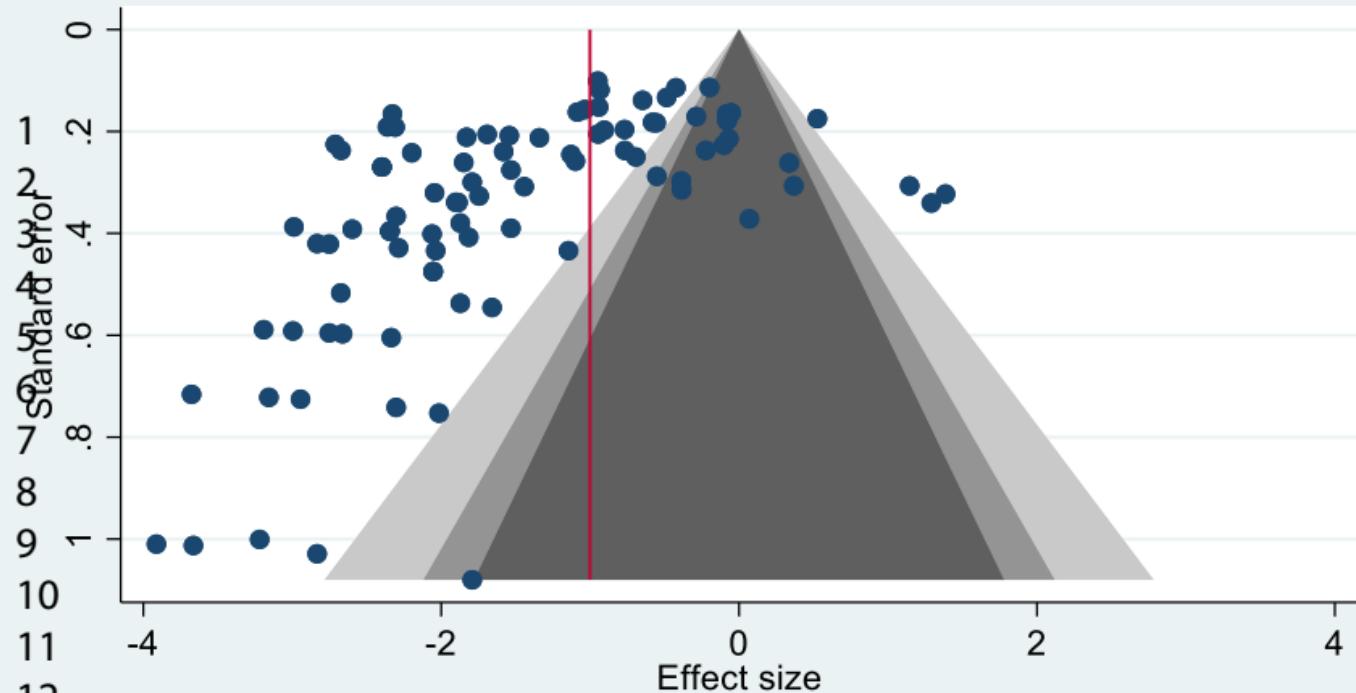
	Group	Rate (%)	95% Confidence Interval		P
			Lower (%)	Upper (%)	
Recruitment	Placebo control (n=36)	68.7	59.3	78.1	0.562
	Non-operative control (n=21)	74.1	58.6	89.5	
Attrition (Overall)	Placebo control (n= 54)	21.2	17.2	25.2	0.811
	Non-operative control (n=34)	23.7	18.8	28.6	
Cross-over	Placebo control (n= 54)	8.8	6.3	11.4	0.174
	Non-operative control (n=34)	11.8	8.4	15.2	
Drop-out	Placebo control (n= 54)				
	Non-operative control (n=34)				
Follow-up	Placebo control (n= 54)	10.6	8.2	13.0	0.084
	Non-operative control (n=34)	7.8	5.8	9.8	

overall follow-up rate



overall cross-over rate



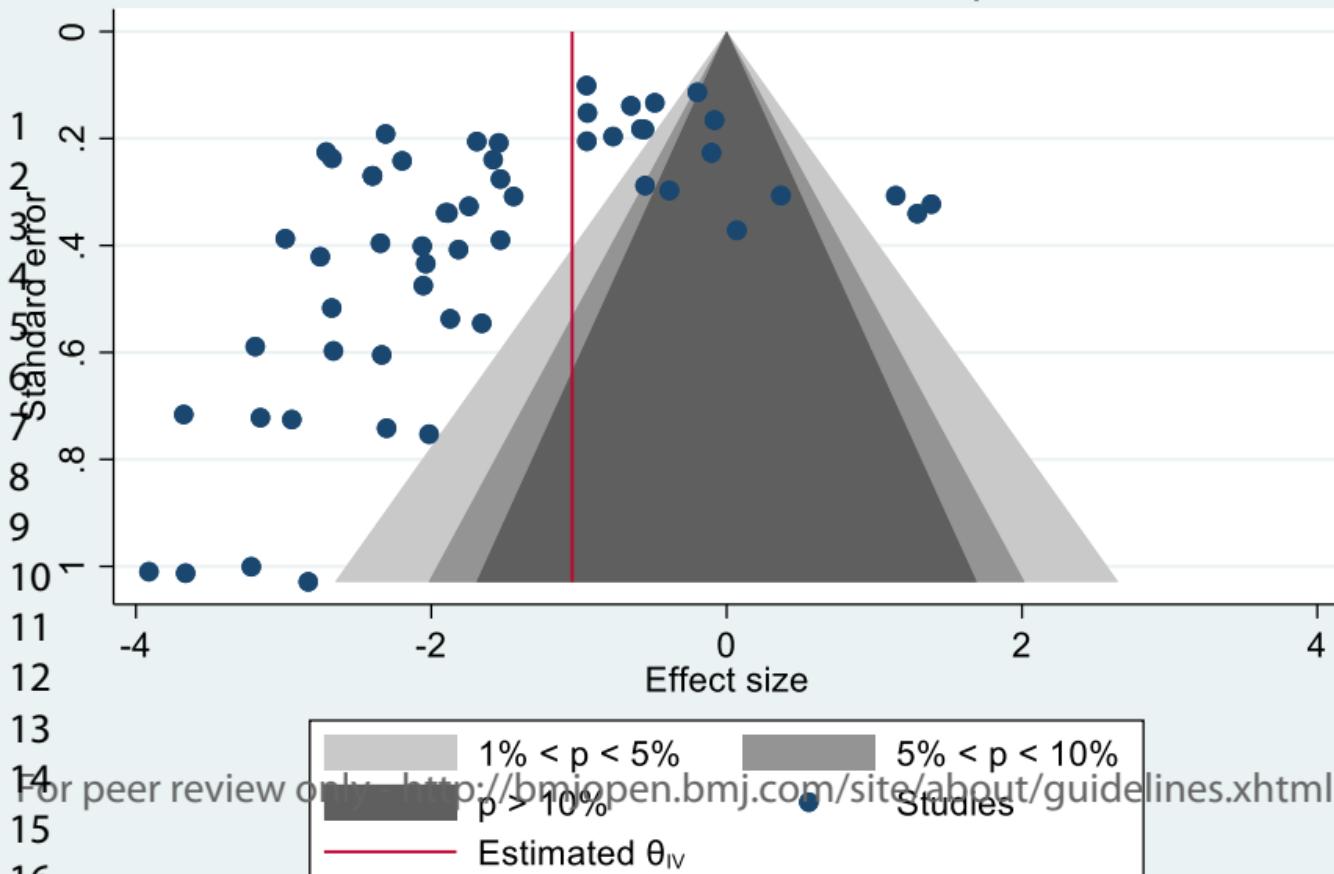


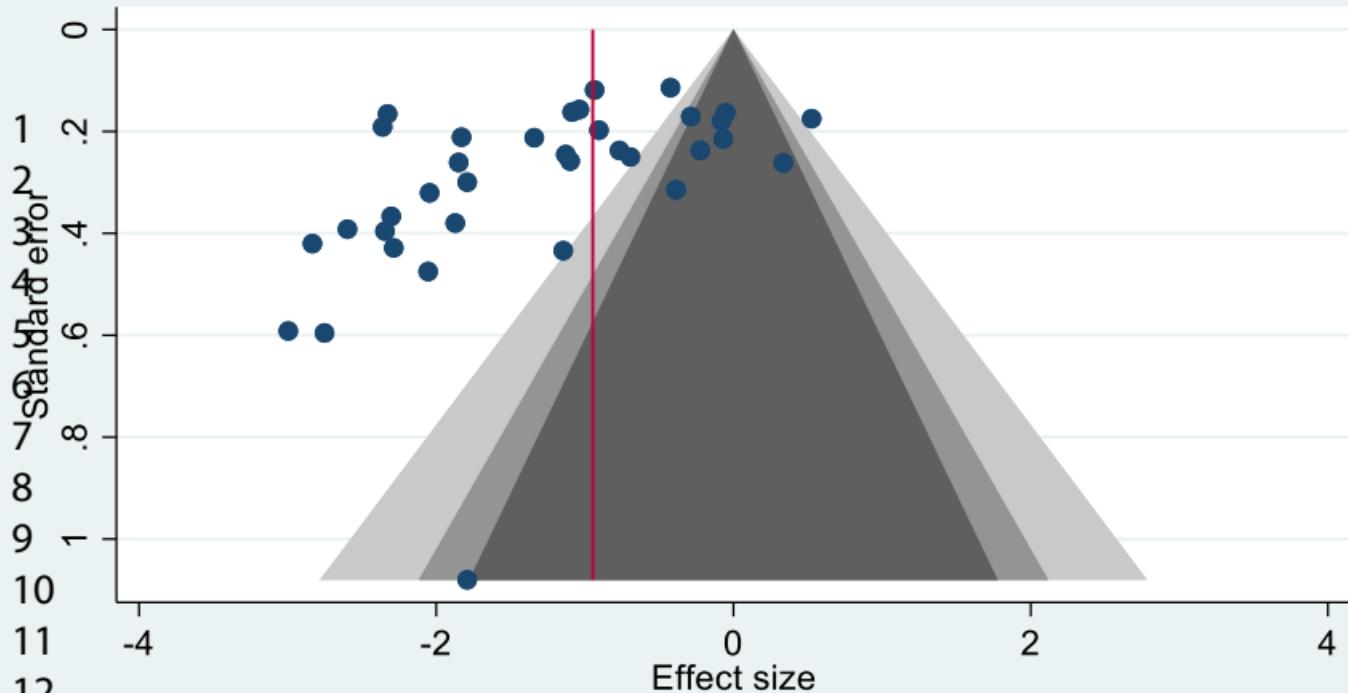
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$1\% < p < 5\%$	$5\% < p < 10\%$
$p > 10\%$	Studies
Estimated θ_{IV}	

Contour-BM Open funnel plot





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1% < p < 5%
5% < p < 10%
 $p > 10\%$
Studies
Estimated θ_{IV}

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

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3 iii) *Subject loss to follow up*, defined as the inability of investigators to obtain
4 information at planned timepoints for reasons other than *subject dropout*.
5 Where available, this will be characterised at different timepoints:
6 a. Prior to first follow up
7 b. Prior to final follow up
8 c. Overall
9
10 iv) *Subject cross-over rates*, defined as an unplanned protocol violation resulting in
11 subjects in the control group receiving the intervention, and vice versa. This will
12 be reported as a proportion of the subject group, and characterised as:
13 a. Subjects crossing over into the surgical intervention
14 b. Subjects crossing over into the non-surgical intervention
15 c. Overall
16
17 v) *Overall attrition of participants*, defined as a composite (or addition) of dropout,
18 loss to follow up and cross-overs, expressed as a proportion of total sample size
19
20 vi) Stoppage prior to recruitment of planned sample size. Where available, the
21 reason for stoppage will be recorded, including due to poor recruitment rates.
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23

24 The primary outcomes of interest will be rates of attrition (due to dropout, loss to follow up
25 and cross-over), participant recruitment rates and number of studies with unplanned
26 stoppage.
27

28 **Statistical Analyses**

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

33 Due to the data nature (varying follow-up duration) mixed effect Poisson regression will be
34 used to examine Incidents Rate Ratio (IRR) and Incident Rate Difference while controlling for
35 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 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

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

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

13 Additional outcome(s) [2 changes]

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

17 Measures of effect

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

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

23 Data extraction (selection and coding)

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

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

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

36 Two authors will also extract the following study characteristics independently:

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

44 Risk of bias (quality) assessment

45 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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9 Review team members and their organisational affiliations [1 change]
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Type and method of review

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

Anticipated or actual start date

22 November 2018

Anticipated completion date [3 changes]

23 August 2022

Funding sources/sponsors

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

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

Conflicts of interest

Language

English

Country

Australia, Finland

Published protocol

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

Stage of review [1 change]

Review Completed published

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

Karjalainen T, Heikkinen J, Busija L, et al. Use of Placebo and Nonoperative Control Groups in Surgical Trials: A Systematic Review and Meta-analysis. *JAMA Netw Open*. 2022;5(7):e2223903.

doi:10.1001/jamanetworkopen.2022.23903

<https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2794704>

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

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

Date of registration in PROSPERO

07 January 2019

Date of first submission

20 November 2018

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

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

Revision note

Review completed. Added publication and link to the paper

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

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

Versions

07 January 2019

15 May 2020

09 November 2020

23 August 2022



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

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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 analyses, 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 bias).	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) 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 the 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

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
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