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The feasibility of surgical randomised controlled trials with a placebo arm – a systematic review.

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ABSTRACT

Objectives: To investigate practical problems with completing placebo-controlled surgical trials and to explain some of the concerns related to their feasibility.

Design: A systematic review.

Data sources and study selection: The analysis involved studies published between 1959 and 2014 that were identified during an earlier systematic review of benefits and harms of placebo-controlled surgical trials, published in 2014.

Results: This review demonstrated that placebo-controlled surgical trials are feasible, at least for procedures with a lower level of invasiveness. Funding, anaesthesia or blinding of patients and assessors were not mentioned as obstacles in completing any of the reviewed trials. Existing placebo trials were funded equally often from commercial and non-commercial sources. General anaesthesia or sedation was used in 41% of studies. Among the reviewed trials, 81% were double-blinded and 19% were single-blinded. The withdrawal rate during the study was similar in the surgical and in the placebo group. The main problem reported in many trials was a very slow recruitment rate, mainly due to the difficulty in finding eligible patients.

Conclusions: Placebo-controlled trials of minimally-invasive procedures are feasible but the recruitment is challenging.

STRENGTHS AND LIMITATIONS OF THE STUDY

- Review of all published surgical RCTs with a placebo arm, spanning the years 1959 to 2014.
- Due to the nature of this review, we could not investigate the obstacles that prevented initiation, completion or publication of trials; therefore, our observations are limited to the successfully published studies.

INTRODUCTION

Progress in surgery is based on practical experience.[1] Surgical randomised controlled trials (RCTs) are uncommon;[2] only about 15% of published RCTs are related to surgical interventions.[3] Novel procedures tend to be developed through an iterative process of trial and error[4] and only 24% of the currently used surgical therapies are supported by results of RCTs.[1]

Apart from not being necessary for approval of new treatment,[5] there are several reasons why surgical RCTs are scarce. These studies are perceived as expensive[2, 6] and unlikely to attract funding.[3, 5, 7] They are difficult to design and conduct because of challenges posed by randomisation, blinding, differences in skills and experience of surgeons, variability of patients as well as lack of consensus on surgical outcomes.[1, 2, 6-8] Moreover, patient recruitment is also believed to be a problem.[6] The inclusion of a placebo control adds another level of complexity to a RCT.[6, 9] Some authors suggest that many patients may be unwilling to undergo an invasive procedure if there is no clear direct benefit to them, which may result in slow recruitment.[6] Others believe blinding of patients and outcome assessors is not feasible and that the surgeon can never be blinded.[10] Consequently, very few interventional procedures have been validated using a placebo-controlled RCT.[1, 2, 5, 9, 11, 12]

Many publications discussing placebo in surgery concentrate on the ethical concerns, such as general equipoise and minimizing the risks,[13, 14] and on conceptual problems, for example

whether surgeons will be willing to test efficacy of an already established procedure.[10, 15] Very little has been written on the methodological challenges of such studies[16, 17] and, to the best of our knowledge, no one has attempted to summarise the evidence from all the published placebo-controlled surgical trials.

When we previously performed a systematic review examining the harms and benefits of placebo-controlled surgical RCTs, we found that there clearly are obstacles to completing such trials, as less than a hundred have been published between 1959 and 2013.[12] Therefore, we conducted a secondary systematic review of these placebo-controlled surgical RCTs to identify practical reasons why these are so uncommon. We did not limit the analysis to any patient group, outcome or any particular type of surgical intervention.

METHODS

Selection criteria

The criteria used to select placebo-controlled surgical RCTs were described previously.[12] In brief, studies were eligible if they were randomised trials, in which the efficacy of surgery was compared to placebo. Surgery was defined as any interventional procedure that changes the anatomy and requires a skin incision or the use of endoscopic techniques; dental studies were excluded. We used the term “placebo” to refer to a surgical placebo, a sham surgery, or an imitation procedure intended to mimic the active intervention. The important criterion was that patients were under general anaesthesia or blinded in some other way, and could not distinguish whether they underwent the actual surgery or placebo. We did not limit the inclusion criteria to any particular condition, patient group, intervention, or type of outcome. We excluded studies investigating anaesthesia or other pharmacological substances used peri-operatively.

In this review, we used the term “surgical placebo”. The word “sham” is preferred by some authors because surgical placebo has to involve an imitation of the investigated intervention

in order to resemble it closely; therefore, it is different from an inactive "sugar pill" placebo used in pharmacological trials.[18] The word "sham " has negative associations and it suggests that a procedure is fake and deceitful; however, in many trials the placebo involved an accepted surgical procedure such as endoscopy or arthroscopy, which was used also for diagnostic purposes with real benefits to the patients.

Search strategy

We searched the MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials databases from the date of their inception to 14th November 2013, with no restriction on language. We did not systematically search for studies reported only as conference abstracts. Search terms were published previously.[12]

Three reviewers (KW, IR, BJFD) independently screened the initial set of records identified from the search and then screened the full-text of any potentially relevant articles. Each reviewer assessed the eligibility of each study and the final list of included studies was agreed by consensus. Moreover, we searched ClinicalTrials.gov (on 14th November 2013), a database of registered randomised clinical trials, to identify any recently completed or ongoing studies. On 15th June 2014 we checked whether results of any of the trials identified in the ClinicalTrials.gov database have been published since the original search.

Dealing with duplicate publications

When there were several articles reporting outcomes from a single trial, i.e., with the same authors, location, patient population, and recruitment dates, we only included the paper reporting the primary outcome for the trial and excluded pilot and follow-up reports.

Data extraction

We used a standardised data extraction form to collect information about the characteristics of each study including: year of publication, country, funding source as well as the type of

anaesthesia, blinding, number of patients who were assessed, eligible, randomised and who declined participation as well as those who completed the trial. To reduce errors, the three review authors (KW, IR, BJFD) extracted data separately and checked the entries for consistency; a single set of data was agreed by all three reviewers.

Data synthesis

We have performed a descriptive analysis of the characteristics of each individual study and presented data in a table.

RESULTS

Study selection

We analysed the studies identified as a part of the systematic review on harms and benefits, including seven trials that were excluded from the systematic review due to lack of a direct comparison between the surgical and the placebo group. We also checked whether the trials identified in the ClinicalTrials.gov database had their results published between November 2013 and June 2014, and found three additional trials.[19-21] This resulted in 63 full-text articles, which were included in this descriptive review (Figure 1).

Placebo-controlled surgical RCTs characteristics

The number of published placebo-controlled surgical trials was small; however, 73% (n=46/63) of included RCTs were published after the year 2000 suggesting an increasing interest in performing such studies. Half of the trials (n=35/63, 55%) used a key-hole surgery, including endoscopy (n=28/63), laparoscopy (n=4/63), arthroscopy (n=2/63) and bronchoscopy (n=1/63). The remaining trials involved other types of minimally-invasive interventions, for example, using catheters for vascular access or needles for injection of fat or exogenous materials to remodel tissue. Very few studies investigated open techniques such as exposure of the internal mammary artery (n=2/63) or exposure of scalp muscles

(n=1/63). Fifteen trials used implants and additional seven used gastric balloons or bubbles (Appendix 1).

Funding sources

One third of the studies (n=21/63, 33%) were non-commercially funded and almost as many were funded by a commercial company (n=18/63, 29%), often the manufacturer of the implant or the endoscope. The source of funding in the remaining studies (n=24/63, 38%) was not reported.

Over half of the trials were undertaken in the USA (n=35/63, 56%), the others were in Canada, the UK, Germany, the Netherlands, Belgium, Italy, Finland, Sweden, Portugal, Norway, Greece, Denmark, Australia, and Brazil.

Sample size

The majority (n=47/63, 75%) of the identified studies were small, with fewer than 100 participants. The median number of patients randomised in the trial was 61 (Interquartile range 66, range 10-298).

About half of the RCTs (n=33/63; 52%) reported a formal sample size calculation, but only a quarter (n=16/63) allowed for dropouts and attrition. Most of the trials that included a sample size calculation (n=23/33, 70%) attained their pre-specified sample size (without accounting for attrition). Ten trials under-recruited, such that the number of randomized patients was lower than the calculated sample size. All ten trials were terminated early: three due to slow recruitment,[22-24] one because at the interim analysis the surgery was highly effective [25] and two because at the interim analysis the active procedure lacked efficacy,[19, 26] two studies were stopped because of serious adverse events either in the trial[27] or at another centre using a similar procedure.[28] One trial was terminated when the sponsoring company was sold.[29] Finally, one study was stopped because the investigated procedure was approved as

a standard care and the equipoise ceased to exist, despite the fact that the study did not show its superiority over placebo.[30] Finally, one trial recruited the intended sample size, but due to a high drop-out rate the number of patients who completed the trial was lower than the required sample size.[31]

Recruitment and screening

Recruitment, sometimes as slow as 1-2 patients per month,[22, 32] was a common problem [19, 22, 28-36] and was the reason for an early termination of three trials.[22-24]

Many of the analysed studies did not provide any details about screening and recruitment; they either stated that they recruited consecutive patients fulfilling the criteria [22] or that they randomised patients who were willing to participate and were eligible.[37] About one third of the trials specified the number of screened (n=24/63, 38%) and eligible patients (n=27/63, 43%) and stated how many patients declined participation or withdrew before the treatment (n=22/63, 34%); only one fifth of the trials (n=13/63, 21%) reported all three numbers (Appendix 1). The available data suggest that the initial assessment of eligibility was the main obstacle in recruitment as patients did not meet the inclusion criteria or were not eligible due to exclusion criteria.

On average, it was necessary to screen more than five patients in order to randomise one, but three in four eligible patients started the trial. (Table 1) The number of patients that had to be screened before the necessary group was recruited varied greatly. This variance was, at least partly, related to the method of identifying potential participants. The trial with the largest number of screened patients recruited using TV and newspaper advertising: out of 4,523 screened patients only 260 were eligible and were willing to participate; however, as 196 had negative discography and only 64 patients were randomised.[24] More targeted recruitment from specialist centres had much higher success rate but often required a multi-site effort.[36]

Many trials had additional inclusion and exclusion criteria that could only be verified after the patient entered into the trial, for example, a verification of diagnosis by positive findings during the endoscopy or on diagnostic imaging. As a consequence of this, many patients were excluded because, either they did not have the investigated condition or they had some concomitant condition that precluded their participation in the trial and, sometimes, required appropriate treatment. Moreover, any technical complications during the assessment or study procedures potentially resulted in patients' drop-out. For example in the trial on laparoscopic adhesiolysis for abdominal pain by Swank and colleagues,[33] nine patients did not have adhesions, one of them had a hernia and was treated laparoscopically, three patients had stricturing adhesions that required therapeutic adhesiolysis, and in one instance a pneumoperitoneum could not be achieved; therefore, out of 121 assessed patients 13 were excluded during laparoscopy.

Fluctuating symptoms were a problem in a few studies, for example, patients became asymptomatic while waiting for the procedure and had to be excluded from the trial [20] or did not report symptoms during the study visit and did not undergo the treatment but were included in the intention-to-treat analysis.[38] This problem also complicated the post-treatment assessment,[39] especially that only one trial included an observational control group.[40]

Refusal to participate

Some of the approached patients declined participation in the trial, withdrew their initial consent, refused to be randomized or to comply with the requirements of the protocol and had a strong preference for one of the treatment options. Most of the trials did not report the reasons for patients' refusal to participate and the available data did not allow us to quantify the percentage of patients that refused to enter the study. Only 22 reviewed trials stated the number of patients who declined to participate but it was not always clear whether these

numbers referred to patients at the screening stage or to patients already identified as eligible. The median percentage of patients who declined participation as a percentage of randomised patients was 18% and varied from 3% to 4,842%. It is important to note, that the two trials with high numbers of patients refusing to participate investigated vertebroplasty, which, at the time, was an established procedure; therefore, patients could easily receive the treatment from a different medical centre, without participating in a trial.[35, 36]

Patient retention

In general, recruitment was more problematic than retention and, once recruited, patients usually remained in the trial. Most of the drop-outs occurred before randomisation. Across the reviewed trials, 96% of randomized patients completed the study (Table 1). A lower completion rate in five trials was caused by an early termination [26, 30, 41] as well as withdrawals or change of patients' health status.[42, 43] In general, the predicted attrition, by which the required sample size was inflated to account for drop-outs, was 10% (median) with the range from 5% to 24%, whereas the actual patients' attrition between randomisation and outcome assessment was 4% (range 0%-50%).

The completion rate was similar in the active and in the placebo arm, except for two trials: one [19] where five times as many patients were lost to follow-up in the active group than in the placebo group and one [31] where the drop out rate was three times higher in the placebo group. Neither of these studies could explain this difference. The reported reasons for drop-out during the trial were withdrawals, loss to follow-up, or discontinuation without known cause [21, 40, 42, 44, 45], patients' request to be unblinded,[25] adverse events,[26, 27] change of medical status such as pregnancy or concurrent illness.[24, 46, 47] A long wait between the screening and procedure did not necessarily result in patient withdrawal.[44] A variable reporting did not allow us to quantitatively evaluate the reasons for post-randomisation drop-outs across the trials.

Blinding was possible and some studies attempted to blind surgeons

In twelve trials (19%) only patients were blinded, but in the majority of RCTs (n=51/63, 81%) both patients and outcome assessors were blinded; including three trials, in which there was also an attempt to blind the operator. For example, in two trials the implant delivery system was pre-loaded by manufacturer – the devices looked identical but only one contained an implant.[29, 48] In another trial, the surgeon placed the catheter but then handed the procedure over to a technician who delivered the treatment according to the randomisation.[22]

Authors of the reviewed trials went to great lengths to imitate the visual, verbal and physical cues and to make the placebo as similar as possible to the active procedure. For example, patients wore goggles or had the view obscured so that they could not see the device.[49] The preparation for the placebo intervention was done in the same way as for the active procedure.[36, 50] Similar verbal instructions were given as during the surgery [43, 51] and there were attempts to imitate the noises made by the devices.[52] In trials that used exogenous substances, the container was opened so that the distinct smell was present also during the placebo condition.[36] Some researchers attempted to keep the duration of the procedure the same in both arms [40, 44, 53] whereas others thought that it was more ethical to shorten the placebo intervention.[32]

Very few studies assessed the success of blinding. Often authors thought that it was reasonable to assume that patients in the study were not able to distinguish between placebo and surgery due to minimally-invasive characteristics of the procedure and minimally post-operative treatment-related symptoms.[54, 55] In one trial, the post-treatment symptoms were believed to be a sign of correctly placed effective gastroplication as patients with these symptoms had better outcomes.[40] Blinding was reported as successful in n=13/63 (21%) studies. In four trials[36, 43, 56, 57] a larger proportion of patients in the active group guessed correctly; however, the placebo group did not guess the treatment allocation. In one study, two patients were definitely unblinded early due to implant extrusion.[58]

Anaesthesia

In the reviewed trials, patients in both groups received some type of anaesthesia. General anaesthesia or sedation were used in n=26/63 trials (41%), including one trial in which general anaesthesia was used in the surgical group but patients in the placebo group were sedated without intubation.[30] Local analgesia was used in n=16/63 (25%) RCTs, four studies used a mixture of methods, and n=17/63 (27%) trials did not describe the type of anaesthesia used. None of the trials reported that anaesthesia was a barrier in conducting their study.

DISCUSSION

We found that, although, there were very few surgical RCTs with a placebo arm published between 1959 and 2014, there was a rising trend. This may be related to an increasing interest in placebo and placebo-controlled trials in general [59] or to the increasing popularity of minimally-invasive procedures since 1980s. The latter explanation is supported by the fact that most of the reviewed trials used some type of key-hole surgery.

The analysed placebo-controlled trials were funded equally often by industry as by non-commercial funding bodies. The number of commercially-funded older trials may be underestimated in our review because surgical RCTs funded by industry have lower odds of being published.[60] However, the recent trials are registered in the ClinicalTrials.gov database and would have been identified. The distribution of the source of funding was similar to that described by other authors.[11] This is encouraging, as it shows that there is an interest within the industry to validate the efficacy of their products and also that the non-commercial bodies are willing to investigate the efficacy of surgical procedures. The costs of running surgical RCTs are high[2] but in the long run preferential funding of treatment with proven efficacy may help to improve the allocation of resources and to lower the costs of health care.[61] For example, the trial by Moseley and colleagues [53] demonstrated that

arthroscopic the arthroscopic debridement and the arthroscopic lavage were not better than a placebo arthroscopy and, consequently, there was a decline in the use of these procedures for knee osteoarthritis.[62]

Recruitment into placebo-controlled surgical trials was possible but was often very slow and resulted in an early termination of several trials. Slow recruitment is the most frequent reason for discontinuation of RCTs, including surgical RCTs. For example, 21% of reviewed surgical RCTs were discontinued early and 44% of these were due to problems with recruitment.[60] Authors sometimes underappreciate the fact that the target population in surgical trials is small; therefore, it may be challenging to recruit a required number of patients in a reasonable period of time.[2] The right timing of a trial may also affect its completion,[7] for example, initiating a trial too early in the intervention's development may result in more procedure-related adverse events,[27] whereas, when a procedure has been already established, like vertebroplasty, it may be difficult to recruit participants.[35, 36]

In the reviewed trials, the number of patients that had to be screened in order to recruit necessary participant group was larger than in other RCTs but the proportion of eligible patients that started the study was comparable to other types of RCTs.[63] The often-reported challenge in placebo-controlled surgical trials was finding sufficient number of eligible patients within a reasonable period of time.

Reporting of the recruitment process and eligibility was generally poor and often difficult to interpret as the reviewed studies usually did not describe in detail why eligible patients did not enter the trial, which is in line with observations from other reviews.[63] The quality of reporting in analysed RCTs was poor but this is a known problem in surgical trials.[7, 63]

There is an assumption that patients are unwilling to take part in surgical RCTs, especially patients in severe pain.[64] Interestingly, in the trial by Moseley and colleagues [53] patients in

more pain were more likely to agree to participate. Also patients tend to choose the new treatment even if it was not proven to be superior over placebo. For example, in the trials on Parkinson's disease, patients actually opted for the transplantation when they were given a choice after the end of the trial, despite the fact that it was not demonstrated to be more effective than placebo.[50] In a recent orthopaedic placebo-controlled RCT, patients were willing to participate and screening failures were a larger problem than refusals or withdrawals.[16] The clinical characteristics of patients who entered into a placebo-controlled RCT were comparable to the non-enrolment group as well as to patients in other trials.[16]

Only about half of published trials reported the necessary sample size, which is in line with another review of surgical trials, which found that sample size calculations were reported only in 63% of RCTs.[11] However, it is important to note that some of the reviewed trials were published before the CONSORT (Consolidated Standards of Reporting Trials) were introduced and before the sample size calculation became required by the board review. Some trials were small because of the author's assumption that surgical studies have a large effect size; therefore, inferring a smaller sample size is required in surgical trials than in drug trials.[48, 65] However, surgical RCTs may require larger numbers of patients to reach the required sample size.[66] Recent systematic reviews demonstrated that the effect size of a surgical procedure in comparison to a placebo intervention in the existing trials was often small.[12, 67] It is likely that the apparent lack of difference between the active treatment and placebo might have been related to the small sample size and the effect not reaching the statistical significances.[48, 68, 69] It might be also caused by a large placebo effect; however, the magnitude of the true placebo effect in surgical procedures, i.e., the effect in the placebo arm vs. non-treatment arm, is unknown because only one reviewed trial included a non-interventional group to control for these non-specific effects.[40] Please not that the magnitude of response in the placebo arm is related not only to the true placebo effect, i.e., response directly related to the placebo intervention, but also to non-specific changes such as regression to the mean, natural history of disease, effect of participation in the trial.[70]

A placebo procedure can successfully imitate a minimally-invasive surgery. Blinding in interventional trials is more challenging than in pharmaceutical ones;[11, 71] however, there are many strategies to blind the patients and outcome assessors[71] and the reviewed trials often used ingenious methods to achieve the blinding. The success of blinding was rarely assessed, but it is not necessary according to the current reporting standards. The requirement to assess blinding was removed from the CONSORT checklist because of evidence that testing for blindness is not valid because it cannot distinguish the success of blinding from "hunches" about treatment's efficacy.[72]

Blinding of patients and outcome assessors is especially important if the outcomes are subjective or difficult to quantify.[73] Softer outcomes are difficult to evaluate in unblinded trials due to patient- or assessor-related bias, which may distort the treatment effect.[74, 75] In this analysis, we have demonstrated that the withdrawal rate was generally low and was similar in the active and the placebo group. This provides supporting evidence that blinding reduces the attrition bias, as patients do not know to which treatment they had been allocated.[76]

Future implications for clinicians and unanswered questions

What remains to be understood is why eligible patients decline participation or withdraw their consent before the randomisation.[77] Addressing these issues may improve the recruitment procedure in future trials.

There is also a need to estimate the magnitude of placebo effect in interventional trials. Several authors have highlighted the fact [12, 66, 67] that for softer outcome measures, the magnitude of placebo effect in surgical trials is underestimated while the effect size of the surgical intervention is overestimated and, as a result of that, many trials do not recruit sufficient numbers of patients to detect differences between the effects of surgery and placebo.

Journals should encourage authors to report the details of patient recruitment and allocation, including the reasons for withdrawals and screening failures. Data like this are very useful when planning future trials. There has been an improvement in the reporting quality of recent trials[21] and these guidelines were included in the CONSORT extension for non-pharmacological interventions.[78]

In conclusion, surgical randomised clinical trials with a placebo arm are feasible but there is a need to better understand the factors that make those trials challenging so that future trials are not terminated early and contribute good-quality evidence to surgical practice.

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Patient consent Not required

PRISMA statement The PRISMA flow chart is presented in Figure 1.

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Table 1 Participants flow through the reviewed trials as a percentage of the number of patients who were randomised into each trial

	Number of studies	Median % of sample randomised	First and third quartile	Minimum and maximum
Screened	24	530%	243%, 773%	100%, 7067%
Eligible	27	132%	108%, 172%	100%, 448%
Declined	22	18%	8%, 144%	3%, 4942%
Sample size	33	96%	90%, 110%	49%, 323%
Outcome assessed	61	96%	90%, 100%	52%, 100%

Note: “Number of studies” refers to the number of trials that provided relevant data. Trials terminated early are included in these analyses. “Sample size” relates to the sample size required to reach statistical power, not inflated to account for drop-outs. “Outcome assessed” relates to total number of patients, in both arms. The denominator is the number of patients actually randomised into each trial.

Figure 1 PRISMA Flow Diagram

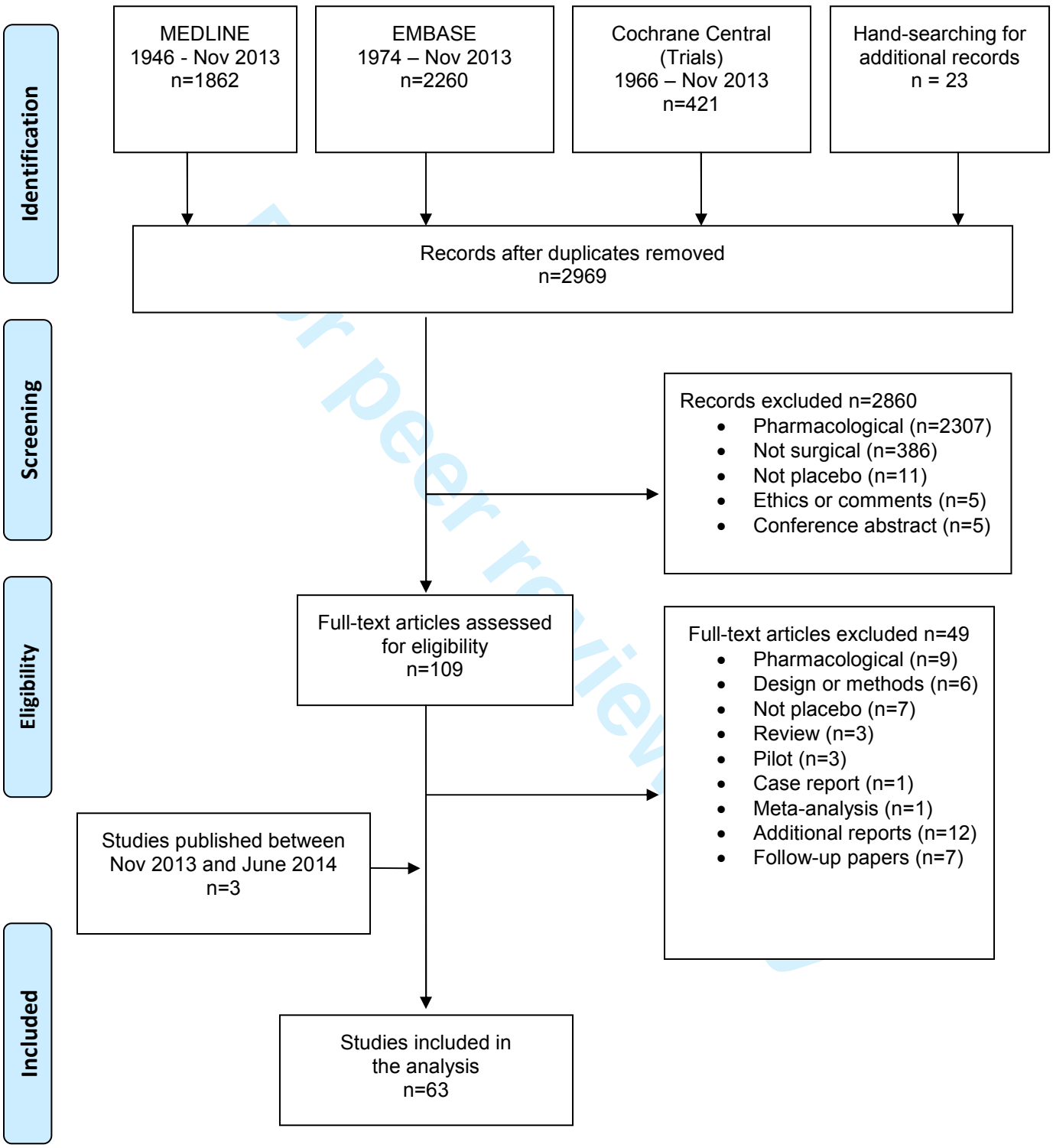

Table 1 Characteristics of the reviewed trials

Study	Year	Condition	Active intervention	Placebo intervention	Country	Screened as % of randomised	Eligible as % of randomised	Declined as % of randomised	Number of randomised	Completed as % of randomised	Completed as % of randomised in surgery arm	Completed as % of randomised in placebo arm	Calculated sample size	Completed as % of sample size	Randomised as % of sample size	Blinding	Analgesia
Abbott et al.	2004	Endometriosis	Laparoscopy + ablation	Laparoscopy	UK	NA	323%	6%	52	75%	100%	50%	40^	98%	130%	double	NA
Arts et al.	2010	GERD	Endoscopy + RF treatment	Endoscopy + setup but no RF delivery	Belgium	NA	NA	NA	22	100%	100%	100%	22	100%	100%	double	SE (1subj GA)
Baeck et al.	2009	Sleep apnea	RF surgery of the palate	Applicator insertion but no RF delivery	Finland	250%	106%	6%	32	100%	100%	100%	26^	123%	123%	single	LA
Bajbouj et al.	2009	Globus sensation	Endoscopy + ablation using argon plasma coagulation	Endoscopy + connected applicator but no current	Germany	NA	NA	NA	21	90%	91%	90%	40	48%	53%	double	SE
Benjamin et al.	1988	Obesity	Endoscopy + gastric bubble + diet	Endoscopy + balloon imitation + diet	USA	NA	NA	NA	90	68%	crossover	crossover	NA	NA	NA	double	SE
Bradley et al.	2002	Osteoarthritis	Tidal irrigation of the joint	Saline injection and leg manipulation	USA	NA	NA	NA	180	99%	98%	100%	150^	119%	120%	double	LA
Buchbinder et al.	2009	Osteoporotic vertebral fractures	Percutaneous vertebroplasty	Injection of anaesthetic but not cement +cephalosporin	Australia	600%	281%	181%	78	94%	95%	93%	48	152%	163%	double	LA
Castro et al.	2010	Severe asthma	Bronchoscopy + RF treatment	Bronchoscopy + placebo procedure	USA, Brazil, Canada, Australia, UK	201%	103%	3%	288	97%	92%	96%	225	124%	128%	double	SE
Cobb et al.	1959	Coronary disease	Ligation of internal mammary artery	Skin incision and exposure of vessels but no ligation.	USA	NA	NA	NA	17	100%	100%	100%	NA	NA	NA	single	LA
Corley et al.	2003	GERD	Endoscopy + RF treatment	Endoscopy + setup but no RF delivery	USA	NA	NA	NA	64	81%	89%	72%	64	81%	100%	double	SE
Cotton et al.	2014	Sphincter of Oddi dysfunction	Endoscopy + sphincterectomy + ERCP	Endoscopy + ERCP	USA	740%	169%	35%	214	81%	84%	75%	193^	90%	111%	double	SE
Davys et al.	2005	Plantar callosities in RA	Scalpel debridement of the callosity	Simulation using blunt-edged scalpel	UK	145%	134%	34%	38	100%	100%	100%	38	100%	100%	single	NA
Deviere et al.	2005	GERD	Endoscopy + a nonresorbable copolymer	Endoscopy without implant + prophylactic antibiotics	Germany, Belgium, Italy	NA	NA	NA	64	100%	100%	100%	NA	NA	NA	single	SE
Dimond et al.	1960	Coronary disease	Ligation of internal mammary artery and vein	Skin incision and exposure of vessels but no ligation	USA	NA	NA	NA	18	100%	100%	100%	NA	NA	NA	single	LA
Dowson et al.	2008	Migraine	Implant for patent foramen ovale + heparin	Skin incision in the groin + transesophageal US + aspirin and clopidogrel - no heparin	UK	301%	111%	NA	147	93%	88%	97%	132^	103%	111%	double	GA
Eid et al.	2014	Obesity	Endoscopy + gastroplication (StomaphyX)	Endoscopy	USA	848%	316%	206%	90	82%	76%	84%	135^	55%	67%	single	GA
Fleischer et al.	1985	Bleeding esophageal varices	Endoscopy + laser + cimetidine or antiacids + vasopressin if bleeding persisted	Endoscopy + setup (laser was turned on, a verbal order was given to activate the laser but not used) + cimetidine or antiacids after endoscopy + vasopressin if bleeding persisted	USA	NA	NA	NA	20	100%	100%	100%	NA	NA	NA	double	NA
Fockens et al.	2010	GERD	Endoscopy + Gatekeeper implant	Endoscopy + saline instead of implant and instead of antibiotics	USA , Netherlands	335%	150%	NA	118	65%	68%	60%	NA	NA	NA	single	SE
Freed et al.	2001	Parkinson's disease	Fetal dopamine neurons transplantation+trepanation + PET + MRI + phenytoin	Incomplete trepanation (dura intact) + PET + MRI + phenytoin - sham-transplantation	USA	NA	NA	NA	40	98%	95%	100%	NA	NA	NA	single	LA
Freeman et al.	2005	Discogenic low back pain	Electrothermal therapy	Catheter inserted but not connected + cephazolin +CT	Australia	NA	NA	NA	57	96%	95%	100%	75	73%	76%	triple	SE
Freitas et al.	1985	Bleeding from gastric/duodenal ulcers	Endoscopy + electrocoagulation + cimetidine	Sham + cimetidine	Portugal	615%	215%	NA	78	100%	100%	100%	NA	subgroups	NA	single	SE
Friedman et al.	2008	Sleep apnea	Palatal implants	Identical implementation device without an implant + antibiotics	USA	181%	129%	NA	62	89%	94%	84%	54^	102%	115%	double	NA
Fullarton et al.	1989	Bleeding from peptic ulcers	Endoscopy + heater probe + ranitidine	Endoscopy + heater probe activated in the gut lumen + ranitidine	UK	1465%	119%	NA	43	100%	100%	100%	NA	NA	NA	double	NA
Geenen et al.	1989	Sphincter of Oddi dysfunction	Endoscopy + sphincterectomy + ERCP + manometry + morphine/neostigmine provocation test	Endoscopy + device activated in the lumen of the duodenum + ERCP + manometry + morphine/neostigmine provocation test	USA	615%	109%	9%	47	100%	100%	100%	NA	NA	NA	double	NA
Geliebter et al.	1990	Obesity	Endoscopy + balloon	Endoscopy + deflated balloon	USA	NA	NA	NA	10	100%	100%	100%	NA	NA	NA	double	LA

Genco et al.	2006	Obesity	Endoscopy + balloon (BioEnterics)	Endoscopy but no balloon	Italy	NA	NA	NA	32	100%	100%	100%	NA	NA	NA	double	SE
Gillespie et al.	2010	Sleep apnea	Palatal implants	Identical implementation device without an implant	USA	NA	NA	NA	51	98%	NA	NA	80^	63%	64%	triple	LA
Gross et al.	2011	Parkinson's disease	Pigmental cells transplantation	Scalp incisions and partial-thickness burr holes + MRI - the same duration	USA, Germany	221%	135%	10%	71	94%	89%	100%	68	99%	104%	double	GA
Guyron et al.	2009	Migraine	Surgical "deactivation" of migraine trigger points	Exposure of muscles and nerves without changing their integrity	USA	417%	100%	NA	76	99%	100%	100%	NA	NA	NA	double	NA - occipital group GA, other - not stated
Hartigan et al.	1994	Esophageal varices	Endoscopy + sclerotherapy	Endoscopy + placebo solution released to the gut lumen	USA	NA	116%	16%	253	100%	100%	100%	244^	104%	104%	single	NA
Hogan et al.	1989	Obesity	Endoscopy + gastric bubble	Endoscopy + sham insertion	USA	271%	NA	NA	59	95%	100%	98%	NA	NA	NA	double	SE
Jarrell et al.	2005	Endometriosis	Laparoscopy + biopsy + sharp excision	Laparoscopy + biopsy	Canada	NA	NA	3%	29	52%	47%	97%	84^	18%	35%	double	NA
Kallmes et al.	2009	Osteoporotic vertebral fractures	Percutaneous vertebroplasty	Simulated (audio, sensory, even smell) vertebroplasty - injection of anaesthetic but not cement	USA, UK, Australia	1384%	329%	229%	131	98%	99%	97%	130	98%	101%	double	LA
Koutsourelakis et al.	2008	Sleep apnea	Septoplasty	Simulated resection with manipulation of instruments - the same amount of time	Greece	NA	104%	4%	49	100%	100%	100%	24	204%	204%	double	LA
Laine et al.	1987	Upper GI tract bleeding (ulcers)	Endoscopy + electrocoagulation	Endoscopy + probe activated in the lumen of the gut	USA	748%	NA	16%	44	93%	100%	100%	NA	NA	NA	double	NA
Lee et al.	2001	Urinary stress incontinence	Autologous fat injection	Fat harvested but discarded + saline injection + trimetoprim-sulfamethoxazole or nitrofurantoin	Canada	NA	NA	NA	68	82%	77%	98%	90	62%	76%	double	LA and SE occasional GA
Leon et al.	2005	Coronary disease	Percutaneous myocardial laser revascularisation	Setup but no laser procedure	USA	NA	NA	NA	298	100%	100%	100%	NA	NA	NA	double	NA
Lindor et al.	1987	Obesity	Endoscopy + balloon + diet	Endoscopy + empty introducer tube + diet	USA	NA	NA	NA	22	95%	91%	100%	71	30%	31%	double	SE
MacLeod et al.	1983	Bleeding from a peptic ulcers	Endoscopy + laser + cimetidine	Endoscopy + cimetidine	UK	1551%	120%	NA	45	100%	100%	100%	NA	NA	NA	double	NA
Mathus-Vliegen et al.	1990	Obesity	Endoscopy + balloon	Endoscopy + manipulation without balloon insertion + simulated "click" of device disconnection	Netherlands	NA	NA	NA	28	96%	100%	100%	NA	NA	NA	double	SE
Maurer et al.	2012	Sleep apnea	Palatal implants	Identical implementation device without an implant	Germany	NA	NA	NA	22	91%	91%	91%	NA	NA	NA	double	LA
Meshkinpour et al.	1988	Obesity	Endoscopy + balloon	Endoscopy + empty introducer tube + simulation of inflation process	USA	NA	265%	NA	23	91%	100%	100%	NA	NA	NA	double	SE
Montgomery et al.	2006	GERD	Endoscopy + EndoCinch plication technique	Endoscopy - the same duration	Sweden	NA	NA	NA	46	93%	100%	98%	NA	NA	NA	double	GA
Moseley et al.	2002	Osteoarthritis	Arthroscopy + debridement with chondroplasty but not spur removal or arthroscopy + lavage	Skin incision without arthroscopy	USA	NA	180%	80%	180	91%	90%	92%	164^	99%	110%	double	GA but SE and no intubation in placebo
Olanow et al.	2003	Parkinson's disease	Fetal tissue transplantation + a-biotics + cyclosporine + PET	Partial burr holes + a-biotics + cyclosporine + PET	USA	NA	NA	NA	34	91%	NA	NA	NA	NA	NA	double	GA
Pauza et al.	2004	Discogenic low back pain	Electrothermal therapy +discography + CT + prophylactic a-biotics + analgesics + rehabilitation	Introducing a needle onto the disc (visual and auditory feedback)+discography + CT + prophylactic a-biotics + analgesics + rehabilitation.	USA	7067%	NA	4942%	64	88%	86%	89%	67	84%	96%	double	LA
Porter et al.	2006	Turbinate hypertrophy	RF surgery	Placement of the probe, anaesthesia, and sound from the RF generator	USA	NA	NA	NA	32	100%	100%	100%	NA	NA	NA	single	LA
Rothstein et al.	2007	GERD	Endoscopy + plication	Endoscopy + setup but device not activated	USA, Germany, Belgium	NA	NA	NA	159	82%	81%	95%	NA	NA	NA	double	SE
Salem et al.	2004	Coronary disease	Percutaneous myocardial laser revascularisation	Setup but no laser activated	Norway	NA	NA	NA	82	96%	98%	96%	78^	101%	105%	double	NA
Schwartz et al.	2007	GERD	Endoscopy + gastroplication (Endocinch)	Endoscopy + setup without needle and thread loaded	Netherlands	NA	NA	NA	60	95%	100%	100%	54^	106%	111%	double	SE

Scolapio et al.	2001	Dysphagia	Endoscopy + balloon cathether (temporary inflation)	Endoscopy + balloon cathether - not inflated	USA	NA	NA	NA	86	NA	NA	NA	NA	NA	NA	single	SE
Shaheen et al.	2009	Barrett's esophaguss	Endoscopy + RF ablation+ biopsy + esmoprazole	Endoscopy + biopsy + esmoprazole	USA	594%	150%	158%	127	92%	93%	51%	NA	NA	NA	double	SE
Sihvonen et al.	2013	Degenerative meniscus tear	Arthroscopic partial meniscectomy	Arthroscopy and sham	Finland	NA	140%	16%	146	100%	100%	100%	112^	130%	130%	double	NA
Silverberg et al.	2008	Alzheimer's disease	Ventriculoperitoneal shunt + brain irrigation + ventricular fluid exchange	Identical shunt but occluded	USA	171%	120%	20%	230	71%	80%	88%	256	64%	90%	double	GA
Steward et al.	2008	Sleep apnea	Palatal implants	Identical implementation device without an implant + a-biotics	USA	968%	448%	348%	100	100%	100%	100%	100	100%	100%	double	LA
Stone et al.	2002	Coronary disease	Percutaneous coronary intervention + percutaneous myocardial laser revascularisation	No placebo intervention but patients were blinded during the percutaneous coronary intervention	USA	NA	NA	NA	141	100%	100%	100%	128^	110%	110%	double	SE
Stuck et al	2005	Snoring	RF surgery of the palate	Device was inserted but not activated	Germany	NA	NA	NA	26	88%	92%	85%	24^	96%	108%	double	LA
Sutton et al.	1994	Endometriosis	Laparoscopy + laser ablation + adhesiolysis + uterine nerve ablation	Laparoscopy	UK	NA	100%	NA	74	85%	NA	NA	NA	NA	NA	double	NA
Swank et al.	2003	Chronic abdominal pain	Laparoscopy + adhesiolysis	Laparoscopy	Netherlands	NA	NA	8%	100	96%	98%	94%	100	96%	100%	double	NA
Thompson et al.	2013	Obesity	Endoscopic Suturing for Transoral Outlet Reduction	Sham	USA	465%	168%	100%	77	90%	NA	NA	132	52%	58%	double	GA
Thomsen et al.	1981	Meniere's disease	Endolymphatic sac decompression	Simple mastoidectomy	Denmark	100%	NA	NA	30	100%	100%	100%	NA	NA	NA	double	NA
Toouli et al.	2000	Sphincter of Oddi dysfunction	Endoscopy + sphincterectomy + ERCP + manometry + morphine/neostigmine provocation test	Endoscopy + papillotome introduced into duodenum, noise made but not cut) + ERCP + manometry + morphine/neostigmine provocation test	Australia	NA	NA	NA	81	98%	NA	NA	NA	NA	NA	double	SE
van Schie et al.	2000	Diabetic foot	Silicone injection	Saline injection	UK	NA	NA	NA	28	NA	NA	NA	NA	NA	NA	double	LA

Note: NA – data not reported in the reviewed trial; types of analgesia: GA – general anesthesia, SE – sedation, LA – local analgesia; Condition: GERD – gastro-esophageal reflux disease, RA – rheumatoid arthritis, GI – gastro-intestinal; Intervention: RF – radiofrequency, ERCP - endoscopic retrograde cholangiopancreatography, PET - Positron emission tomography, MRI – magnetic resonance imaging, CT – computer tomography; Countries: UK – the United Kingdom, USA – the United States of America; Sample-size: ^ - sample size was inflated to account for potential drop-out, the number given in the table is the non-inflated sample size; Blinding: refers to double- and single-blinding.

36/bmjopen-2015-010194 on 15 March 2016.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	X
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Pages 4-5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Page 5 and http://www.bmj.com/content/348/bmj.g3253
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	N/A – this is a review of methods rather than results

PRISMA 2009 Checklist

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Descriptive summary
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Descriptive summary

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Published http://www.bmj.com/content/348/bmj.g3253
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	X
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Appendix http://www.bmj.com/content/348/bmj.g3253
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Appendix – this review analysed the study characteristics/methods rather than outcomes
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Descriptive summary. Pages 6-11
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	X
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	X
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 15

PRISMA 2009 Checklist

FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 1

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The feasibility of surgical randomised controlled trials with a placebo arm – a systematic review.

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The feasibility of surgical randomised controlled trials with a placebo arm – a systematic review.

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ABSTRACT

Objectives: To find evidence, either corroborating or refuting, for many persisting beliefs regarding the feasibility of carrying out surgical randomised controlled trials with a placebo arm, with emphasis on the challenges related to recruitment, funding, anaesthesia or blinding.

Design: Systematic review.

Data sources and study selection: The analysis involved studies published between 1959 and 2014 that were identified during an earlier systematic review of benefits and harms of placebo-controlled surgical trials, published in 2014.

Results: Sixty-three trials were included in the review. The main problem reported in many trials was a very slow recruitment rate, mainly due to the difficulty in finding eligible patients. Existing placebo trials were funded equally often from commercial and non-commercial sources. General anaesthesia or sedation was used in 41% of studies. Among the reviewed trials, 81% were double-blinded and 19% were single-blinded. Across the reviewed trials, 96% (range 50-100%) of randomised patients completed the study. The withdrawal rate during the study was similar in the surgical and in the placebo group.

Conclusions: This review demonstrated that placebo-controlled surgical trials are feasible, at least for procedures with a lower level of invasiveness, but also that recruitment is difficult. Many of the presumed challenges to undertaking such trials, for example, funding, anaesthesia or blinding of patients and assessors, were not reported as obstacles to completion in any of the reviewed trials.

STRENGTHS AND LIMITATIONS OF THE STUDY

- Review of all published surgical RCTs with a placebo arm, spanning the years 1959 to 2014.
- Due to the nature of this review, we could not investigate the obstacles that prevented initiation or completion of trials and, subsequently, our observations are

limited to the successfully published trials. However, this review of all published trials provides different evidence than a report from a single discontinued trial.

- Many of the problems reported in reviewed trials are not unique to placebo-controlled surgical trials, but are also relevant to other surgical trials and randomised controlled trials in general.

INTRODUCTION

Progress in surgery is based on practical experience.[1] Surgical randomised controlled trials (RCTs) are uncommon;[2] only about 15% of published RCTs are related to surgical interventions.[3] Novel procedures tend to be developed through an iterative process of trial and error[4] and only 24% of the currently used surgical therapies are supported by results of RCTs.[1]

Apart from not being necessary for approval of new treatment,[5] several reasons have been mentioned in the literature that may explain why surgical RCTs are scarce. Such studies are perceived as expensive[2, 6] and unlikely to attract funding.[3, 5, 7] They are considered to be difficult to design and conduct because of challenges posed by randomisation, blinding, differences in skills and experience of surgeons, variability of patients as well as lack of consensus on surgical outcomes.[1, 2, 6-8] Moreover, patient recruitment is also believed to be a problem.[6] The inclusion of a placebo control adds another level of complexity to a RCT.[6, 9] For example, some authors suggest that many patients may be unwilling to undergo an invasive procedure if there is no clear direct benefit to them, which may result in slow recruitment.[6] Others believe blinding of patients and outcome assessors is not feasible and that the surgeon can never be blinded.[10] As a result of that, very few interventional procedures have been validated using a placebo-controlled RCT.[1, 2, 5, 9, 11, 12] It is important to note that some of these opinions come from personal experience from a single trial, while others are just perceptions and assumptions. There have also been many publications discussing placebo in surgery that concentrate on ethical concerns, such as general

equipoise and minimizing the risks,[13, 14] and on conceptual problems, for example, whether surgeons will be willing to test efficacy of an already established procedure.[10, 15] However, very little has been written on the methodological challenges of such studies[16, 17] and, to the best of our knowledge, no one has attempted to summarise the evidence from all the published placebo-controlled surgical trials.

When we previously performed a systematic review examining the harms and benefits of placebo-controlled surgical RCTs, we found that there clearly are obstacles to completing such trials, as less than a hundred have been published between 1959 and 2013.[12] Therefore, we conducted a secondary review of these studies to find evidence corroborating or refuting persisting beliefs regarding the feasibility of carrying out placebo controlled surgical trials.

METHODS

Selection criteria

The criteria used to select placebo-controlled surgical RCTs were described previously.[12] In brief, studies were eligible if they were randomised trials, in which the efficacy of surgery was compared to placebo. Surgery was defined as any interventional procedure that changes the anatomy and requires a skin incision or the use of endoscopic techniques; dental studies were excluded. We used the term “placebo” to refer to a surgical placebo, a sham surgery, or a procedure intended to mimic the active intervention. A quasi-placebo, i.e., diagnostic procedure that could imitate the surgery, was also included. The important criterion was that patients were under general anaesthesia or blinded in some other way, and could not distinguish whether they underwent the actual surgery or placebo. We did not limit the inclusion criteria to any particular condition, patient group, intervention, or type of outcome. We excluded studies investigating anaesthesia or other pharmacological substances used peri-operatively.

In this review, we used the term “surgical placebo”. The word “sham” is preferred by some authors because surgical placebo has to involve an imitation of the investigated intervention in order to resemble it closely; therefore, it is different from an inactive “sugar pill” placebo used in pharmacological trials.[18] The word “sham“ has negative associations and it suggests that a procedure is fake and deceitful; however, in many trials the placebo involved an accepted surgical procedure such as endoscopy or arthroscopy, which was used also for diagnostic purposes with real benefits to the patients.

Search strategy

We searched the MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials databases from the date of their inception to 14th November 2013, with no restriction on language. We did not systematically search for studies reported only as conference abstracts. Search terms were published previously.[12]

Three reviewers (KW, IR, BJFD) independently screened the initial set of records identified from the search and then screened the full-text of any potentially relevant articles. Each reviewer assessed the eligibility of each study and the final list of included studies was agreed by consensus. Moreover, we searched ClinicalTrials.gov (on 14th November 2013), a database of registered randomised clinical trials, to identify any recently completed or ongoing studies. On 15th June 2014 we checked whether results of any of the trials identified in the ClinicalTrials.gov database have been published since the original search.

Dealing with duplicate publications

When there were several articles reporting outcomes from a single trial, i.e., with the same authors, location, patient population, and recruitment dates, we only included the paper reporting the primary outcome for the trial and excluded pilot and follow-up reports.

Data extraction

We used a standardised data extraction form to collect information about the characteristics of each study including: year of publication, country in which the trial was conducted, funding source, details of the active and placebo intervention as well as the type of anaesthesia, blinding, number of patients who were assessed, eligible, randomised and who declined participation as well as those who completed the trial. To reduce errors, the three review authors (KW, IR, BJFD) extracted data separately and checked the entries for consistency; a single set of data was agreed by all three reviewers.

Data synthesis

We have performed a descriptive analysis of the characteristics of each individual study and presented data in a table.

RESULTS

Study selection

We analysed the studies identified as a part of the systematic review on harms and benefits, including seven trials that were excluded from the systematic review due to lack of a direct comparison between the surgical and the placebo group. We also checked whether the trials identified in the ClinicalTrials.gov database had their results published between November 2013 and June 2014, and found three additional trials.[19-21] This resulted in 63 full-text articles, which were included in this review (Figure 1).

Placebo-controlled surgical RCTs characteristics

The number of published placebo-controlled surgical trials was small; however, 73% (n=46/63) of included RCTs were published after the year 2000, suggesting an increasing interest in performing such studies. Half of the trials (n=35/63, 55%) used a key-hole surgery, including endoscopy (n=28/63), laparoscopy (n=4/63), arthroscopy (n=2/63) and bronchoscopy (n=1/63). The remaining trials involved other types of minimally-invasive interventions, for example, using catheters for vascular access or needles for injection of fat

or exogenous materials to remodel tissue. Very few studies investigated open techniques such as exposure of the internal mammary artery (n=2/63) or exposure of scalp muscles (n=1/63). Fifteen trials used implants and additional seven used gastric balloons or bubbles (Characteristics of the reviewed trials are presented in Appendix 1).

Funding sources

One third of the studies (n=21/63, 33%) were non-commercially funded and almost as many were funded by a commercial company (n=18/63, 29%), often the manufacturer of the implant or the endoscope. The source of funding in the remaining studies (n=24/63, 38%) was not reported.

Over half of the trials were undertaken in the USA (n=35/63, 56%), the others were in Canada, the UK, Germany, the Netherlands, Belgium, Italy, Finland, Sweden, Portugal, Norway, Greece, Denmark, Australia, and Brazil.

Sample size

The majority (n=47/63, 75%) of the identified studies were small, with fewer than 100 participants. The median number of patients randomised in a trial was 61 (Interquartile range 66, range 10-298).

About half of the RCTs (n=33/63; 52%) reported a formal sample size calculation, but only a quarter (n=16/63) allowed for dropouts and attrition. Most of the trials that included a sample size calculation (n=23/33, 70%) attained their pre-specified sample size (without accounting for attrition). Ten trials under-recruited, such that the number of randomized patients was lower than the calculated sample size. All ten trials were terminated early: three due to slow recruitment,[22-24] one because at the interim analysis the surgery was highly effective [25] and two because at the interim analysis the active procedure lacked efficacy,[19, 26] two studies were stopped because of serious adverse events either in the trial[27] or at another centre

using a similar procedure.[28] One trial was terminated when the sponsoring company was sold.[29] Finally, one study was stopped because the investigated procedure was approved as a standard care and the equipoise ceased to exist, despite the fact that the study did not show its superiority over placebo.[30] Finally, one trial recruited the intended sample size, but due to a high drop-out rate the number of patients who completed the trial was lower than the required sample size.[31]

Recruitment and screening

Recruitment, sometimes as slow as 1-2 patients per month,[22, 32] was a common problem [19, 22, 28-36] and was the reason for an early termination of three trials.[22-24]

Many of the analysed studies did not provide any details about screening and recruitment; they either stated that they recruited consecutive patients fulfilling the criteria [22] or that they randomised patients who were willing to participate and were eligible.[37] About one third of the trials specified the number of screened (n=24/63, 38%) and eligible patients (n=27/63, 43%) and stated how many patients declined participation or withdrew before the treatment (n=22/63, 34%); only one fifth of the trials (n=13/63, 21%) reported all three numbers (Appendix 1). The available data suggest that the initial assessment of eligibility was the main obstacle in recruitment as patients did not meet the inclusion criteria or were not eligible due to exclusion criteria.

On average, it was necessary to screen more than five patients in order to randomise one, but three in four eligible patients started the trial (Table 1). The number of patients that had to be screened before the necessary group was recruited varied greatly. This variance was, at least partly, related to the method of identifying potential participants. The trial with the largest number of screened patients recruited using TV and newspaper advertising: out of 4,523 screened patients only 260 were eligible and were willing to participate; however, 196 had negative discography and only 64 patients were randomised.[24] More targeted

recruitment from specialist centres had much higher success rate but often required a multi-site effort.[36]

Many trials had additional inclusion and exclusion criteria that could only be verified after the patient entered into the trial, for example, a verification of diagnosis by positive findings during the endoscopy or on diagnostic imaging. As a consequence of this, many patients were excluded because either they did not have the investigated condition or they had some concomitant condition that precluded their participation in the trial and, sometimes, required appropriate treatment. Moreover, any technical complications during the assessment or study procedures potentially resulted in patients' drop-out. For example, in the trial on laparoscopic adhesiolysis for abdominal pain by Swank and colleagues,[33] nine patients did not have adhesions, one of them had a hernia and was treated laparoscopically, three patients had stricturing adhesions that required therapeutic adhesiolysis, and in one instance a pneumoperitoneum could not be achieved; therefore, out of 121 assessed patients 13 were excluded during laparoscopy.

Fluctuating symptoms were a problem in a few studies, for example, patients became asymptomatic while waiting for the procedure and had to be excluded from the trial [20] or did not report symptoms during the study visit and did not undergo the treatment but were included in the intention-to-treat analysis.[38] This problem also complicated the post-treatment assessment,[39] especially that only one trial included an observational control group.[40]

Refusal to participate

Some of the approached patients declined participation in the trial, withdrew their initial consent, refused to be randomized or to comply with the requirements of the protocol and had a strong preference for one of the treatment options. Most of the trials did not report the reasons for patients' refusal to participate and the available data did not allow us to quantify

the percentage of patients that refused to enter the study. Only 22 reviewed trials stated the number of patients who declined to participate but it was not always clear whether these numbers referred to patients at the screening stage or to patients already identified as eligible. The median percentage of patients who declined participation as a percentage of randomised patients was 18% and varied from 3% to 4,842%. It is important to note, that the two trials with high numbers of patients refusing to participate investigated vertebroplasty, which, at the time, was an established procedure; therefore, patients could easily receive the treatment from a different medical centre, without participating in a trial.[35, 36]

Patient retention

In general, recruitment was more problematic than retention and, once recruited, patients usually remained in the trial. Across the reviewed trials, 96% of randomized patients completed the study (Table 1). A lower completion rate in five trials was caused by an early termination[26, 30, 41] as well as withdrawals or change of patients' health status.[42, 43] In general, the predicted attrition, by which the required sample size was inflated to account for drop-outs, was 10% (median) with the range from 5% to 24%, whereas the actual patients' attrition between randomisation and outcome assessment was 4% (range 0%-50%).

The completion rate was similar in the active and in the placebo arm, except for two trials: one[19] where five times as many patients were lost to follow-up in the active group than in the placebo group and one[31] where the drop out rate was three times higher in the placebo group. Neither of these studies could explain this difference.

Most of the drop-outs occurred before randomisation. The reported reasons for drop-out during the trial were withdrawals, loss to follow-up, or discontinuation without known cause [21, 40, 42, 44, 45], patients' request to be unblinded,[25] adverse events,[26, 27] change of medical status such as pregnancy or concurrent illness.[24, 46, 47] A long wait between the screening and procedure did not necessary result in patient withdrawal.[44] A variable reporting did not

allow us to evaluate quantitatively the reasons for drop-outs.

Blinding was possible and some studies attempted to blind surgeons

In twelve trials (19%) only patients were blinded, but in the majority of RCTs (n=51/63, 81%) both patients and outcome assessors were blinded; including three trials, in which there was also an attempt to blind the operator. For example, in two trials the implant delivery system was pre-loaded by manufacturer – the devices looked identical but only one contained an implant.[29, 48] In another trial, the surgeon placed the catheter but then handed the procedure over to a technician who delivered the treatment according to the randomisation.[22]

Authors of the reviewed trials went to great lengths to imitate the visual, verbal and physical cues and to make the placebo as similar as possible to the active procedure. For example, patients wore goggles or had the view obscured so that they could not see the device.[49] The preparation for the placebo intervention was done in the same way as for the active procedure.[36, 50] Similar verbal instructions were given as during the surgery[43, 51] and there were attempts to imitate the noises made by the devices.[52] In trials that used exogenous substances, the container was opened so that the distinct smell was present also during the placebo condition.[36] Some researchers attempted to keep the duration of the procedure the same in both arms[40, 44, 53] whereas others thought that it was more ethical to shorten the placebo intervention.[32]

Very few studies assessed the success of blinding. Often authors thought that it was reasonable to assume that patients in the study were not able to distinguish between placebo and surgery due to minimally-invasive characteristics of the procedure and minimally post-operative treatment-related symptoms.[54, 55] In one trial, the post-treatment symptoms were believed to be a sign of correctly placed effective gastroplication as patients with these symptoms had better outcomes.[40] Blinding was reported as successful in n=13/63 (21%) studies. In four trials,[36, 43, 56, 57] a larger proportion of patients in the active group

guessed correctly; however, the placebo group did not guess the treatment allocation. In one study, two patients were definitely unblinded early due to implant extrusion.[58]

Anaesthesia

In the reviewed trials, patients in both groups received some type of anaesthesia. General anaesthesia or sedation were used in n=26/63 trials (41%), including one trial in which general anaesthesia was used in the surgical group but patients in the placebo group were sedated without intubation.[30] Local analgesia was used in n=16/63 (25%) RCTs, four studies used a mixture of methods, and n=17/63 (27%) trials did not describe the type of anaesthesia used. None of the trials reported that anaesthesia was a barrier in conducting their study.

DISCUSSION

This review has demonstrated that surgical randomised controlled trials with a placebo arm are feasible, at least for procedures with a lower level of invasiveness. Many of the presumed challenges, such as funding, anaesthesia or blinding of patients and assessors, were not reported as obstacles in any of the reviewed trials. The main hurdle in completing a trial was finding a sufficient number of eligible patients.

We found that, although, there were very few surgical RCTs with a placebo arm published between 1959 and 2014, there was a rising trend. This may be related to an increasing interest in placebo and placebo-controlled trials in general[59] or to the increasing popularity of minimally-invasive procedures since 1980s. The latter explanation is supported by the fact that most of the reviewed trials used some type of key-hole surgery.

The analysed placebo-controlled trials were funded equally often by industry as by non-commercial funding bodies. The number of commercially-funded older trials may be underestimated in our review because surgical RCTs funded by industry have lower odds of

being published.[60] However, the recent trials are registered in the ClinicalTrials.gov database and would have been identified. The distribution of the source of funding was similar to that described by other authors.[11] This is encouraging, as it shows that there is an interest within the industry to validate the efficacy of their products and also that the non-commercial bodies are willing to investigate the efficacy of surgical procedures. The costs of running surgical RCTs are high[2] but in the long run preferential funding of treatment with proven efficacy may help to improve the allocation of resources and to lower the costs of health care.[61] For example, the trial by Moseley and colleagues[53] demonstrated that arthroscopic surgery had no benefits because the outcomes in the arthroscopic debridement arm and the lavage arm were not better than in the placebo group and, consequently, there was a decline in the use of this procedure for knee osteoarthritis.[62]

Recruitment into placebo-controlled surgical trials was possible but was often very slow and resulted in an early termination of several trials. Slow recruitment is the most frequent reason for discontinuation of RCTs, including surgical RCTs. For example, 21% of reviewed surgical RCTs were discontinued early and 44% of these were due to problems with recruitment.[60] Authors often underappreciate the fact that the target population in surgical trials is small; therefore, it may be challenging to recruit a required number of patients in a reasonable period of time.[2] The right timing of a trial may also affect its completion,[7] for example, initiating a trial too early in the intervention's development may result in more procedure-related adverse events,[27] whereas, when a procedure has been already established, like vertebroplasty, it may be difficult to recruit participants.[35, 36]

In the reviewed trials, the number of patients that had to be screened in order to recruit necessary participant group was larger than in other RCTs but the proportion of eligible patients that started the study was comparable to other types of RCTs.[63] This is another argument suggesting that the main challenge in those trials was finding suitable patients rather than persuading potential participants to enter the trial and this is a bigger problem

than in other types of RCTs.[63] Reporting of the recruitment process and eligibility was generally poor and often difficult to interpret as the reviewed studies usually did not describe in detail why eligible patients did not enter the trial, which is in line with observations from other reviews.[63] The quality of reporting in analysed RCTs was poor but this is a known problem in surgical trials.[7, 63]

There is an assumption that patients are unwilling to take part in surgical RCTs, especially patients in severe pain.[64] Interestingly, in the trial by Moseley and colleagues [53] patients in more pain were more likely to agree to participate. Also patients tend to choose the new treatment even if it was not proven to be superior over placebo. For example, in the trials on Parkinson's disease, patients actually opted for the transplantation when they were given a choice after the end of the trial, despite the fact that it was not demonstrated to be more effective than placebo.[50] In a recent orthopaedic placebo-controlled RCT, patients were willing to participate and screening failures were a larger problem than refusals or withdrawals.[16] The clinical characteristics of patients who entered into a placebo-controlled RCT were comparable to the non-enrolment group as well as to patients in other trials.[16]

Only about half of published trials reported a sample size calculation, which is in line with another review of surgical trials, which found that sample size calculations were reported only in 63% of RCTs.[11] However, it is important to note that some of the reviewed trials were published before the CONSORT (Consolidated Standards of Reporting Trials) were introduced and before the sample size calculation became required by the board review. Some trials were small because of the author's assumption that surgical studies have a large effect size; therefore, inferring a smaller sample size is required in surgical trials than in drug trials.[48, 65] However, surgical RCTs may require larger numbers of patients to reach the required sample size.[66] Recent systematic reviews demonstrated that the effect size of the surgical procedure in comparison to placebo in the existing trials was often small.[12, 67] It is likely that the apparent lack of difference between the active treatment and placebo might

have been related to the small sample size and the effect not reaching the statistical significances.[48, 68, 69] It might be also caused by a large placebo effect; however, the magnitude of the placebo effect in surgical procedures is unknown. The magnitude of response in the placebo arm is related not only to the placebo effect, i.e., response directly related to the placebo intervention, but also to non-specific changes such as regression to the mean, natural history of disease, effect of participation in the trial.[70] Only one reviewed trial included a non-interventional group to control for these non-specific effects.[40]

A placebo procedure can successfully imitate a minimally-invasive surgery. Blinding in interventional trials is more challenging than in pharmaceutical ones;[11, 71] however, there are many strategies to blind the patients and outcome assessors[71] and the reviewed trials often used ingenious methods to achieve blinding. The success of blinding was rarely assessed, but it is not necessary according to the current reporting standards. The requirement to assess blinding was removed from the CONSORT checklist because of evidence that testing for blindness is not valid because it cannot distinguish the success of blinding from "hunches" about treatment's efficacy.[72]

Blinding of patients and outcome assessors is especially important if the outcomes are subjective or difficult to quantify.[73] Softer outcomes are difficult to evaluate in unblinded trials due to patient- or assessor-related bias, which may distort the treatment effect.[74, 75] In this analysis, we have demonstrated that the withdrawal rate was generally low and was similar in the active and the placebo group. This provides supporting evidence that blinding reduces the attrition bias, as patients do not know to which treatment they had been allocated.[76]

Future implications for clinicians and unanswered questions

What remains to be understood is why eligible patients decline participation or withdraw their consent before randomisation.[77] Addressing these issues may improve the recruitment procedure in future trials.

There is also a need to estimate the magnitude of placebo effect in interventional trials. Several authors have highlighted the fact[12, 66, 67] that for softer outcome measures, the magnitude of placebo effect in surgical trials is underestimated while the effect size of the surgical intervention is overestimated and, as a result of that, many trials do not recruit sufficient numbers of patients to detect differences between the effects of surgery and placebo.

Journals should encourage authors to report the details of patient recruitment and allocation, including the reasons for withdrawals and screening failures. Data like this are very useful when planning future trials. There has been an improvement in the reporting quality of recent trials[21] and these guidelines were included in the CONSORT extension for non-pharmacological interventions.[78]

In conclusion, not every surgical procedure has a viable placebo control; however, surgical RCTs with a placebo arm are feasible for many less invasive procedures. Although placebo-controlled surgical RCTs are challenging, they should not be dismissed as a potential trial design in surgical research. There is a need to better understand the factors that make those trials challenging so that future trials are not terminated early and contribute good-quality evidence to surgical practice.

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PRISMA statement The PRISMA flow chart is presented in Figure 1.

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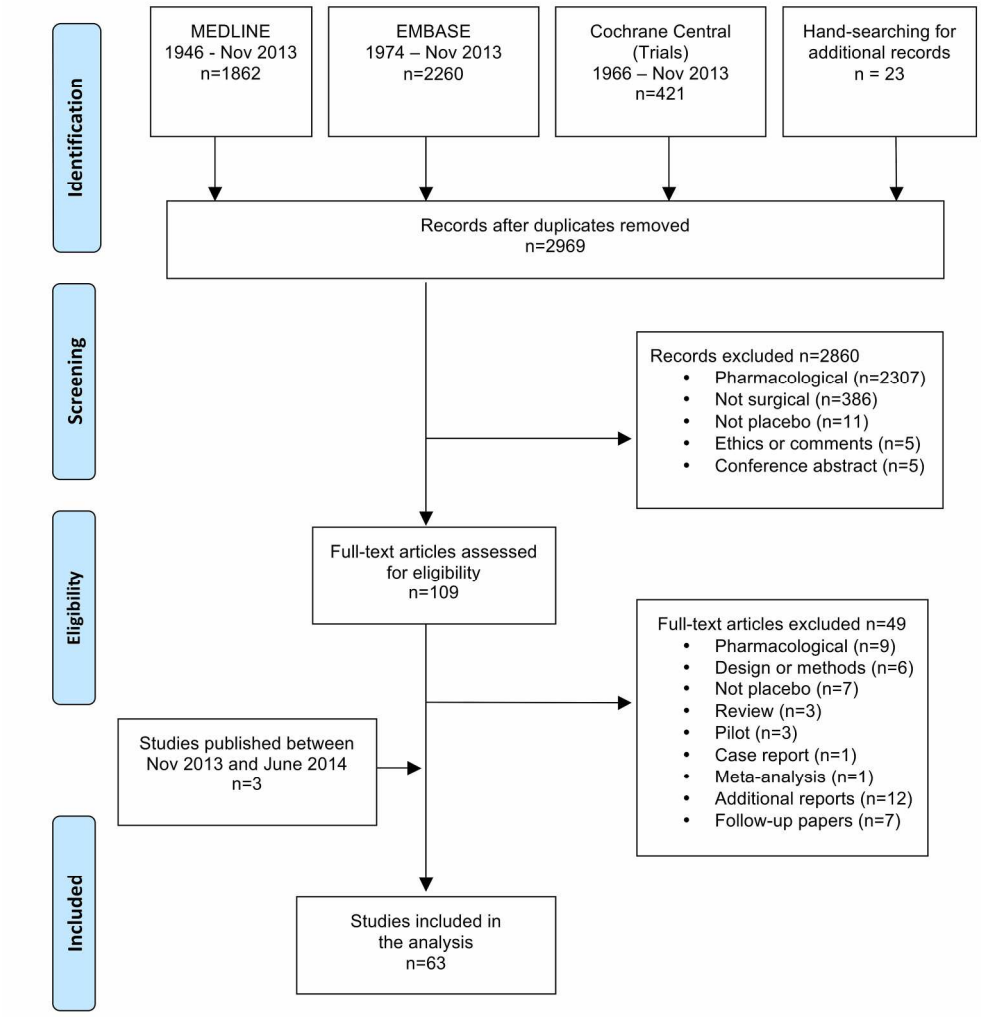
Table 1 Participants flow through the reviewed trials as a percentage of the number of patients who were randomised into each trial

	Number of studies	Median % of sample randomised	First and third quartile	Minimum and maximum
Screened	24	530%	243%, 773%	100%, 7067%
Eligible	27	132%	108%, 172%	100%, 448%
Declined	22	18%	8%, 144%	3%, 4942%
Sample size	33	96%	90%, 110%	49%, 323%
Outcome assessed	61	96%	90%, 100%	52%, 100%

Note: “Number of studies” refers to the number of trials that provided relevant data. Trials terminated early are included in these analyses. “Sample size” refers to the sample size required to reach statistical power, not inflated to account for drop-outs. “Outcome assessed” refers to total number of patients, in both arms. The denominator is the number of patients actually randomised into each trial.



PRISMA flow chart
212x230mm (300 x 300 DPI)

Appendix 1 Characteristics of the reviewed trials

Study	Year	Condition	Active intervention	Placebo intervention	Country	Screened as % of randomised	Eligible as % of randomised	Declined as % of randomised	Number of randomised	Completed as % of randomised	Completed as % of randomised in surgery arm	Completed as % of randomised in placebo arm	Calculated sample size	Completed as % of sample size	Randomised as % of sample size	Blinding	Analgesia
Abbott et al.	2004	Endometriosis	Laparoscopy + ablation	Laparoscopy	UK	NA	323%	6%	52	75%	100%	100%	40^	98%	130%	P&A	NA
Arts et al.	2010	GERD	Endoscopy + RF treatment	Endoscopy + setup but no RF delivery	Belgium	NA	NA	NA	22	100%	100%	100%	22	100%	100%	P&A	SE (1subj GA)
Baeck et al.	2009	Sleep apnea	RF surgery of the palate	Applicator insertion but no RF delivery	Finland	250%	106%	6%	32	100%	100%	100%	26^	123%	123%	P	LA
Bajbouj et al.	2009	Globus sensation	Endoscopy + ablation using argon plasma coagulation	Endoscopy + connected applicator but no current	Germany	NA	NA	NA	21	90%	91%	100%	40	48%	53%	P&A	SE
Benjamin et al.	1988	Obesity	Endoscopy + gastric bubble + diet	Endoscopy + balloon imitation + diet	USA	NA	NA	NA	90	68%	crossover	crossover	NA	NA	NA	P&A	SE
Bradley et al.	2002	Osteoarthritis	Tidal irrigation of the joint	Saline injection and leg manipulation	USA	NA	NA	NA	180	99%	98%	100%	150^	119%	120%	P&A	LA
Buchbinder et al.	2009	Osteoporotic vertebral fractures	Percutaneous vertebroplasty	Injection of anaesthetic but not cement +cephalosporin	Australia	600%	281%	181%	78	94%	95%	93%	48	152%	163%	P&A	LA
Castro et al.	2010	Severe asthma	Bronchoscopy + RF treatment	Bronchoscopy + placebo procedure	USA, Brazil, Canada, Australia, UK	201%	103%	3%	288	97%	92%	96%	225	124%	128%	P&A	SE
Cobb et al.	1959	Coronary disease	Ligation of internal mammary artery	Skin incision and exposure of vessels but no ligation.	USA	NA	NA	NA	17	100%	100%	100%	NA	NA	NA	P	LA
Corley et al.	2003	GERD	Endoscopy + RF treatment	Endoscopy + setup but no RF delivery	USA	NA	NA	NA	64	81%	89%	72%	64	81%	100%	P&A	SE
Cotton et al.	2014	Sphincter of Oddi dysfunction	Endoscopy + sphincterectomy + ERCP	Endoscopy + ERCP	USA	740%	169%	35%	214	81%	84%	76%	193^	90%	111%	P&A	SE
Davys et al.	2005	Plantar callosities in RA	Scalpel debridement of the callosity	Simulation using blunt-edged scalpel	UK	145%	134%	34%	38	100%	100%	100%	38	100%	100%	P	NA
Deviere et al.	2005	GERD	Endoscopy + a nonresorbable copolymer	Endoscopy without implant + prophylactic antibiotics	Germany, Belgium, Italy	NA	NA	NA	64	100%	100%	100%	NA	NA	NA	P	SE
Dimond et al.	1960	Coronary disease	Ligation of internal mammary artery and vein	Skin incision and exposure of vessels but no ligation	USA	NA	NA	NA	18	100%	100%	100%	NA	NA	NA	P	LA
Dowson et al.	2008	Migraine	Implant for patent foramen ovale + heparin	Skin incision in the groin + transoesophageal US + aspirin and clopidogrel - no heparin	UK	301%	111%	NA	147	93%	88%	97%	132^	103%	111%	P&C&A	GA
Eid et al.	2014	Obesity	Endoscopy + gastroplication (StomaphyX)	Endoscopy	USA	848%	316%	206%	90	82%	76%	84%	135^	55%	67%	P	GA
Fleischer et al.	1985	Bleeding esophageal varices	Endoscopy + laser + cimetidine or antacids + vasopressin if bleeding persisted	Endoscopy + setup (laser was turned on, a verbal order was given to activate the laser but not used) + cimetidine or antacids after endoscopy + vasopressin if bleeding persisted	USA	NA	NA	NA	20	100%	100%	100%	NA	NA	NA	P&C&A	NA
Fockens et al.	2010	GERD	Endoscopy + Gatekeeper implant	Endoscopy + saline instead of implant and instead of antibiotics	USA , Netherlands	335%	150%	NA	118	65%	68%	60%	NA	NA	NA	P	SE
Freed et al.	2001	Parkinson's disease	Fetal dopamine neurons transplantation+trepanation + PET + MRI + phenytoin	Incomplete trepanation (dura intact) + PET + MRI + phenytoin - sham-transplantation	USA	NA	NA	NA	40	98%	95%	100%	NA	NA	NA	P	LA
Freeman et al.	2005	Discogenic low back pain	Electrothermal therapy	Catheter inserted but not connected + cephazolin +CT	Australia	NA	NA	NA	57	96%	95%	100%	75	73%	76%	P&S&A	SE
Freitas et al.	1985	Bleeding from gastric/duodenal ulcers	Endoscopy + electrocoagulation + cimetidine	Sham + cimetidine	Portugal	615%	215%	NA	78	100%	100%	100%	NA	subgroups	NA	P	SE
Friedman et al.	2008	Sleep apnea	Palatal implants	Identical implementation device without an implant + antibiotics	USA	181%	129%	NA	62	89%	94%	84%	54^	102%	115%	P&A	NA
Fullarton et al.	1989	Bleeding from peptic ulcers	Endoscopy + heater probe + ranitidine	Endoscopy + heater probe activated in the gut lumen + ranitidine	UK	1465%	119%	NA	43	100%	100%	100%	NA	NA	NA	P&C&A	NA
Geenen et al.	1989	Sphincter of Oddi dysfunction	Endoscopy + sphincterectomy + ERCP + manometry + morphine/neostigmine provocation test	Endoscopy + device activated in the lumen of the duodenum + ERCP + manometry + morphine/neostigmine provocation test	USA	615%	109%	9%	47	100%	100%	100%	NA	NA	NA	P&C&A	NA

Geliebter et al.	1990	Obesity	Endoscopy + balloon	Endoscopy + deflated balloon	USA	NA	NA	NA	10	100%	100%	100%	NA	NA	NA	P&A	LA
Genco et al.	2006	Obesity	Endoscopy + balloon (BioEnterics)	Endoscopy but no balloon	Italy	NA	NA	NA	32	100%	100%	100%	NA	NA	NA	P&A	SE
Gillespie et al.	2010	Sleep apnea	Palatal implants	Identical implementation device without an implant	USA	NA	NA	NA	51	98%	NA	NA	80^	63%	64%	P&S&An	LA
Gross et al.	2011	Parkinson's disease	Pigmental cells transplantation	Scalp incisions and partial-thickness burr holes + MRI - the same duration	USA, Germany	221%	135%	10%	71	94%	89%	100%	68	99%	104%	P&A	GA
Guyuron et al.	2009	Migraine	Surgical "deactivation" of migraine trigger points	Exposure of muscles and nerves without changing their integrity	USA	417%	100%	NA	76	99%	100%	100%	NA	NA	NA	P&A&An	NA - occipital group GA, other - not stated
Hartigan et al.	1994	Esophageal varices	Endoscopy + sclerotherapy	Endoscopy + placebo solution released to the gut lumen	USA	NA	116%	16%	253	100%	100%	100%	244^	104%	104%	P	NA
Hogan et al.	1989	Obesity	Endoscopy + gastric bubble	Endoscopy + sham insertion	USA	271%	NA	NA	59	95%	100%	98%	NA	NA	NA	P&A	SE
Jarrell et al.	2005	Endometriosis	Laparoscopy + biopsy + sharp excision	Laparoscopy + biopsy	Canada	NA	NA	3%	29	52%	47%	97%	84^	18%	35%	P&C&A	NA
Kallmes et al.	2009	Osteoporotic vertebral fractures	Percutaneous vertebroplasty	Simulated (audio, sensory, even smell) vertebroplasty - injection of anaesthetic but not cement	USA, UK, Australia	1384%	329%	229%	131	98%	99%	97%	130	98%	101%	P&A	LA
Koutsourelakis et al.	2008	Sleep apnea	Septoplasty	Simulated resection with manipulation of instruments - the same amount of time	Greece	NA	104%	4%	49	100%	100%	100%	24	204%	204%	P&A	LA
Laine et al.	1987	Upper GI tract bleeding (ulcers)	Endoscopy + electrocoagulation	Endoscopy + probe activated in the lumen of the gut	USA	748%	NA	16%	44	93%	100%	100%	NA	NA	NA	P&C&A	NA
Lee et al.	2001	Urinary stress incontinence	Autologous fat injection	Fat harvested but discarded + saline injection + trimetoprim-sulfamethoxazole or nitrofurantoin	Canada	NA	NA	NA	68	82%	77%	88%	90	62%	76%	P&A	LA and SE occasional GA
Leon et al.	2005	Coronary disease	Percutaneous myocardial laser revascularisation	Setup but no laser procedure	USA	NA	NA	NA	298	100%	100%	100%	NA	NA	NA	P&A	NA
Lindor et al.	1987	Obesity	Endoscopy + balloon + diet	Endoscopy + empty introducer tube + diet	USA	NA	NA	NA	22	95%	91%	100%	71	30%	31%	P&A	SE
MacLeod et al.	1983	Bleeding from a peptic ulcers	Endoscopy + laser + cimetidine	Endoscopy + cimetidine	UK	1551%	120%	NA	45	100%	100%	100%	NA	NA	NA	P	NA
Mathus-Vliegen et al.	1990	Obesity	Endoscopy + balloon	Endoscopy + manipulation without balloon insertion + simulated "click" of device disconnection	Netherlands	NA	NA	NA	28	96%	100%	100%	NA	NA	NA	P&C&A	SE
Maurer et al.	2012	Sleep apnea	Palatal implants	Identical implementation device without an implant	Germany	NA	NA	NA	22	91%	91%	91%	NA	NA	NA	P&C&A	LA
Meshkinpour et al.	1988	Obesity	Endoscopy + balloon	Endoscopy + empty introducer tube + simulation of inflation process	USA	NA	265%	NA	23	91%	100%	100%	NA	NA	NA	P&A	SE
Montgomery et al.	2006	GERD	Endoscopy + EndoCinch plication technique	Endoscopy - the same duration	Sweden	NA	NA	NA	46	93%	100%	98%	NA	NA	NA	P&C&A	GA
Moseley et al.	2002	Osteoarthritis	Arthroscopy + debridement with chondroplasty but not spur removal or arthroscopy + lavage	Skin incision without arthroscopy	USA	NA	180%	80%	180	91%	90%	92%	164^	99%	110%	P&A	GA but SE and no intubation in placebo
Olanow et al.	2003	Parkinson's disease	Fetal tissue transplantation + antibiotics + cyclosporine + PET	Partial burr holes + antibiotics + cyclosporine + PET	USA	NA	NA	NA	34	91%	NA	NA	NA	NA	NA	P&A	GA
Pauza et al.	2004	Discogenic low back pain	Electrothermal therapy +discography + CT + prophylactic antibiotics + analgesics + rehabilitation	Introducing a needle onto the disc (visual and auditory feedback)+discography + CT + prophylactic antibiotics + analgesics + rehabilitation.	USA	7067%	NA	4942%	64	88%	86%	99%	67	84%	96%	P&C&A	LA
Porter et al.	2006	Turbinate hypertrophy	RF surgery	Placement of the probe, anaesthesia, and sound from the RF generator	USA	NA	NA	NA	32	100%	100%	100%	NA	NA	NA	P	LA
Rothstein et al.	2007	GERD	Endoscopy + plication	Endoscopy + setup but device not activated	USA, Germany, Belgium	NA	NA	NA	159	82%	81%	96%	NA	NA	NA	P&A	SE

Salem et al.	2004	Coronary disease	Percutaneous myocardial laser revascularisation	Setup but no laser activated	Norway	NA	NA	NA	82	96%	98%	96%	78^	101%	105%	P&A	NA
Schwartz et al.	2007	GERD	Endoscopy + gastroplication (Endocinch)	Endoscopy + setup without needle and thread loaded	Netherlands	NA	NA	NA	60	95%	100%	100%	54^	106%	111%	P&A	SE
Scolapio et al.	2001	Dysphagia	Endoscopy + balloon cathether (temporary inflation)	Endoscopy + balloon cathether - not inflated	USA	NA	NA	NA	86	NA	NA	NA	NA	NA	NA	P	SE
Shaheen et al.	2009	Barrett's oesophagus	Endoscopy + RF ablation+ biopsy + esmoprazole	Endoscopy + biopsy + esmoprazole	USA	594%	150%	158%	127	92%	93%	91%	NA	NA	NA	P&An	SE
Sihvonen et al.	2013	Degenerative meniscus tear	Arthroscopic partial meniscectomy	Arthroscopy and sham	Finland	NA	140%	16%	146	100%	100%	100%	112^	130%	130%	P&C&A	NA
Silverberg et al.	2008	Alzheimer's disease	Ventriculoperitoneal shunt + brain irrigation + ventricular fluid exchange	Identical shunt but occluded	USA	171%	120%	20%	230	71%	80%	83%	256	64%	90%	P&C&A	GA
Steward et al.	2008	Sleep apnea	Palatal implants	Identical implementation device without an implant + antibiotics	USA	968%	448%	348%	100	100%	100%	100%	100	100%	100%	P&C&A	LA
Stone et al.	2002	Coronary disease	Percutaneous coronary intervention + percutaneous myocardial laser revascularisation	No placebo intervention but patients were blinded during the percutaneous coronary intervention	USA	NA	NA	NA	141	100%	100%	100%	128^	110%	110%	P&C&A	SE
Stuck et al	2005	Snoring	RF surgery of the palate	Device was inserted but not activated	Germany	NA	NA	NA	26	88%	92%	85%	24^	96%	108%	P&A	LA
Sutton et al.	1994	Endometriosis	Laparoscopy + laser ablation + adhesiolysis + uterine nerve ablation	Laparoscopy	UK	NA	100%	NA	74	85%	NA	NA	NA	NA	NA	P&A	NA
Swank et al.	2003	Chronic abdominal pain	Laparoscopy + adhesiolysis	Laparoscopy	Netherlands	NA	NA	8%	100	96%	98%	94%	100	96%	100%	P&A	NA
Thompson et al.	2013	Obesity	Endoscopic Suturing for Transoral Outlet Reduction	Sham	USA	465%	168%	100%	77	90%	NA	NA	132	52%	58%	P&A	GA
Thomsen et al.	1981	Meniere's disease	Endolymphatic sac decompression	Simple mastoidectomy	Denmark	100%	NA	NA	30	100%	100%	100%	NA	NA	NA	P&A	NA
Toouli et al.	2000	Sphincter of Oddi dysfunction	Endoscopy + sphincterectomy + ERCP + manometry + morphine/neostigmine provocation test	Endoscopy + papillotome introduced into duodenum, noise made but not cut) + ERCP + manometry + morphine/neostigmine provocation test	Australia	NA	NA	NA	81	98%	NA	NA	NA	NA	NA	P&A	SE
van Schie et al.	2000	Diabetic foot	Silicone injection	Saline injection	UK	NA	NA	NA	28	NA	NA	NA	NA	NA	NA	P&A	LA

Note: NA – data not reported in the reviewed trial; blinded: P – patients, C – care givers, S – surgeons, A – assessors, An – analysis ; types of analgesia: GA – general anaesthesia, SE – sedation, LA – local analgesia; Condition: GERD – gastro-oesophageal reflux disease, RA – rheumatoid arthritis, GI – gastro-intestinal; Intervention: RF – radiofrequency, ERCP - endoscopic retrograde cholangiopancreatography, PET - Positron emission tomography, MRI – magnetic resonance imaging, CT – computer tomography; Countries: UK – the United Kingdom, USA – the United States of America; Sample-size: ^ - sample size was inflated to account for potential drop-out, the number given in the table is the non-inflated sample size; Blinding: refers to double- and single-blinding.