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Research waste in surgical randomised controlled trials: Cross-sectional observational study

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Plain English Summary

Research waste is when research studies are unable to make useful contributions to what we already know. This may happen for several reasons. Firstly, research may be wasted due to bad design. This means that the methods are not suitable to achieve the study aims. Secondly, research may be wasted if the results are not published. This means that the results remain hidden and are never seen by scientific and public communities. Finally, research may be wasted if the clarity of published results is not good enough to understand and use.

This study found that research waste is common in surgical clinical trials. On average, 85 out of every 100 trials had at least one example of research waste. The results suggested that larger clinical trials in receipt of financial support were less associated with waste. Knowing this information could help researchers to find suitable targets for improvement in the future. Reducing waste in surgical trials could benefit healthcare systems and patients by making research more efficient.

Abstract

Background: Research waste is a major challenge for evidence-based medicine. It implicates misused resources and increased risks applied to research participants. The aim of this study was to quantify constituent components of waste in surgical randomised controlled trials (RCTs) and explore targets for improvement.

Methods: ClinicalTrials.gov was searched for RCTs registered between January 2011 and December 2012 using the keyword “surgery”. The primary outcome was research waste, defined as non-publication, inadequate reporting, or presence of an avoidable design weakness. Serial systematic searches of PubMed and Scopus databases were performed to determine publication status. Adequacy of reporting was assessed using the CONSORT Checklist. Avoidable design weaknesses were assessed according to the presence of bias and/or the absence of a cited systematic review of the literature.

Results: Of 5617 registered RCTs, 304 met all eligibility criteria. Overall, 259/304 (85%) demonstrated at least one feature of waste. Of these, 221 (73%) were published in a peer-reviewed journal and 219 were accessible for full-text review. Only 73/131 (56%) RCTs with a pharmacological intervention and 24/88 (27%) with a non-pharmacological intervention were adequately reported, and 159/219 (73%) demonstrated an avoidable design weakness. Multi-centre (OR: 0.31; 95% CI: 0.11 to 0.88) and externally funded (OR: 0.35; 95% CI: 0.15 to 0.82) RCTs were less associated with research waste

Conclusions: This study identified a considerable burden of research waste in surgical RCTs. Future improvement initiatives should target single-centre, less supported RCTs.

Introduction

Each year, approximately USD 100 billion is invested in health research worldwide. It is estimated that 85% of this research is wasted; this leads to misused resources and unjustified risks being applied to study participants.[1] Reducing the burden of research waste is an urgent priority. In 2014, a Lancet series documented the most pressing issues relating to the design, regulation, and accessibility of health research, leading to 17 recommendations for increasing its value.[2-6] These have informed a number of campaigns to tackle waste, such as the National Institute of Health Research Adding Value in Research Framework and the Reward Alliance.[7,8]

Research waste may occur at any stage of the research cycle. Firstly, research may be wasted through avoidable design weaknesses, such as poor execution of randomisation or blinding procedures in randomised controlled trials (RCTs).[2] These weaknesses may also arise through a failure to systematically consider the context of previous work. Next, research may be wasted if it remains unpublished and therefore hidden from relevant stakeholders. This leads to unnecessary duplication and an increased risk of harm to future participants.[3] Finally, research that is published may be wasted through poor reporting. This leads to research reports that are difficult or impossible to use and replicate.[4]

Surgical research is associated with a number of methodological and practical challenges. These relate to the assessment of complex interventions, the absence of clinical equipoise, and the lack of standardised study interventions. Few of these are unique to surgery but the evaluation of surgical research is demanding because many of these challenges coincide simultaneously.[9] The importance of minimising waste in this setting is therefore paramount to ensure appropriate, safe, and efficient translation

of new treatments into surgical practice. This study was conceptualised to assess the burden of research waste in surgery and to explore targets for improvement specific to surgical RCTs.

Methods

Ethics & Governance

As a cross-sectional review of registered RCTs, research ethics approval was not required. The results are reported with consideration of the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) checklist.[10]

Aims & Objectives

The aim of this study was to quantify research waste in RCTs involving patients undergoing a surgical procedure. The following sources of research waste were considered:

1. Non-publication[2] – trials should be published somewhere that is accessible to the end-user, most commonly in a peer-reviewed journal.
2. Inadequate reporting[3] – trials should be reported clearly and completely, including what was done and what the findings mean.
3. Correctable design weaknesses[4] – trials should be free from avoidable bias. In addition, they should consider previous evidence, and the need for further research

Definitions

The ClinicalTrials.gov database identifies trials according to recruitment status. This study focused on trials with a “completed” status, defined as a clinical study that has ended normally with participants no longer being examined.[11] A surgical RCT was defined as any randomised study involving patients undergoing surgery irrespective of the primary intervention. Radiological procedures performed without additional surgical interventions were not considered to be within the definition of a surgical trial.

Data Sources

ClinicalTrials.gov is a publicly-available online trial registry. It is the most comprehensive database of completed and ongoing trials worldwide and is maintained by the United States National Library of Medicine. Data are provided by study investigators and sponsors according to a minimum set of mandatory data elements. Records are identified by a unique identifier (NCT Number) and include information about recruitment status, study intervention, funding source, and other key elements which are audited by ClinicalTrials.gov review staff.[12]

Search Strategy

The ClinicalTrials.gov database was queried on a single day (10th June 2017) using the keyword “surgery”. Titles and trial summaries were initially screened to exclude observational studies, followed by further detailed inspection to determine final eligibility. Two independent investigators (MA, SC) performed the assessments and resolved discrepancies through consensus.

Study Eligibility Criteria

Eligible studies were phase III or IV, interventional RCTs involving adults undergoing surgery. These were further limited to RCTs registered on the ClinicalTrials.gov database between 1st January 2011 and 31st December 2012 with a final completion date no later than 31st December 2014. This period was chosen to allow sufficient time for manuscript preparation and submission, peer-review, and editorial processes prior to the search for published manuscripts. Phase I and II trials were excluded as their main objective is to demonstrate preliminary evidence of efficacy and safety, and publication may not be routinely planned. Paediatric trials and were excluded as these are associated with unique methodological challenges which require dedicated review.

Publication Search

Manual searches of PubMed and Scopus were performed using the last name of the principle investigator and relevant keywords. Manuscripts were identified by crosschecking the study intervention, recruitment setting, and dates of recruitment with information contained on the registry. If no manuscript was identified, the corresponding author was contacted for clarification. In cases of no response, the RCT was considered unpublished by default. All searches were performed by two independent investigators (MA and SC), with the last search being performed on 1st November 2018 (shortest time from study completion to final search: 47 months) and with disagreements resolved through consensus. A trial was considered to be published if a full-text manuscript (available in print and/or online) was identified in a peer-reviewed journal.

Reporting Assessment

Completeness of reporting was assessed according to the CONSORT Statement.[13] Manuscripts were first masked (concealment of editorial artwork and descriptors) to minimise journal and author recognition biases. This was done by a single investigator (MA) using Portable Document Format masking software (PDFescape, Red Software, Ca). Next, two independent investigators (SC and CD) assessed manuscripts using the CONSORT 2010 Checklist, with discrepancies resolved through consensus. A score out of 37 items was assigned to each manuscript, with conditional/non-applicable items receiving a positive score by default. RCTs involving a non-pharmacological treatment (such as a surgical device or procedure) were scored according to three additional criteria relating to the description of non-pharmacological interventions, producing a score out of 40 items (Suppl. Table 1).[14] Manuscripts were

considered to be adequately reported if at least 75% of items (28/37 and 30/40 respectively) were satisfied. This was set retrospectively according to the median reporting compliance, but was a pre-planned approach.

Design Weakness

All masked RCTs were evaluated using the Cochrane Tool for Assessing Risk of Bias.[15] This assesses bias according to key domains, including selection, detection, attrition, and reporting bias, which are assessed within the specific context of the study. All manuscripts were assessed by independent investigators (SC and CD) with discrepancies resolved through consensus. Items with an "unclear" risk of bias were considered together with "high" risk items in the statistical analyses. This is because unclear descriptions of key methods preclude informed judgements on the study's ability to inform practice. The presence of a relevant systematic review, or justification as to why one was not necessary in novel settings, was also assessed. This had to be cited in the full-text manuscript and be considered capable of informing the final study design. The presence of bias and/or the absence of a systematic review were considered to represent an avoidable design weakness.

Study Outcomes & Analysis

The primary outcome was the presence of at least one source of research waste (non-publication, inadequate reporting, or design weakness). The secondary outcomes were the relative incidence of each source. The χ^2 test was used to compare differences in key study variables (intervention type, randomised design, number of arms, blinding, recruitment setting (national or international), number of centres (single or multi-centre), sample size (<100 or ≥100) and funding status (industry, other external, or none/departmental). Adjusted binary logistic regression was used to test

the effect of these variables on the primary outcome. The variables were prospectively chosen and entered into the analysis irrespective of significance at the univariate level. This produced an odds ratio (OR) and 95% confidence interval (CI), such that values greater than 1.0 indicated a greater likelihood of research waste. Statistical tests were considered to be significant at the level of $P<0.05$. All analyses were performed using SPSS (version 21.0., IBM Corp., New York, USA).

Results

Study Characteristics

The search of ClinicalTrials.gov identified 5617 studies, of which 304 met all of the eligibility criteria (Figure 1). The most common surgical specialties were trauma and orthopaedics (75/304; 25%), general surgery (63/304; 21%), and cardiothoracics (47/304; 15%). The majority of RCTs examined a drug intervention (178/304; 59%) or a surgical procedure (65/304; 21%) and most recruited from a single centre (239/304; 79%). Industry had a role in supporting 85/304 (28%) of RCTs (Table 2).

Non-publication

Overall, 221 (73%) registered RCTs were published in a peer-reviewed journal with a median time to publication of 24 months (interquartile range: 15.5-35.5 months). Of these, 133 (60%) included a pharmacological intervention and 88 (40%) included a non-pharmacological intervention. Unpublished RCTs were more likely to have smaller populations (<100 participants) (65% versus 54%; P=0.046) and less likely to be in receipt of non-commercial external funding (13% versus 20%; P<0.001) compared to published RCTs. There were no significant differences in any other design variable between published and unpublished RCTs (Table 2).

Adequacy of reporting

A total of 219 out of 221 published RCTs were accessible for full-text review. Of 131 RCTs with a pharmacological intervention, 73 (56%) were reported adequately. These were more likely to include a double-blinded design (80% versus 62%; P=0.026), to recruit from multiple centres (29% versus 10%; P=0.010), to include larger study populations (≥100 participants) (56% versus 35%; P=0.013), and to be in receipt of

non-commercial external funding (32% versus 12%; P=0.014) than RCTs reported inadequately (Suppl. Table 2a). The most notable deficits in reporting were descriptions of trial design (present in 32% of RCTs), random allocation sequence (38%), and availability of the full study protocol (8%) (Suppl. Table 1). Of 88 RCTs with a non-pharmacological intervention, 24 (27%) were reported adequately. As with pharmacological RCTs, these tended to have a double-blinded design, to recruit from multiple centres, and to include larger populations, but none of these trends reached statistical significance (Suppl. Table 2b). The most notable deficits were descriptions of trial design (present in 19% of RCTs), evaluation of adherence with the treatment protocol (0%), and availability/access to the full study protocol (3%) (Suppl. Table 1).

Design Weakness

Of 219 RCTs available for full-text review, 104 (47%) did not cite a relevant systematic review and 117 (53%) had at least one feature indicating high/unclear risk of bias; the most common reasons for high risk were assessor blinding (15%) and selective reporting (13%) (Figure 2). When both of these factors were considered together, 159 (73%) RCTs were found to have an avoidable design weakness. These were more likely to include a surgical device intervention (21% versus 3%; P=0.002), to include simple two-arm designs (92% versus 75%; P=0.001), and to have an open-label format (26% versus 8%; P<0.001) (Suppl. Table 3).

Predictors of Research Waste

When publication status, adequacy of reporting, and presence of design weaknesses were considered compositely, 259 out of 304 RCTs (85%) demonstrated features of research waste. Within a multiple regression model, RCTs with a double-blinded design (OR: 0.13; 95% CI: 0.03 to 0.50), recruiting across multiple sites (OR: 0.31;

95% CI: 0.11 to 0.88), and in receipt of non-commercial external funding (OR: 0.35; 95% CI: 0.15 to 0.82) were less likely to exhibit features of research waste (Table 3). RCTs with a drug intervention and RCTs with multi-arm designs predicted the absence of waste on univariable analysis, but these trends were lost in the multi-variable model. The support of industry did not impact on the risk of research waste (OR: 1.68; 95% CI: 0.54 to 5.21).

Discussion

This study identified a considerable burden of research waste in surgical RCTs, with 85% demonstrating at least one feature of waste. Promisingly, three quarters of RCTs were published in a peer-reviewed journal, but fewer than half were designed or reported adequately. RCTs recruiting from multiple sites and in receipt of external funding were less associated with waste, but these were a minority. This suggests that single-centre and less supported RCTs may be targets for reducing research waste.

Once described as “comic opera”, the quality of surgical RCTs in the United Kingdom has seen a step-improvement due to initiatives such as the Royal College of Surgeons (RCS) Surgical Trials Initiative, trainee-led surgical research collaboratives, the IDEAL framework for surgical innovation, and strong links with patient advisory groups.[19-25] The historic inclusion of RCTs in this study precedes some of these initiatives, but the results clearly suggest the need for efficient, collaborative, and well-supported study designs going forwards. Single-centre and less supported RCTs were most at risk of waste relative to those recruiting across multiple centres and in receipt of external funding. These attributes alone should not be synonymous with waste, since small, appropriately-powered, and locally-supported RCTs can be a source of efficiency. However, if these design features arise through insufficient resources, mechanisms to encourage collaboration and reduce duplication are required. Currently, this may be achieved through involvement of an accredited clinical trials research unit or local support infrastructure, which provide essential logistical and methodological support.

The burden of research waste has been estimated previously for a broad scope of healthcare research.[1] Individual considerations of waste in surgical research, such as non-publication and reporting quality, have also been reported.[17,18] This study

permitted a granular assessment of waste by assessing its constituent components and using this to explore opportunities for improvement. Masked assessment of RCTs was a strength as it reduced bias related to the recognition of specific journals and authors. The definition of a surgical RCT was pragmatic and included trials of peri-operative interventions, providing that these were applied to patients undergoing surgery. This is considered a source of generalisability since these RCTs share some common methodological challenges. The inclusion of RCTs was historic (2011-2012) and is considered to be a permissible weakness. This was necessary to provide an assessment of publication, which may take several years after follow up and completion of study procedures. Whilst it is possible that the burden of waste has improved or progressed in the meantime, the results of this study are considered to offer the most current insight into the issue.

Quantifying research waste is a complex and imperfect exercise, and limitations must be recognised. Firstly, this study considered waste from three successive stages of the research cycle, identified from a Lancet series of expert viewpoints.[2-4] These are by no means exhaustive, since waste may also arise through pursuits of low-priority research questions or publication in exclusively closed access journals. Secondly, the RCTs included in this study represent a sample; although ClinicalTrials.gov is a comprehensive registry of trials, the World Health Organisation endorses several other country-specific registries which were not considered.[12] In addition, previous evidence suggests that only 83% of surgical trials are registered on a trial registry, and some studies may surpass their anticipated completion date.[26] It is therefore possible that some trials remain excluded from the scope of this study. Thirdly, although this study systematically assessed publication status, reporting, and design, these assessments are not entirely decisive. Peer-reviewed publication, for example, is not the only format

by which research is disseminated, although other formats are limited by unstandardised reporting.[16] The assessments also focused exclusively on randomised designs, meaning that the conclusions drawn by this study cannot be extrapolated to the body of non-randomised surgical research.

This study was unable to explore the reasons or mechanisms as to why single-centre RCTs are more associated with waste than larger, multicentre studies. This may be explained through barriers to accessing infrastructure support in the planning and/or management of surgical RCTs. It is possible that recent efforts, such as the RCS Surgical Trials initiative and the IDEAL framework, are actively addressing these issues, and the results of this study may represent a baseline for exploring their impact. Dedicated efforts, however, may be required to support local study teams who initiate trials without essential support. The solution should not discourage single-centre studies, since these are a source of efficiency and a platform for earlier phase research. Instead, quality improvement initiatives that aim to expand the availability of essential support (such as statistics and trial management) should be considered. These should be informed by an appropriate needs assessment.

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Table 1 – Surgical specialty of 304 included randomised controlled trials

Surgical Speciality*	Number of trials (n=304)	%
Trauma and orthopaedics	75	25%
General surgery	63	21%
Cardiothoracic	47	15%
Gynaecology	28	9%
Urology	17	6%
Ophthalmic surgery	16	5%
Breast and endocrine	13	4%
Neurosurgery	7	2%
Oral and Maxillofacial	6	2%
Otolaryngology	6	2%
Vascular	4	1%
Plastics	2	1%
Other	20	7%

Table 2 – Characteristics of RCTs according to publication status.

		Published (n=221)	Not published (n=83)	Total (n=304)	p-value
Intervention	Drug	133 (60%)	45 (54%)	178 (59%)	0.161
	Medical Device	36 (16%)	9 (11%)	45 (15%)	
	Procedural	43 (20%)	22 (27%)	65 (21%)	
	Other*	9 (4%)	7 (8%)	16 (5%)	
Study design	Parallel-group	218 (99%)	81 (98%)	299 (98%)	0.748
	Crossover	2 (1%)	1 (1%)	3 (1%)	
	Factorial	1 (<1%)	1 (1%)	2 (1%)	
Number of arms	2	193 (87%)	73 (88%)	266 (88%)	0.724
	3	22 (10%)	9 (11%)	31 (10%)	
	≥4	6 (3%)	1 (1%)	7 (2%)	
Blinding	None/Open-label	46 (21%)	26 (31%)	72 (24%)	0.110
	Single**	57 (26%)	15 (18%)	72 (24%)	
	Double	118 (53%)	42 (51%)	160 (53%)	
Recruitment	National	212 (96%)	79 (95%)	291 (96%)	0.259
	International	9 (4%)	3 (4%)	12 (4%)	
	Missing	0 (0%)	1 (1%)	1 (<1%)	
No. of centres	Single-centre	170 (77%)	69 (83%)	239 (79%)	0.104
	Multi-centre	51 (23%)	13 (16%)	64 (21%)	
	Missing	0 (0%)	1 (1%)	1 (<1%)	
No. Participants	<100	119 (54%)	54 (65%)	173 (57%)	0.046
	≥100	102 (46%)	28 (34%)	130 (43%)	
	Missing	0 (0%)	1 (1%)	1 (<1%)	
Funding	Industry	65 (29%)	20 (24%)	85 (28%)	<0.001
	Other External	44 (20%)	11 (13%)	55 (18%)	
	None/departmental	88 (40%)	52 (63%)	140 (46%)	
	Missing	24 (11%)	0 (0%)	24 (8%)	

* relates to a primary intervention which does not include a drug, medical device, or procedure
** relates to investigator, assessor, or patient blinding

Table 3 – Adjusted logistic regression for the effect of key study characteristics on presence of research waste

		Univariable Odds Ratio (95% CI)	p-value	Multi-variable Odds Ratio (95% CI)	p-value
Intervention	Procedural	Reference	-	Reference	
	Drug	0.35 (0.13 to 0.93)	0.036	0.72 (0.24 to 2.19)	0.559
	Medical Device	1.79 (0.33 to 9.67)	0.498	1.56 (0.26 to 9.46)	0.631
	Other*	1.25 (0.14 to 11.51)	0.844	0.93 (0.08 to 10.74)	0.985
Number of arms	Two arms	Reference	-	Reference	
	Multi-arm	0.33 (0.15 to 0.72)	0.006	0.46 (0.18 to 1.16)	0.098
Blinding	None	Reference	-	Reference	
	Single**	1.00 (0.20 to 5.13)	0.999	0.76 (0.13 to 4.32)	0.758
	Double	0.15 (0.04 to 0.50)	0.002	0.13 (0.03 to 0.50)	0.003
Recruitment	National	Reference	-	Reference	
	International	1.82 (0.23 to 14.46)	0.572	2.00 (0.18 to 22.12)	0.572
No. of centres	Single-centre	Reference	-	Reference	
	Multi-centre	0.55 (0.27 to 1.13)	0.102	0.31 (0.11 to 0.88)	0.028
No. Participants	<100	Reference	-	Reference	
	≥100	0.59 (0.31 to 1.13)	0.111	0.67 (0.30 to 1.50)	0.327
Funding	None/departmental	Reference	-	Reference	
	Industry	1.11 (0.47 to 2.63)	0.725	1.68 (0.54 to 5.21)	0.367
	Other external	0.32 (0.15 to 0.70)	0.004	0.35 (0.15 to 0.82)	0.016

After removal of cases with at least one missing variable, the analysis was performed on 288/304 cases.

* relates to a primary intervention which does not include a drug, medical device, or procedure
** relates to investigator, assessor, or patient blinding

Suppl. Table 1 – Compliance to items of the CONSORT 2010 Checklist

CONSORT Item		Pharmacological	NPI
1a	Identification as a randomised trial in the title	99/131 (76%)	69/88 (78%)
1b	Structured summary of trial design, methods, results, and conclusions	120/131 (92%)	78/88 (89%)
2a	Scientific background and explanation of rationale	126/131 (96%)	83/88 (94%)
2b	Specific objectives or hypotheses	121/131 (92%)	74/88 (84%)
3a	Description of trial design (such as parallel, factorial) including allocation ratio	42/131 (32%)	17/88 (19%)
3b*	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	-	-
4a	Eligibility criteria for participants	128/131 (98%)	77/88 (88%)
4b	Settings and locations where the data were collected	80/131 (61%)	48/88 (55%)
5	The interventions for each group with sufficient details to allow replication	121/131 (92%)	81/88 (92%)
5A**	Description of the components of the interventions and, if applicable, the procedure for individualizing treatment	N/A	69/88 (78%)
5B**	Details of how the interventions were standardized	N/A	43/88 (49%)
5C**	Details of how the adherence of care provers with the protocol was assessed or enhanced	N/A	(0/88) 0%
6a	Completely defined pre-specified primary and secondary outcome measures	96/131 (73%)	64/88 (73%)
6b*	Any changes to trial outcomes after the trial commenced, with reasons	-	-
7a	How sample size was determined	121/131 (92%)	74/88 (84%)
7b*	When applicable, explanation of any interim analyses and stopping guidelines	-	-
8a	Method used to generate the random allocation sequence	107/131 (82%)	58/88 (66%)
8b	Type of randomisation; details of any restriction (such as blocking and block size)	58/131 (44%)	26/88 (30%)
9	Mechanism used to implement the random allocation sequence	98/131 (75%)	51/88 (58%)
10	Who generated the random allocation sequence, enrolled participants, and assigned participants to interventions	50/131 (38%)	22/88 (25%)
11a	If done, who was blinded after assignment to interventions and how	125/131 (95%)	65/88 (74%)
11b*	If relevant, description of the similarity of interventions	-	-
12a	Statistical methods used to compare groups for primary and secondary outcomes	118/131 (90%)	80/88 (91%)
12b*	Methods for additional analyses, such as subgroup analyses and adjusted analyses	-	-
13a	The numbers of participants who were randomised, received treatment, and analysed for the primary outcome	112/131 (85%)	74/88 (84%)
13b	For each group, losses and exclusions after randomisation, together with reasons	120/131 (92%)	73/88 (83%)
14a	Dates defining the periods of recruitment and follow-up	89/131 (68%)	58/88 (66%)
14b*	Why the trial ended or was stopped	-	-
15	A table showing baseline demographic and clinical characteristics for each group	127/131 (97%)	78/88 (89%)
16	For each group, number of participants analysed and whether the analysis was by original assigned groups	113/131 (86%)	65/88 (74%)
17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision	54/131 (41%)	33/88 (38%)
17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	53/131 (40%)	24/88 (27%)
18*	Results of any other analyses performed, including subgroup analyses and adjusted analyses	-	-
19	All important harms or unintended effects in each group	103/131 (79%)	69/88 (78%)
20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	109/131 (83%)	63/88 (72%)
21	Generalisability (external validity, applicability) of the trial findings	73/131 (56%)	39/88 (44%)
22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	117/131 (89%)	76/88 (86%)
23	Registration number and name of trial registry	112/131 (85%)	72/88 (82%)
24	Where the full trial protocol can be accessed, if available	10/131 (8%)	3/88 (3%)
25	Sources of funding and other support (such as supply of drugs), role of funders	102/131 (78%)	63/88 (72%)

* indicates a conditional item for which not all manuscripts were scored; ** items relate to non-pharmacological (NPI) RCTs only

Suppl. Table 2a – Characteristics of RCTs with a pharmacological intervention according to reporting adequacy.

		Adequate reporting (n=73)	Inadequate reporting (n=58)	Total (n=131) **	p-value
Study design	Parallel-group	73 (100%)	57 (98%)	130 (99%)	0.260
	Crossover	0 (0%)	0 (0%)	0 (0%)	
	Factorial	0 (0%)	1 (2%)	1 (1%)	
Number of arms	2	58 (79%)	49 (85%)	107 (82%)	0.514
	3	11 (15%)	8 (14%)	19 (15%)	
	≥4	4 (5%)	1 (2%)	5 (4%)	
Blinding	None/Open-label	8 (11%)	6 (10%)	14 (11%)	0.026
	Single*	7 (10%)	16 (28%)	23 (18%)	
	Double	58 80%)	36 (62%)	94 (72%)	
Recruitment	National	69 (95%)	58 (100%)	127 (97%)	0.070
	International	4 (6%)	0 (0%)	4 (3%)	
No. of centres	Single-centre	52 (71%)	52 (90%)	104 (79%)	0.010
	Multi-centre	21 (29%)	6 (10%)	27 (21%)	
No. Participants	<100	32 (44%)	38 (66%)	70 (53%)	0.013
	≥100	41 (56%)	20 (35%)	61 (47%)	
Funding	Industry	20 (27%)	14 (24%)	34 (26%)	0.014
	Other External	23 (32%)	7 (12%)	30 (23%)	
	None/departmental	26 (36%)	27 (47%)	53 (40%)	
	Missing	4 (5%)	10 (17%)	14 (11%)	

Well reported RCTs are defined according to a cutoff of ≥75% compliance with the CONSORT 2010 checklist (≥27/37 items), as per the Methods

* relates to investigator, assessor, or patient blinding
** assessment of full texts was possible on 131/133 of publications

Suppl. Table 2b – Characteristics of RCTs with a non-pharmacological intervention according to reporting adequacy.

		Adequate reporting (n=24)	Inadequate reporting (n=64)	Total (n=88)	p-value
Study design	Parallel-group	24 (100%)	62 (97%)	86 (98%)	0.381
	Crossover	0 (0%)	2 (3%)	2 (2%)	
	Factorial	0 (0%)	0 (0%)	0 (0%)	
Number of arms	2	22 (92%)	62 (97%)	84 (96%)	0.250
	3	1 (4%)	2 (3%)	3 (3%)	
	≥4	1 (4%)	0 (0%)	1 (1%)	
Blinding	None/Open-label	6 (25%)	26 (41%)	32 (36%)	0.197
	Single*	9 (38%)	25 (39%)	34 (39%)	
	Double	9 (38%)	13 (20%)	22 (25%)	
Recruitment	National	21 (88%)	62 (97%)	83 (94%)	0.091
	International	3 (13%)	2 (3%)	5 (6%)	
No. of centres	Single-centre	14 (58%)	50 (78%)	64 (73%)	0.063
	Multi-centre	10 (42%)	14 (22%)	24 (27%)	
No. Participants	<100	10 (42%)	37 (58)	47 (53%)	0.176
	≥100	14 (58%)	27 (42%)	41 (47%)	
Funding	Industry	11 (46%)	20 (31%)	31 (35%)	0.362
	Other External	5 (21%)	9 (14%)	14 (16%)	
	None/departmental	6 (25%)	27 (42%)	33 (38%)	
	Missing	2 (8%)	8 (13%)	10 (11%)	

Well reported RCTs are defined according to a cutoff of ≥75% compliance with a modified CONSORT 2010 checklist (≥30/40 items), as per the Methods

* relates to investigator, assessor, or patient blinding

Suppl. Table 3 – Characteristics of RCTs according to the presence of avoidable design weaknesses.

		Absence of design weakness (n=60)	Presence of design weakness (n=159)	Total (n=219) ***	p-value
Intervention	Drug	47 (78%)	84 (53%)	131 (60%)	0.002
	Medical Device	2 (3%)	34 (21%)	36 (16%)	
	Procedural	10 (17%)	33 (21%)	43 (20%)	
	Other*	1 (2%)	8 (5%)	9 (4%)	
Study design	Parallel-group	59 (98%)	157 (99%)	216 (99%)	0.182
	Crossover	0 (0%)	2 (1%)	2 (1%)	
	Factorial	1 (2%)	0 (0%)	1 (<1%)	
Number of arms	2	45 (75%)	146 (92%)	191 (87%)	0.001
	3	10 (17%)	12 (8%)	22 (10%)	
	≥4	5 (8%)	1 (1%)	6 (3%)	
Blinding	None	5 (8%)	41 (26%)	46 (21%)	<0.001
	Single**	8 (13%)	49 (31%)	57 (26%)	
	Double	47 (78%)	69 (43%)	116 (53%)	
Recruitment	National	59 (98%)	151 (95%)	210 (96%)	0.263
	International	1 (2%)	8 (5%)	9 (4%)	
No. of centres	Single-centre	45 (75%)	123 (77%)	168 (77%)	0.713
	Multi-centre	15 (25%)	36 (23%)	51 (23%)	
No. Participants	<100	31 (52%)	86 (54%)	117 (53%)	0.749
	≥100	29 (48%)	73 (46%)	102 (47%)	
Funding	Industry	14 (23%)	51 (32%)	65 (30%)	0.047
	Other External	18 (30%)	26 (17%)	44 (20%)	
	None/departmental	25 (42%)	61 (38%)	86 (39%)	
	Missing	3 (5%)	21 (13%)	24 (11%)	

Design weaknesses include trials with high risk of bias (according to the Cochrane Tool for Assessing Risk of Bias tool) and/or absence of a cited systemic review that is relevant to the trial aim, as per the Methods.

* relates to a primary intervention which does not include a drug, medical device, or procedure
** relates to investigator, assessor, or patient blinding
*** assessment of full texts was possible on 219/221 of publications.

Figure 1 – Flow chart of inclusion and exclusion

Secondary reports relate to manuscripts reporting a secondary analysis after publication of the main results. Multiple trial reports relate to manuscripts reporting the results of more than one trial concurrently.

Figure 2 – Cochrane Tool for Assessing Risk of Bias Assessment

Individual components of the Cochrane Tool for Assessing Risk of Bias Assessment are shown. Items *with an "unclear" risk of bias were considered together with "high" risk items in the analyses*, as per the Methods