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TITLE PAGE

Title: Is registration status associated with reported outcomes in physiotherapy randomised controlled trials? Analysis of 323 trials published in 2017.

Concise Title: Physiotherapy RCT registration and outcomes

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ABSTRACT

Background: Clinical trial registration is proposed to mitigate selective reporting in scientific research. It remains unknown whether trial registration is associated with reported outcomes in physiotherapy trials.

Aims: To analyse the association between trial registration status and reported outcomes for physiotherapy RCTs.

Methods: All RCTs reporting a physiotherapy intervention, published in PubMed between 1st January 2017 and 30th June 2017, were included. Trial registration was determined based on the reporting of a registration number in the primary paper or by identifying trials through trial registry databases.

Findings: Of the 291 trials analysed, 176 (61%) were registered; 115 (40%) were not. There was no significant association between trial registration and outcome on multivariate analyses (OR: 1.65; 95% CI: 0.92 to 2.96; p=0.09). Only 22% of trials were prospectively registered.

Conclusions: Registration status and trial outcome are not associated in physiotherapy RCTs. The frequency of registration of physiotherapy trials remains low.

Keywords: Clinical trial; reporting; rehabilitation; outcomes; trial methodology

DECLARATIONS

Funding: No funding was receive to support this study.

Ethical Approvals: Ethical approval was not required to conduct this analysis.

Conflict of interest: No author declares a conflict of interest in relation to this work.

KEY POINTS

1. Trial registration is inconsistently undertaken in physiotherapy randomised controlled trials.
2. Outcome of trials reported does not appear to be related to them being registered or not.
3. There was no significant association between reported outcome and timing of registration (prospective versus retrospective).
4. Further support is required to increase trial registration in physiotherapy research to improve reporting rigor.

INTRODUCTION

Clinical trials constitute the most robust source of research to underpin evidence-based practice in healthcare (Howick et al. 2009). Despite the advantages conferred by appropriate randomised controlled trial (RCT) designs for minimising bias in individual studies, the value of this evidence to clinical practice can be undermined by other sources of bias. These include selective trial reporting, which may arise from researchers not submitting their work for peer-review or publishers not accepting a research report (De Angelis et al. 2004; Costa et al. 2013).

To address this issue of selective outcome reporting, the International Committee of Medical Journal Editors (ICMJE) mandated prospective trial registration as a prerequisite for publishing clinical trial reports (De Angelis et al. 2004). This initiative was followed by a similar recommendation from the International Society of Physiotherapy Journal Editors (ISPJE) in 2013 (Costa et al. 2013). The Food and Drug Administration Amendments Act of 2007 (FDAAA) even places a legal obligation on sponsors and investigators to register certain clinical trials of FDA-regulated biologics, drugs and devices prospectively on ClinicalTrials.gov (Zarin et al. 2016).

Trial registration offers transparency to other researchers and the public (to avoid duplicating research efforts, highlight opportunities for further research and permit quality improvement), exists as a record to hold investigators accountable to their original research aims, and eventually captures data – regardless of their impact – on outcomes that might otherwise go unreported.

Despite the implementation of large-scale projects to reduce reporting bias, cross-sectional investigations of published RCTs have revealed incomplete uptake and mixed approaches to trial registration since the release of the ICMJE statement in 2004 (Costa et al. 2013). Babu et al. (2014) reported that only 29% of English articles reported trial registration in MEDLINE-indexed ISPJE journals. More recently, an investigation of trials dual-registered on the websites ClinicalTrials.gov

and EU Clinical Trials Register (EUCTR) also identified discrepancies in the completion statuses of 16% of 10,492 trials (Fleminger and Goldacre 2018).

Epidemiological studies have previously assessed the association between trial registration status and outcome (the rejection or acceptance of a primary null hypothesis) without an overarching consensus (Rasmussen et al. 2009; Emdin et al. 2015; Dechartres et al. 2016; Odutayo et al. 2017). If the results of a trial are found to be independently associated with its registration status, this may constitute another variable that stakeholders in healthcare and publishing need to consider when appraising RCTs.

Physiotherapy practice has become increasingly evidence-based (Kerry 2017) with the assistance of improved RCT quality/quantity (Kelly et al. 2018), and the discipline is considered an important and cost-effective component of the national health infrastructure of many countries, including the NHS in the United Kingdom (NHS England 2019). Modern physiotherapy's perceived utility – from the perspectives of commissioners, practitioners and the public – is therefore guided by the scientific method and susceptible to biases in reporting.

No study has evaluated whether trial registration status (an item of best practice in reporting) and trial outcome (the indicator of physiotherapy's utility) – two notionally independent variables – are linked in physiotherapy research. Therefore, this study aimed to determine the nature of this relationship in a large sample of recently published physiotherapy RCTs, while simultaneously providing demographic data on recent registration practice in this field. Based on the existing trends in the literature, we hypothesised that trials registered on a publicly available database would be less likely to report a positive primary outcome than trials that are unregistered.

METHODS

Trial identification

A literature search for RCTs where physiotherapy was a trial intervention (control or experimental) was conducted using the PubMed database on 18th November 2017. PubMed was selected because it ranks amongst the most comprehensive databases for physiotherapy research (Michaleff et al. 2011). All eligible trials published between 1st January 2017 and 30th June 2017 were included. The search terms are presented in **Supplementary File 1**.

Trials were included if they reported an RCT (including feasibility/pilot RCTs) pertinent to physiotherapy practice in human subjects. Trials were excluded if any of the following applied: were secondary analyses of an RCT; non-RCT design; no control group; the topic was deemed not to be directly relevant to physiotherapy; the full-text was unavailable in English; viewpoint, protocol, outcome validation or qualitative report; or the paper was a follow-up to multiple RCTs with potentially differing original registration characteristics.

All search strategy titles and abstracts were independently reviewed against the eligibility criteria by two reviewers (CE-B, HK). Citations deemed potentially eligible were independently assessed in full-text papers by the same reviewers to determine final inclusion. Any disagreement was adjudicated by a third reviewer (TS).

Data extraction

Data were extracted from each included trial independently by two reviewers (CE-B, HK) with disagreements resolved through adjudication by a third reviewer (TS). For follow-up RCTs that did

not contain, but rather cited, full details of the methods used, the referenced article was consulted to extract appropriate trial characteristics.

a. Trial characteristics

The following data were extracted: research funding (industry-funded, non-industry-funded or having unknown funding sources); the type (clinical, university, residential, other, multiple types or unclear) and number (single-centre, multicentre, or unknown number) of study centres; country and continent of origin; sample size; reporting of an *a priori* sample size calculation; reporting of random sequence generation and allocation concealment based on the Cochrane Collaboration's Risk of Bias criteria (Higgins and Green 2011); blinding (single-blind, double-blind, no blinding, unclear blinding); reporting of participant numbers/attrition at trial end (with reasons for any dropouts; without reasons; not reported); journal name; trial registration status and reported outcomes.

b. Registration status

Registration status was ascertained from the trial registry record for each trial. Where the trial registration number was specified, the record was accessed and the presented trial dates and topic were cross-referenced with the published paper. Where no trial registration number was specified, the international trial registries EUCTR, the World Health Organisation International Clinical Trials Registry Platform (WHO ICTRP), ClinicalTrials.gov, and the International Standard Randomised Controlled Trial Number (ISRCTN) were searched using the surname of the first author and keywords for the article topic. This approach has been previously recommended (Glanville et al. 2014; Odutayo et al. 2017). If the study could not be found in a trial registry, it was classified as unregistered.

A trial was classified as prospectively registered when the listed registration date preceded or was no more than one month later than the date of first participant enrolment. When registered later than this point, it was classified as retrospectively registered.

c. Trial outcome

A significant outcome was attributed when the primary outcome was reported as statistically significant ($p<0.05$) and/or an effect estimate with a confidence interval (CI) that excluded the value of no effect, for the intervention group relative to at least one control group. If the null hypothesis could not be rejected, the trial was attributed as having a null outcome. For non-inferiority trials, the rejection of the null hypothesis entailed no statistical difference between the two assessed treatments (Mallat 2017). Where the results included per-protocol and intention-to-treat analyses, rejection of the null hypothesis by either analysis led to classification of the trial as significant. Where a primary outcome was not explicitly defined, the outcome discussed most prominently was considered the primary outcome.

Quality assurance

Quality assurance assessments were conducted for a random selection of approximately 10% (n=22) of the trial data extraction forms. This reported a reliability of 91%. Consistent discrepancies in data extraction were discussed and concordance established between the two reviewers (CE-B, HK) prior to continuing the remaining data extraction.

Data analysis

A power calculation was used to determine the sample size based on a significance level (alpha) of 5% and power (1-β) of 90%, where the percentage of registered studies was 61% and unregistered was 39%. This indicated that a minimum of 208 studies would be required.

Univariate analyses were performed for all study variables with trial outcome as the response variable. Discrete and continuous variables were analysed using a chi-squared test and ANOVA, respectively. Significance was set at $p<0.10$ for the univariate analyses to detect factors that correlate with trial outcome (for use in the multivariate analysis) with greater sensitivity.

Logistic regression was adopted with the independent variables comprising those determined to be significant in the univariate analysis and with trial outcome remaining the response (dependent) variable. Regression analyses were presented as odds ratios and 95% confidence intervals (CIs). A $p<0.05$ was deemed statistically significant.

Exploratory univariate (chi-squared) analyses of the association between trial outcome and registration status were also performed with registration status stratified alternatively. The first exploratory analysis excluded unregistered trials, comparing prospectively registered trials with retrospectively registered trials. The second exploratory analysis grouped retrospectively registered and unregistered trials and compared these with prospectively registered trials.

All analyses were conducted on IBM SPSS Statistics version 25.0 (IBM, New York, USA).

RESULTS

Search strategy

The results of the search strategy and number of included trials is illustrated in **Supplementary File 2**. In brief, from 630 potentially eligible titles, 323 met the eligibility criteria and were included.

Characteristics of included trials

The characteristics of the included trials are summarised in **Table 1**. The journals in which they were published are presented in **Supplementary File 3**. In brief, of the 323 trials, 71 trials (22%) were prospectively registered and 122 (38%) were retrospectively registered; 130 trials (40%) being unregistered. The number of trials with a significant outcome was 215 (67%), null outcome was 76 (24%) and unclear outcome was 32 (10%). The frequency of trials by outcome when assessed by country of origin is presented in **Supplementary File 4**.

Association between outcome and registration status

The univariate analysis of associations between trial outcome and the other trial variables of interest revealed significant ($p<0.10$) interactions for registration status ($p=0.03$), funding source ($p=0.03$), country of origin ($p=0.04$), and large sample size ($p=0.10$) (**Table 2**). Specifically, trials were more likely to report a significant outcome if they were unregistered (versus registered), non-industry-funded or lacking in funding details (versus industry-funded) or small ($N<99$) in initial sample size. Although significant, the precise relationship between the country of a study's origin and trial outcome is unclear based on the described analysis alone.

The results for the multivariate analysis of the interaction between these trial characteristics and trial outcome are shown in **Table 3**. No association was detected between trial outcome and the variables tested in the multivariate analysis, including registration status (OR: 1.65; 95% CI: 0.92 to 2.96; $p=0.09$).

Secondary exploratory analyses

There was no association between registration status and reported outcome when trials were grouped as prospectively versus retrospectively registered (p=0.15; **Table 4**) or when grouped unregistered and retrospectively registered trials versus prospectively registered (p=0.69).

DISCUSSION

This study has shown, for the first time, that there is no statistical association between registration status (or any other variable) and trial outcome for physiotherapy RCTs (p=0.09). However, the significant association between registration status and study outcome identified in the primary univariate analysis (p=0.03) described an inverse relationship between trial registration and significant outcome reporting.

The lack of any significant association according to the multivariate analysis (**Table 3**) suggests that trial outcome is not significantly influenced by any single investigated variable, including registration status, in recently published physiotherapy RCTs. Instead, trial registration status, funding source, country of origin and sample size appear (altogether or in part) to collinearly influence trial outcome; the extent of this collinearity has not been specifically confirmed, as it is beyond the scope of this study. The exclusion of an independent association between trial registration and outcome is a significant and encouraging finding for physiotherapy as a discipline, due to its aforementioned role in national healthcare (NHS England 2019) and growing reliance on evidence from trials to inform clinical practice (Scurlock-Evans et al. 2014; Kerry 2017).

Despite the lack of an association through the multivariate analysis, it is clear from the result of the univariate analyses and other statistical observations that reporting practice in physiotherapy

research requires improvement. More than one-third of the included trials were unregistered even at the time of article publication. Prospective registration of only 22% of included papers also suggests that adherence to the specific ICMJE, ISPJE and Declaration of Helsinki recommendations is not widespread (De Angelis et al. 2004; World Medical Association 2008; Costa et al. 2013). This prospective registration figure falls slightly short of that of 31% identified by Harriman and Patel (2016) in a search of all clinical trials published in the BMC series in 2013. Such figures provide further impetus to encourage protocol registration as mandatory for all clinical trials.

Of the registered trials that passed the screening process for this study, 37% were registered prospectively and 63% retrospectively. This contrasts with the findings of Hunter et al. (2018) in their descriptive review of interventional trials registered on Australian New Zealand Clinical Trials Register (ANZCTR). They reported that, since 2012, 64% of registered trials were filed prospectively. This indicates that adherence to prospective trial registration standards among physiotherapy trials falls considerably below that for clinical trials more generally. Such figures provide evidence that further measures to enforce prospective physiotherapy trial registration are required.

According to the univariate analysis, the results of which are shown in **Table 2**, trials appeared more likely to report a positive outcome if they were (1) non-industry-funded or lacking in funding details, (2) small (≤99) in initial sample size, or (3) unregistered; possible reasons for these findings will be discussed briefly. It is probable that other variables (not extracted in this study) would also have shown an association with trial outcome. Future cross-sectional studies might benefit from assessing overall trial quality during the data extraction process using a validated measure, such as the Physiotherapy Evidence Database (PEDro) rating scale, to offer a potentially useful variable to test for an association with trial outcome or registration likelihood (Maher et al. 2003; de Morton 2009).

The association found for non-industry-funded research contrasts interestingly with observations in drug and medical device (Lundh et al. 2017) and "nondrug" (Bhandari et al. 2004) trials that industry-sponsored trials tend to favour the sponsor's product/intervention. It cannot be excluded that this difference is due to the small number of industry-funded studies (and/or poor reporting of funding sources among industry-funded trials) herein leading to a type I error (falsely positive): When articles reporting industry funding and unclear funding are pooled together, the proportion of pooled trials with a positive outcome rises to 68.5% (versus 77.2% for non-industry-funded trials). Additionally, the possibility of not-for-profit organisations with undisclosed for-profit support indirectly or directly influencing trial design/findings should be borne in mind (Hakoum et al. 2017).

Trials with an initial sample size of more than 99 participants were found to be less likely to report a positive outcome (66.2%) than those with fewer (76.2%). Clearly, the appropriate minimum sample size will differ between studies, depending on effect size. However, this finding is consistent with an increase in the likelihood of obtaining a type I error (falsely positive) or type II error (falsely negative – rendering the finding less likely to be published and thus outside the content of interest in this study) if the sample size is smaller rather than larger (Hackshaw 2008). Furthermore, larger studies might have improved prospects of publication if they present negative findings through having greater power (Weller 2002).

The most obvious implication of the univariate association between positive trial outcome and a lack of trial registration is that trial registration functions in some way to reduce selective outcome reporting. The mechanism by which this occurs may include the publicly available registry inducing researchers both to publish their findings in a form that corresponds to the capabilities of their prespecified methods and to avoid negative attention from publishers by omitting or reprioritising prespecified study outcomes (Emdin et al. 2015). However, it is likely that this is not the complete picture, given that that the two exploratory univariate analyses identified no association between

registration status and trial outcome (p=0.151 and p=0.693; **Table 4**). Further work to identify the cause of this apparent discrepancy is clearly warranted and might include assessing the agreement between registry outcomes and reported outcomes in practice.

This analysis presented three important limitations. Firstly, only papers published in English were included, and these may not be representative of the wider field of physiotherapy publishing practice. Secondly, there is considerable subjectivity in defining and specifically selecting 'physiotherapy' trials, which was mitigated to an extent by an inclusive approach and through discussion between the three reviewers. Thirdly, a significant result was determined by statistical significance only, and it is acknowledged that a statistically significant outcome does not necessarily equate to a clinically significant outcome.

CONCLUSIONS

This study demonstrates that there is no statistical association between trial registration status (registered versus unregistered) and primary study outcome (positive versus negative) among physiotherapy trials when accounting for funding source, initial sample size and country of origin in a multivariate analysis. This study has also identified incomplete and mixed registration practice among physiotherapy RCTs, with low adherence (22%) to widespread recommendations for prospective registration. Resolution of these issues will improve the completeness and integrity of the scientific record, minimisation of reporting bias and growth of robust clinical evidence.

REFERENCES

De Angelis CD, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, Kotzin S, Laine C, Marusic A, Overbeke JPM, et al. 2004. Clinical trial registration: A statement from the International Committee of Medical Journal Editors. JAMA. 292(11):1363–1364. doi:10.1001/jama.292.11.1363.

Babu AS, Veluswamy SK, Rao PT, Maiya AG. 2014. Clinical trial registration in physical therapy

journals: a cross-sectional study. Phys Ther. 94(1):83–90. doi:10.2522/ptj.20120531.

Bhandari M, Busse JW, Jackowski D, Montori VM, Schünemann H, Sprague S, Mears D, Schemitsch EH, Heels-Ansdell D, Devereaux PJ. 2004. Association between industry funding and statistically significant pro-industry findings in medical and surgical randomized trials. C Can Med Assoc J. 170(4):477–480.

Costa LOP, Christine Lin CW, Grossi DB, Mancini MC, Swisher AK, Cook C, Vaughn D, Elkins MR, Sheikh U, Moore A, et al. 2013. Clinical trial registration in physiotherapy journals: Recommendations from the International Society of Physiotherapy Journal Editors. Man Ther. 18(1):1–3. doi:10.1016/j.math.2012.10.009.

Dechartres A, Ravaud P, Atal I, Riveros C, Boutron I. 2016. Association between trial registration and treatment effect estimates: a meta-epidemiological study. BMC Med. 14(1):100. doi:10.1186/s12916-016-0639-x.

Emdin C, Odutayo A, Hsiao A, Shakir M, Hopewell S, Rahimi K, Altman DG. 2015. Association of cardiovascular trial registration with positive study findings: Epidemiological Study of Randomized Trials (ESORT). JAMA Intern Med. 175(2):304–7. doi:10.1001/jamainternmed.2014.6924.

Fleminger J, Goldacre B. 2018. Prevalence of clinical trial status discrepancies: A cross-sectional study of 10,492 trials registered on both ClinicalTrials.gov and the European Union Clinical Trials Register. Beiki O, editor. PLoS One. 13(3):e0193088. doi:10.1371/journal.pone.0193088.

Glanville JM, Duffy S, McCool R, Varley D. 2014. Searching ClinicalTrials.gov and the International Clinical Trials Registry Platform to inform systematic reviews: what are the optimal search approaches? J Med Libr Assoc. 102(3):177–183. doi:10.3163/1536-5050.102.3.007.

Hackshaw A. 2008. Small studies: Strengths and limitations. Eur Respir J. 32:1141–1143. doi:10.1183/09031936.00136408.

Hakoum MB, Jouni N, Abou-Jaoude Eliane A, Hasbani DJ, Abou-Jaoude Elias A, Lopes LC, Khaldieh M, Hammoud MZ, Al-Gibbawi M, Anouti S, et al. 2017. Characteristics of funding of clinical trials: cross-sectional survey and proposed guidance. BMJ Open. 7(10):e015997.

Harriman SL, Patel J. 2016. When are clinical trials registered? An analysis of prospective versus retrospective registration. Trials. 17(1):187. doi:10.1186/s13063-016-1310-8.

Higgins JPT, Green S. 2011. Table 8.5.d: Criteria for judging risk of bias. In: Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011].

Howick J, Phillips B, Ball C, Sackett D, Badenoch D, Straus S, Haynes B, Dawes M. 2009. Levels of evidence and grades of recommendation. Oxford Cent Evidence-based Med.

Hunter KE, Seidler AL, Askie LM. 2018. Prospective registration trends, reasons for retrospective

registration and mechanisms to increase prospective registration compliance: descriptive analysis and survey. BMJ Open. 8(3):e019983.

Kelly G, Reilly A, Moloney H, Moran J, Cunningham C, Broderick J. 2018. 50 years of randomised controlled trials published in the journal Physiotherapy: A review 1967–2017. Physiotherapy. Accepted. doi:https://doi.org/10.1016/j.physio.2018.08.005.

Kerry R. 2017. Expanding our perspectives on research in musculoskeletal science and practice. Musculoskelet Sci Pract. 32(C):114–119. doi:https://doi.org/10.1016/j.msksp.2017.10.004.

Lundh A, Lexchin J, Mintzes B, Schroll JB, Bero L. 2017. Industry sponsorship and research outcome. Lundh A, editor. Cochrane Database Syst Rev. doi:10.1002/14651858.MR000033.pub3.

Maher CG, Sherrington C, Herbert RD, Moseley AM, Elkins M. 2003. Reliability of the PEDro scale for rating quality of randomized controlled trials. Phys Ther.

Mallat J. 2017. Understanding the null hypothesis (H(0)) in non-inferiority trials. Crit Care. 21:101. doi:10.1186/s13054-017-1685-2.

Michaleff ZA, Costa LOP, Moseley AM, Maher CG, Elkins MR, Herbert RD, Sherrington C. 2011. CENTRAL, PEDro, PubMed and EMBASE are the most comprehensive databases indexing randomized controlled trials of physical therapy interventions. Phys Ther. 91(2):190–197.

de Morton NA. 2009. The PEDro scale is a valid measure of the methodological quality of clinical trials: a demographic study. Aust J Physiother. 55(2):129–33. doi:10.1016/S0004-9514(09)70043-1.
NHS England. 2019. NHS Long Term Plan.

Odutayo A, Emdin CA, Hsiao AJ, Shakir M, Copsey B, Dutton S, Chiocchia V, Schlussel M, Dutton P, Roberts C, et al. 2017. Association between trial registration and positive study findings: cross sectional study (Epidemiological Study of Randomized Trials—ESORT). BMJ.:j917. doi:10.1136/bmj.j917.

Rasmussen N, Lee K, Bero L. 2009. Association of trial registration with the results and conclusions of published trials of new oncology drugs. Trials. 10(1):116. doi:10.1186/1745-6215-10-116.

Scurlock-Evans L, Upton P, Upton D. 2014. Evidence-Based Practice in physiotherapy: A systematic review of barriers, enablers and interventions. Physiother (United Kingdom). doi:10.1016/j.physio.2014.03.001.

Weller AC. 2002. Editorial Peer Review: Its Strengths and Weaknesses. 2nd ed. Bryans JB, editor. Medford: American Society for Information Science and Technology.

World Medical Association. 2008. WMA Declaration of Helsinki -Ethical Principles for Medical Research Involving Human Subjects.

Zarin DA, Tse T, Williams RJ, Carr S. 2016. Trial Reporting in ClinicalTrials.gov — The Final Rule. N Engl J Med. 375(20):1998–2004. doi:10.1056/NEJMsr1611785.

FIGURE AND TABLE LEGENDS

Table 1. Demographic characteristics of the included randomised controlled trials.

Table 2. Primary univariate analysis of the association between trial characteristics and trial outcome, excluding trials with an unclear primary outcome and without stratifying registration as prospective or retrospective.

Table 3. Primary multivariate analysis (multinomial logistic regression) of the association between trial characteristics (established to be significant in the univariate analysis) and primary trial outcome.

Table 4. Exploratory univariate (chi-squared) analyses of the association between trial registration status and outcome with alternative stratification by registration status.

Supplementary File 1: Search terms used on PubMed.

Supplementary File 2: Flow diagram of articles through the screening processes.

Supplementary File 3: Table illustrating the journals where the 323 included papers were published.

Supplementary File 4: Table illustrating the country of origin for each included trial and the frequency of significant, null and unclear outcomes per country.

Table 1: Demographic characteristics of the 323 included randomised controlled trials.

Study characteristic		**Number and percentage of papers**
Registration status	Prospectively registered	71 (22%)
	Retrospectively registered	122 (37.8%)
	Unregistered	130 (40.2%)
Primary outcome	Significant	215 (66.6%)
	Null	76 (23.5%)
	Unclear	32 (9.9%)
Funding source	Industry	30 (9.3%)
	Non-industry	205 (63.5%)
	Unclear	88 (27.2%)
Continent of origin	Asia	69 (21.4%)
	Africa	1 (0.3%)
	North America	61 (18.9%)
	South America	39 (12.1%)
	Europe	134 (41.5%)
	Australia and Oceania	19 (5.9%)
Number of centres	Single	225 (69.7%)
	Multiple	38 (11.8%)
	Unclear	60 (18.6%)
Setting type	Clinical	125 (38.7%)
	University	60 (18.6%)
	Residential	23 (7.1%)
	Other	14 (4.3%)
	Multiple	46 (14.2%)
	Unclear	55 (17%)
Initial sample size > 99	Yes	74 (22.9%)
	No	249 (77.1%)
Sample size calculations described	Yes	174 (53.9%)
	No	149 (46.1%)
Adequate random sequence generation described	Yes	201 (62.2%)
	No	122 (37.8%)
Adequate allocation concealment described	Yes	112 (34.7%)
	No	211 (65.3%)
Blinding	Single	135 (41.8%)
	Double	42 (13%)
	None	50 (15.5%)
	Unclear	96 (29.7%)
Attrition described	Yes, details provided	251 (77.7%)
	Yes, no details provided	29 (9%)
	No	43 (13.3%)

Table 2: Primary univariate analysis of the association between trial characteristics and trial outcome, excluding trials with an unclear primary outcome and without stratifying registration as prospective or retrospective.

Study characteristic		**Articles with a significant outcome**	**Articles with a null outcome**	**P value***
Registration status	Registered	122 (69.3%)	54 (30.7%)	0.028
	Unregistered	93 (80.9%)	22 (19.1%)	
Funding source	Industry	15 (53.6%)	13 (46.4%)	0.03
	Non-industry	139 (77.2%)	41 (22.8%)	
	Unclear	61 (73.5%)	22 (26.5%)	
Country of origin**				0.042
Continent of origin**				0.306
Number of centres	Single	150 (74.3%)	52 (25.7%)	0.208
	Multiple	22 (62.9%)	13 (37.1%)	
	Unclear	43 (79.6%)	11 (20.4%)	
Setting type	Clinical	85 (76.6%)	26 (23.4%)	0.952
	University	38 (70.4%)	16 (29.6%)	
	Residential	16 (72.7%)	6 (27.3%)	
	Other	9 (69.2%)	4 (30.8%)	
	Multiple	30 (71.4%)	12 (28.6%)	
	Unclear	37 (75.5%)	12 (24.5%)	
Initial sample size (#)				0.133
Initial sample size > 99	Yes	45 (66.2%)	23 (33.8%)	0.098
	No	170 (76.2%)	53 (23.8%)	
Journal**				0.587
Sample size calculations described	Yes	110 (71.0%)	45 (29.0%)	0.227
	No	105 (77.2%)	31 (22.8%)	
Adequate random sequence generation described	Yes	135 (72.2%)	52 (27.8%)	0.379
	No	80 (77.0%)	24 (23.0%)	
Adequate allocation concealment described	Yes	71 (68.9%)	32 (31.1%)	0.155
	No	144 (76.6%)	44 (23.4%)	
Blinding	Single	91 (73.4%)	33 (26.6%)	0.782
	Double	31 (77.5%)	9 (22.5%)	
	None	28 (68.3%)	13 (31.7%)	
	Unclear	65 (75.6%)	21 (24.4%)	
Attrition described	Yes, details provided	162 (72%)	63 (28%)	0.149
	Yes, no details provided	20 (71.4%)	8 (28.6%)	
	No	33 (86.8%)	5 (13.2%)	

*Determined with outcome as the response variable, using ANOVA for "Initial sample size (#)" and a chi-squared test for the remaining variables. For this univariate analysis, significance was determined as $p<0.10$. **Data on these variables are presented in the Appendix (Sections 2 and 3).

Table 3: Primary multivariate analysis (multinomial logistic regression) of the association between trial characteristics (established to be significant in the univariate analysis) and primary trial outcome.

Study characteristic	Odd Ratio (95% CI)	P value*
Registration status	1.65 (0.92-2.96)	0.094
Funding source	1.22 (0.77-1.94)	0.406
Country of origin	1.01 (0.99-1.03)	0.352
Initial sample size (Large/Small)	1.54 (0.84-2.81)	0.165

*For this multinomial logistic regression, significance was determined as $p<0.05$.

Table 4: Exploratory univariate (chi-squared) analyses of the association between trial registration status and outcome with alternative stratification by registration status.

Study characteristic		**Articles with a significant outcome**	**Articles with a null outcome**	**P value**
First exploratory analysis	Prospectively registered	50 (75.8%)	16 (24.2%)	0.151
	Retrospectively registered	72 (65.5%)	38 (34.5%)	
Second exploratory analysis	Prospectively registered	50 (75.8%)	16 (24.2%)	0.693
	Retrospectively registered and unregistered	165 (73.3%)	60 (26.7%)	