Journal of Clinical Epidemiology 113 (2019) 64–74

Journal of Clinical Epidemiology

REVIEW

Prevalence of trial registration varies by study characteristics and risk of bias

Aidan Christopher Tan[1], Ivy Jiang[1], Lisa Askie, Kylie Hunter, Robert John Simes, Anna Lene Seidler*

NHMRC Clinical Trials Centre, University of Sydney, Sydney, Australia

Accepted 17 May 2019; Published online 20 May 2019

Abstract

Objectives: The objective of this study was to determine the prevalence of trial registration in health research, whether trial registration status and timing vary depending on trial characteristics, and the relationship between trial registration status and risk of bias.

Study Design and Setting: We systematically reviewed all clinical trials published from January to June 2017 in 28 high- and low-impact factor general and specialty medicine journals.

Results: We identified 370 trials and assessed risk of bias in 183 trials. Trial registration rates were high; 95% of trials were registered prospectively or retrospectively before enrollment completion. Larger sample size, multiple recruitment countries, and primary industry funding were all predictors of earlier trial registration. Prospectively registered trials had a significantly lower risk of bias compared to unregistered trials across all domains. Prospectively registered trials had a similar risk of bias compared to retrospectively registered trials across four out of six domains, and a lower risk of bias across the remaining two domains.

Conclusion: Trial registration is an imperfect proxy for risk of bias. Systematic reviewers should assess risk of bias on a case-by-case basis and conduct sensitivity analyses excluding high risk of bias studies. In the longer term, mechanisms should be implemented to facilitate prospective registration of all trials.

Keywords: Prospective registration; Clinical trials; Publication bias; Risk of bias; Systematic review; Clinical trial registration

1. Introduction

1.1. Background

Publication and selective outcome reporting bias describe the phenomena that positive research findings are more likely to be reported and published than inconclusive or negative research findings [1]. These biases skew the medical literature in favor of interventions by making them appear artificially advantageous and thereby misguide evidence-based practice guidelines [2]. To reduce publication bias and selective outcome reporting and improve accountability and transparency in clinical research, the International Committee of Medical Journal Editors (ICMJE) introduced a prospective registration requirement in 2005. All trials submitted for publication must be registered in a recognized clinical trial registry before enrollment of the first participant [3].

While the ICMJE registration requirement has increased trial registration, publication of unregistered trials remains prevalent. There is wide variation in prospective trial registration rates across studies, ranging from 4% to 83% [4–9]. In 2016, 28% of trials in the six highest impact factor general medicine journals were retrospectively registered [8]. In Latin America and the Caribbean, only 17% of randomized controlled trials published in 2010 were registered in a recognized trial registry, and only 4% were registered prospectively [7]. More recently, Farquhar et al. reported that only 44% of randomized controlled trials in the field of fertility treatment were registered, of which only 43% were prospectively registered [10].

Conflict of interest: A.C.T. and I.J. were supported by the University of Sydney Medical School Summer Research Scholarships for the duration of this research project. The funder had no role in the study design, collection, analysis, and interpretation of data; writing of the report; or decision to submit the article for publication. A.L.S., L.A., K.H., and R.J.S. are affiliated with the Australian New Zealand Clinical Trials Registry.

[1] Authors contributed equally to this study.

* Corresponding author. NHMRC Clinical Trials Centre, University of Sydney, Locked bag 77, Camperdown, New South Wales 1450, Australia. Tel.: +61-2-95625082; fax: +61-2-9565-1863.

E-mail address: lene.seidler@ctc.usyd.edu.au (A.L. Seidler).

https://doi.org/10.1016/j.jclinepi.2019.05.009

What is new?

Key findings

- Trial registration rates are high and appear to be increasing compared to earlier studies on registration rates.
- Recruitment in multiple countries, larger sample sizes, and primary industry funding are all predictors of earlier trial registration.

What this adds to what is known?

- While trials that comply with the prospective registration requirement tend to display lower risk of bias, trial registration is an imperfect proxy for risk of bias.

What are the implications and what should change now?

- Excluding all trials that were not prospectively registered from systematic reviews could introduce new bias.
- Systematic reviewers should assess risk of bias on a case-by-case basis and conduct sensitivity analyses excluding high risk of bias studies.

There has been heated debate on how to address the potentially biased evidence in nonprospectively registered trials. Roberts et al. argued for the exclusion of unregistered and retrospectively registered trials from systematic reviews, to avoid magnifying publication bias [2,11]. They argue that unregistered trials are more likely to have statistically significant results and are associated with lower methodological quality and larger treatment effect estimates [2,12].

This position has been investigated by studies in specific medical subfields, including psychiatry, pediatric health, and traditional Chinese medicine [13−15]. In Latin America and the Caribbean, registered trials have been shown to have a significantly lower risk of bias than unregistered trials in the domains of random sequence generation and allocation concealment data [7]. However, almost a third of randomized controlled trials registered prospectively or retrospectively before enrollment completion have been found to have a high risk of selective reporting bias, and discrepancies between the registered and reported trial information have been shown to have no influence on publication acceptance [6,16]. Overall, the evidence is inconclusive, and to date, there have been no studies on the relationship between prospective registration compliance and risk of bias in general medicine. Thus, the question of whether unregistered and retrospective trials should be excluded from systematic reviews remains unanswered. A comprehensive picture of current trial registration rates, and associations between trial registration timing, risk of bias, and general study characteristics in health research, is required to inform the debate about registration, bias, and inclusion criteria for systematic reviews.

1.2. Objectives

The aims of this study were to (1) determine the prevalence of trial registration in health research, (2) determine whether trial registration status and timing varies depending on trial characteristics, and (3) analyze the relationship between trial registration status and risk of bias.

2. Methods

2.1. Protocol and registration

A protocol for this review was registered on PROSPERO and can be accessed at https://www.crd.york.ac.uk/prospero/ (CRD42018083801). This review follows the PRISMA reporting guidelines [17].

2.2. Eligibility criteria

Medical journals eligible for inclusion were selected using two strategies to include both general medicine and specialty journals. First, we included the 14 ICMJE member journals— which are all general medicine journals. Second, we selected the three most commonly studied medical specialties (oncology, cardiology, and psychiatry), the least frequently listed medical specialty (anesthesiology), and three randomly selected medical specialties in between (public health, respiratory, and pediatrics) from the Australian New Zealand Clinical Trials Registry's (ANZCTR) most frequent 15 medical specialties by number of Australian clinical trial registrations. From each of these seven medical specialties, we included the highest ranked journal by impact factor that had published a minimum of 10 clinical trials over the period January to June 2017, and a randomly selected journal ranked between 4th and 10th inclusive by impact factor. Randomization of the middle listed medical specialties and lower impact factor specialty journals was performed using a random integer generator (https://www.random.org/integers/).

Studies from medical journals were eligible for inclusion if they were a clinical trial, published between 1 January and 30 June 2017 inclusive, and available in English language. Studies were excluded if they were an incomplete clinical trial or the date of first patient enrollment was before July 2005 as the ICMJE requirement was only introduced after these studies started recruitment.

In total, 28 medical journals (14 general, 14 specialty) representing a range of impact factors (0.450 to 72.406) and geographical localities (six continents) were searched for clinical trials.

2.3. Information sources

Clinical trials in eligible medical journals were searched using the electronic bibliographic databases Medline and EMBASE. Citations were screened by title and abstract for clinical trial characteristics. The full-text publications of relevant abstracts were obtained.

Information on registration status and timing was abstracted and classified as follows:

1. Prospectively registered: trial registration was approved before participant enrollment commenced.
2. Registration approved and enrollment commenced in the same month: trial registration was approved in the same month as participant enrollment commenced; however, the date within the month of either or both events was not reported.
3. Retrospectively registered before enrollment completion: trial registration was approved after participant enrollment commenced but before participant enrollment concluded.
4. Retrospectively registered after enrollment completion: trial registration was approved after participant enrollment concluded.
5. Unregistered: no evidence of trial registration after two investigators (A.C.T. and I.J.) independently searched the clinical trial publication, all primary clinical trial registries in the WHO Registry Network (e.g., ANZCTR, ISRCTN) and ClinicalTrials.gov, and Google. The corresponding authors of all unregistered clinical trials were contacted to confirm their registration status.

The following study characteristics were extracted from all trials: journal type (general medicine, high-ranked specialty journal, low-ranked specialty journal), sample size, center status (single-center, multicenter but one-country, multicenter, and multicountry), primary funding source (industry, nonindustry), intervention type (diagnosis/screening/prevention, drugs, devices/equipment, surgery/procedures, other), trial phase (I, II, III, IV, nonapplicable), and health condition (infectious and parasitic diseases, neoplasms, mental and behavioral, circulatory, respiratory, pediatric, other).

Owing to resource limitations, risk of bias was assessed in a random sample of half of all identified trials, stratified by registration status and journal type. Risk of bias assessment was conducted using the Cochrane Risk of Bias Tool; all reviewers attended Cochrane risk of bias training [18]. The selective reporting outcome domain was only assessed for the primary outcome, as a large number of trials registered 10 or more secondary outcomes. In the Cochrane Handbook, investigators are instructed to grade trials where ''One or more reported primary outcomes were not prespecified (unless clear justification for their reporting is provided, such as an unexpected adverse effect)'' as high risk of bias for selective reporting [19]. We judged the absence of a registration record or some other type of protocol as a failure to prespecify primary outcomes and thus rated them at high risk of bias for selective reporting. A pilot run was performed where two investigators (A.C.T. and I.J.) assessed the same 15 trials and discussed their decision making extensively to allow for standardization of the risk of bias assessment. The remainder of the risk of bias assessments were divided equally between investigators A.C.T. and I.J. Any uncertainties were discussed between the two reviewers and with a third investigator (A.L.S.).

2.4. Post hoc survey

A post hoc online survey of all unregistered or retrospectively registered trials (n = 147) was performed from May to July 2018 to identify barriers and possible mechanisms to improve prospective registration. We used the same survey questions as a recent publication on prospective registration compliance [20]. Publication and registry correspondence e-mails were used to contact the study coordinators of trials that were not prospectively registered. The full survey can be found in Appendix B. The survey was approved by the University of Sydney Human Research Ethics Committee (project no. 2018/267).

2.5. Data analysis

Statistical analysis was performed using the open-source software R. Person's chi-squared test was used to determine whether study characteristics and risk of bias differed by registration status. Where the expected cell counts were smaller than five in more than 80% of the cells, Monte Carlo estimation of exact P-values was applied.

3. Results

3.1. Sample characteristics

We identified 370 trials and assessed risk of bias in a sample of 183 (49%). Included journals and number of trials per journal are detailed in Appendix A and the flow diagram is available in Fig. 1. Trial characteristics are detailed in Table 1. Over half the included trials were published in general medical journals (n = 207), a third in high-impact specialty medical journals (n = 125), and a tenth in lower impact specialty medical journals. The mean sample size was 2,062 and median sample size was 305. Trials were most frequently primarily non–industry funded (60%), multicenter (78%), single country (61%), and drug investigations (57%).

3.2. Registration rates

The prevalence of trials by registration timing is shown in Fig. 2. Registration rates were high; 95% of trials were registered prospectively or retrospectively before

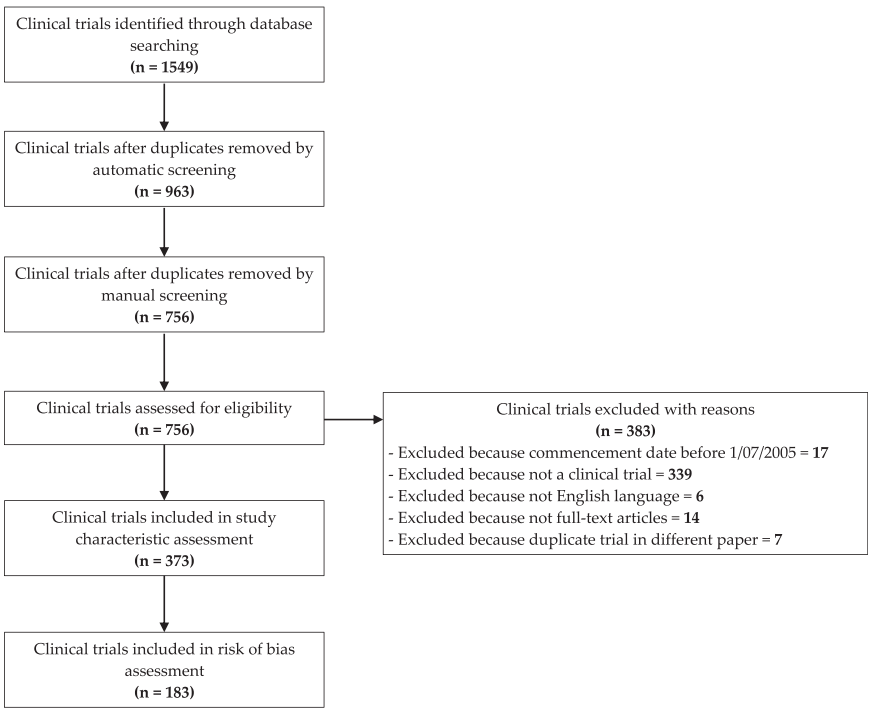

Fig. 1. Flow diagram.

recruitment completion. Only 3% of trials were unregistered. Compared to earlier studies on registration rates, prospective registration has increased, although this was not statistically significant (X^2 [8] = 2.58, P = 0.97). While 55% of trials that commenced between 2005 and 2008 were prospectively registered, this increased to 61% for trials commencing between 2009 and 2012, and 65% for trials that started recruitment between 2013 and 2016.

3.3. Trial characteristics and registration rates

Trial characteristics by registration status and timing are detailed in Table 2. General medical journals had a higher proportion of prospectively registered trials (68%) compared to higher-ranked specialty medical journals (58%) and even more so compared to lower-ranked specialty medical journals (29%). These differences were statistically significant (X^2 [8] = 48.10, $P < 0.001$). Trials with larger sample sizes were more likely to be prospectively registered, with 75% of trials with sample sizes 501−1,000 prospectively registered. Trials with multiple centers were more likely to be prospectively registered than single-center trials (66% vs. 42% prospectively registered). Trials with multiple recruitment countries were similarly more likely to be prospectively registered than single country studies, with 73% of all multiple recruitment country studies prospectively registered compared to 52% of single recruitment country studies. A higher proportion of primarily industry-funded trials were prospectively registered (64%) compared to primarily non−industry-funded trials (58%). Drug trials were more likely to be prospectively registered than other intervention trials. Registration status did not differ by trial phase or health condition. Of the 13 unregistered trials, nine had sample sizes smaller than 50 (69%), 12 were primarily non−industry funded (92%), and all were conducted in a single country.

3.4. Registration rates and risk of bias

As shown in Figures 3 and 4, and in more detail in Appendix C, prospectively registered trials had a lower risk of bias compared to unregistered trials across all domains, and this difference was statistically significant in all domains except the domain of incomplete outcome data. The comparative proportion of prospectively registered and unregistered trials that were low risk of bias was most marked in the domains of random sequence allocation (79% vs. 15%) and selective outcome reporting (78% vs. 0%) but was also large in the other domains of allocation concealment (66% vs. 31%), participant and personnel blinding (58% vs. 31%), outcome assessor blinding (72% vs. 31%), and incomplete outcome data (92% vs. 77%).

Prospectively registered trials had a similar risk of bias compared to trials registered retrospectively before enrollment completion across the four domains of random sequence generation, allocation concealment, incomplete outcome data, and selective reporting. For the remaining two domains, a higher proportion of prospectively registered trials were low risk of bias: participant and personnel

Table 1. Clinical trial characteristics of all included trials and risk of bias sample

Characteristic	All included trials (n = 370)	ROB sample[a] (n = 183)
Journal type		
General	207 (55.9%)	75 (41.0%)
Specialty—high	125 (33.8%)	72 (39.3%)
Specialty—low	38 (10.3%)	36 (19.7%)
Sample size - continuous (mean, SD)	2,061.73 (8,954.81)	2,683.69 (11,712.42)
Sample size—continuous (median, IQR)	304.5 (647)	270 (887)
Sample size—categorical		
1–49	48 (13.0%)	28 (15.3%)
50–99	48 (13.0%)	24 (13.1%)
100–499	141 (38.1%)	67 (36.6%)
500–999	57 (15.4%)	20 (10.9%)
≥1,000	76 (20.5%)	44 (24.0%)
Recruitment country		
Single	224 (60.5%)	135 (73.8%)
Multiple	146 (39.5%)	48 (26.2%)
Center status		
Single	82 (22.2%)	56 (30.6%)
Multiple	288 (77.8%)	127 (69.4%)
Primary funding source		
Industry	147 (39.7%)	57 (31.1%)
Nonindustry	223 (60.3%)	126 (68.9%)
Intervention type		
Diagnosis/screening/prevention	47 (12.7%)	24 (13.1%)
Drugs	211 (57.2%)	83 (45.4%)
Devices/equipment	32 (8.7%)	23 (12.6%)
Surgery	25 (6.8%)	11 (6.0%)
Other	54 (14.6%)	42 (23.0%)
Trial phase		
Phase I	21 (5.7%)	8 (4.4%)
Phase II	68 (18.4%)	28 (15.3%)
Phase III	138 (37.3%)	48 (26.2%)
Phase IV	55 (14.9%)	35 (19.1%)
Not applicable	88 (23.8%)	64 (35.0%)
Health condition		
Infectious and parasitic diseases	28 (7.6%)	15 (8.2%)
Neoplasms	90 (24.3%)	30 (16.4%)
Mental and behavioral	26 (7.0%)	19 (10.4%)
Circulatory	54 (14.6%)	29 (15.8%)
Respiratory	28 (7.6%)	18 (9.8%)
Pediatric	15 (4.1%)	9 (4.9%)
Other	129 (34.9%)	63 (34.4%)
Health condition (general medicine journals only)		
Infectious and parasitic diseases	21 (10.1%)	9 (12.0%)
Neoplasms	23 (11.1%)	6 (8.0%)
Mental and behavioral	13 (6.3%)	6 (8.0%)
Circulatory	35 (16.9%)	13 (17.3%)
Respiratory	14 (6.8%)	7 (9.3%)
Pediatric	9 (4.3%)	4 (5.3%)
Other	92 (44.4%)	30 (40.0%)

Percentages do not add up to 100 as they are rounded to one decimal place.

[a] The random sample was stratified by journal and by registration status.

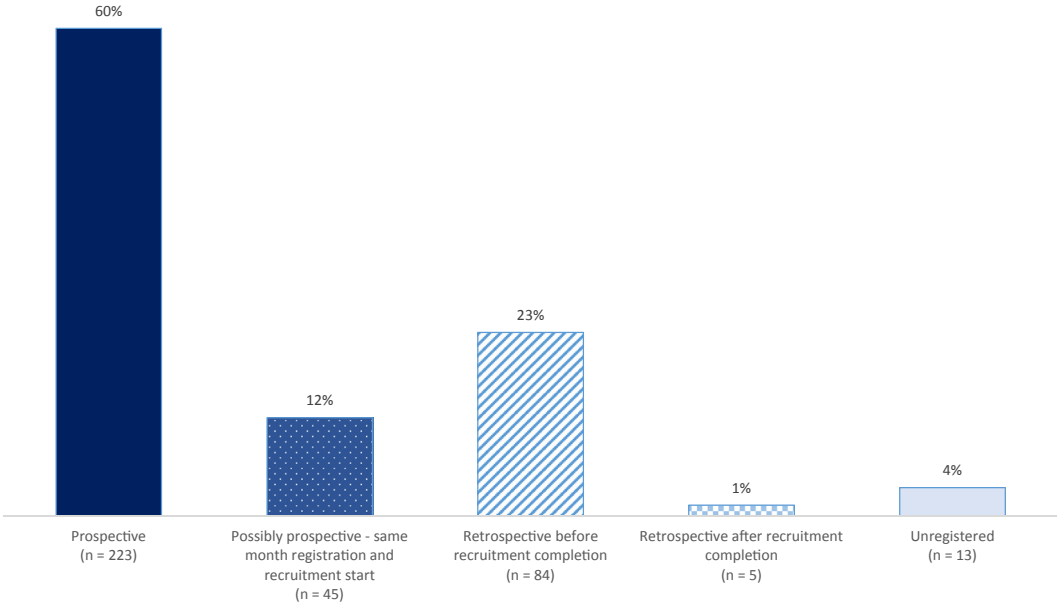

Fig. 2. Prevalence of trials by registration timing.

blinding (58% vs. 31%) and outcome assessor blinding (72% vs. 31%).

3.5. Post hoc survey

Of the 147 unregistered or retrospectively registered trials, seven were uncontactable. From the remaining 140 trials, a response rate of 12% (17/140) was achieved. All respondents agreed with the classification of their trial as registered or unregistered. Half (4/8) of the respondents of trials with registration approval and enrollment commencement in the same month reported prospectively registering their trial. Interestingly, 63% (5/8) of respondents of trials that were retrospectively registered before enrollment completion mistakenly reported that their trial was prospectively registered. The full survey results are displayed in Appendix D.

4. Discussion

This study showed high registration rates; 95% of trials were registered before enrollment completion. However, retrospective registration was still prevalent, with 24% of trials registered retrospectively, and 3% of trials unregistered. Registration compliance varied across types of trials. Earlier registration was associated with publication in general medical journals, primary industry funding, larger sample sizes, multiple centers, multiple recruitment countries, drug investigations, and later trial start dates. In the risk of bias assessments, unregistered and retrospectively registered studies performed worse on average. Yet, some prospectively registered studies were high risk of bias, and some retrospectively registered studies were low risk of bias.

4.1. Strengths and limitations

Our study is the first to classify categories of registration compliance in light of registration timing across different areas of medicine. This provides novel insights into the similarities and differences in study characteristics and risk of bias between trials of different registration timing. We included all studies published in a range of journals over a recent period, making our findings generalizable across many medical fields. Risk of bias was assessed using an established methodology, the Cochrane Risk of Bias Tool.

The post hoc survey was limited by the low response rate of 12.1%, and researchers may have been more likely to respond if they disagreed with the classification of their trial as not prospectively registered. Moreover, as a significant proportion of trials registered 10 or more secondary outcome measures, only primary outcome measures were considered when determining the risk of selective reporting bias. All trials registered retrospectively after enrollment completion were assessed as low risk of bias in the domain of selective reporting, most probably because the publication was being prepared as the primary outcome was being reported in the registry.

The risk of bias assessments were limited by the fact that we did not use independent double assessment. Previous research has pointed to some inconsistencies in risk of bias ratings across different reviewers. Yet, these resulted more often from different interpretation of the tool rather than different information identified in the study reports [21].

Table 2. Clinical trial characteristics by registration status and timing

Characteristic	Registration status and timing					Significant testing
	Prospective, that is, before first participant enrolled ($n = 223$)	In the same month as recruitment start ($n = 45$)	Retrospective before recruitment completion ($n = 84$)	Retrospective after recruitment completion ($n = 5$)	Unregistered ($n = 13$)	X^2 (df) *P*-value
Journal type						$X^2(8) = 50.23$ $P < 0.001$[b]
General	140 (67.6%)	28 (13.5%)	34 (16.4%)	1 (0.5%)	4 (1.9%)	
Specialty—high	72 (57.6%)	13 (10.4%)	36 (28.8%)	2 (1.6%)	2 (1.6%)	
Specialty—low	11 (28.9%)	4 (10.5%)	14 (36.8%)	2 (5.3%)	7 (18.4%)	
Sample size—continuous (median, IQR)	376 (653)	200 (797)	278.5 (858.3)	221 (262)	43 (28)	
Sample size—categorical						$X^2(16) = 49.62$ $P < 0.001$[b]
1–49	21 (43.8%)	6 (12.5%)	11 (22.9%)	1 (2.1%)	9 (18.8%)	
50–99	25 (52.0%)	6 (12.5%)	15 (31.3%)	0 (0.0%)	2 (4.2%)	
100–499	88 (62.4%)	18 (12.8%)	30 (21.3%)	3 (2.1%)	2 (1.4%)	
500–999	43 (75.4%)	6 (10.5%)	8 (14.0%)	0 (0.0%)	0 (0.0%)	
≥1,000	46 (60.5%)	9 (11.8%)	20 (26.3%)	1 (1.3%)	0 (0.0%)	
Recruitment country						$X^2(4) = 23.39$ $P < 0.001$
Single	116 (51.8%)	30 (13.3%)	60 (26.8%)	5 (2.2%)	13 (5.8%)	
Multiple	107 (73.3%)	15 (10.3%)	24 (16.4%)	0 (0.0%)	0 (0.0%)	
Center status						$X^2(4) = 34.71$ $P < 0.001$
Single	34 (41.5%)	11 (13.4%)	24 (29.3%)	4 (4.8%)	9 (11.0%)	
Multiple	189 (65.6%)	34 (11.8%)	60 (20.8%)	1 (0.3%)	4 (1.4%)	
Primary funding source						$X^2(4) = 10.80$ $P = 0.03$
Industry	94 (63.9%)	23 (15.6%)	28 (19.0%)	1 (0.7%)	1 (0.7%)	
Nonindustry	129 (57.8%)	22 (9.9%)	56 (25.1%)	4 (1.8%)	12 (5.4%)	
Intervention type						
Diagnosis/screening/prevention	23 (48.9%)	6 (12.8%)	14 (29.8%)	1 (2.1%)	3 (6.4%)	$X^2(16) = 29.34$ $P = 0.03$[b]
Drugs	145 (68.7%)	25 (11.8%)	36 (17.1%)	1 (0.5%)	4 (1.9%)	
Devices/equipment	13 (40.6%)	6 (18.8%)	9 (28.1%)	2 (6.3%)	2 (6.3%)	
Surgery	14 (56.0%)	3 (12.0%)	6 (24.0%)	1 (4.0%)	1 (4.0%)	
Other	27 (50.0%)	5 (9.3%)	19 (35.2%)	0 (0.0%)	3 (5.6%)	
Trial phase						$X^2(16) = 29.06$ $P = 0.03$[b]
Phase I	10 (47.6%)	4 (19.0%)	6 (28.6%)	0 (0.0%)	1 (4.8%)	
Phase II	43 (63.2%)	12 (17.6%)	10 (14.7%)	0 (0.0%)	3 (4.4%)	
Phase III	97 (70.3%)	14 (10.1%)	24 (17.4%)	2 (1.4%)	1 (0.7%)	
Phase IV	33 (60.0%)	5 (9.1%)	13 (23.6%)	2 (3.6%)	2 (3.6%)	
Not applicable	40 (45.5%)	10 (11.4%)	31 (35.2%)	1 (1.1%)	6 (6.8%)	
Health condition						
Infectious and parasitic diseases	15 (53.6%)	6 (21.4%)	5 (17.9%)	1 (3.6%)	1 (3.6%)	$X^2(24) = 25.95$ $P = 0.35$[b]
Neoplasms	55 (61.1%)	10 (11.1%)	24 (26.7%)	0 (0.0%)	1 (1.1%)	
Mental and behavioral	15 (57.7%)	1 (3.8%)	9 (34.6%)	0 (0.0%)	1 (3.8%)	
Circulatory	33 (61.1%)	8 (14.8%)	13 (24.1%)	0 (0.0%)	0 (0.0%)	
Respiratory	16 (57.1%)	3 (10.7%)	8 (28.6%)	0 (0.0%)	1 (3.6%)	
Pediatric	8 (53.3%)	1 (6.7%)	4 (26.7%)	0 (0.0%)	2 (13.3%	
Other	81 (62.8%)	16 (12.4%)	21 (16.3%)	4 (3.1%)	7 (5.4%)	
Health condition (general medicine journals only)						$X^2(24) = 23.15$ $P = 0.49$[b]
Infectious and parasitic diseases	12 (57.1%)	5 (23.8%)	2 (9.5%)	1 (4.8%)	1 (4.8%)	
Neoplasms	15 (65.2%)	1 (4.3%)	6 (26.1%)	0 (0.0%)	1 (4.3%)	
Mental and behavioral	8 (61.5%)	1 (7.7%)	4 (30.8%)	0 (0.0%)	0 (0.0%)	

(*Continued*)

Table 2. Continued

Characteristic	Registration status and timing					Significant testing
	Prospective, that is, before first participant enrolled (n = 223)	In the same month as recruitment start (n = 45)	Retrospective before recruitment completion (n = 84)	Retrospective after recruitment completion (n = 5)	Unregistered (n = 13)	X^2 (df) P-value
Circulatory	25 (71.4%)	4 (11.4%)	6 (17.1%)	0 (0.0%)	0 (0.0%)	
Respiratory	8 (57.1%)	2 (14.3%)	3 (21.4%)	0 (0.0%)	1 (7.1%)	
Pediatric	7 (77.8%)	1 (11.1%)	1 (11.1%)	0 (0.0%)	0 (0.0%)	
Other	65 (70.7%)	14 (15.2%)	12 (13.0%)	0 (0.0%)	1 (1.1%)	
Registration status by trial commencement year[a]						$X^2(8) = 2.58$ $P = 0.97$[b]
2005–2008	18 (54.5%)	5 (15.2%)	9 (27.3%)	0 (0%)	1 (3.0%)	
2009–2012	99 (60.7%)	21 (12.9%)	38 (23.3%)	2 (1.2%)	3 (1.8%)	
2013–2016	106 (64.6%)	18 (11.0%)	37 (22.6%)	3 (1.8%)	2 (1.2%)	

[a] NA = 8 missing data values from this variable.
[b] For these statistics, we used Monte Carlo estimation of exact P-values due to small expected cell counts.

Extensive measures were thus taken to standardize interpretation of the Cochrane Risk of Bias Tool across our two reviewers. We conducted a pilot run of 15 trials in which each decision was extensively discussed among the reviewers and in consultation with ALS and a Cochrane managing editor, to derive common interpretations and decision rules. In addition, throughout the risk of bias rating process, any uncertainties were discussed, and consensus was reached, to standardize the risk of bias assessment process among our reviewers.

4.2. Interpretation and implications

Registration rates were higher than in studies conducted in previous years. In 2014, 10% of trials published in high-impact journals were unregistered or registered after completion of recruitment [8]. In our study, which looked at trials published 3 years later in 2017, this was the case for less than 4% of trials. Yet, while we sampled a broad range of journals, there were fewer trials in the lower-impact journals, leading to only seven trials (2%) in journals with impact factors below three. Registration rates may have been lower if we had included more trials from lower impact journals as a recent study has shown that approximately 95% of unregistered or retrospectively registered trials not accepted by the *BMJ* were published elsewhere, demonstrating that ICMJE recommendations are not enforced universally [22]. It is worth noting that while our study calculated registration prevalence based on published trials, recent studies including unpublished trials (based on approved trial protocols) have reported very similar rates of prospective registration [23].

In a previous study, Farquhar et al. investigated the association between registration and risk of bias for fertility

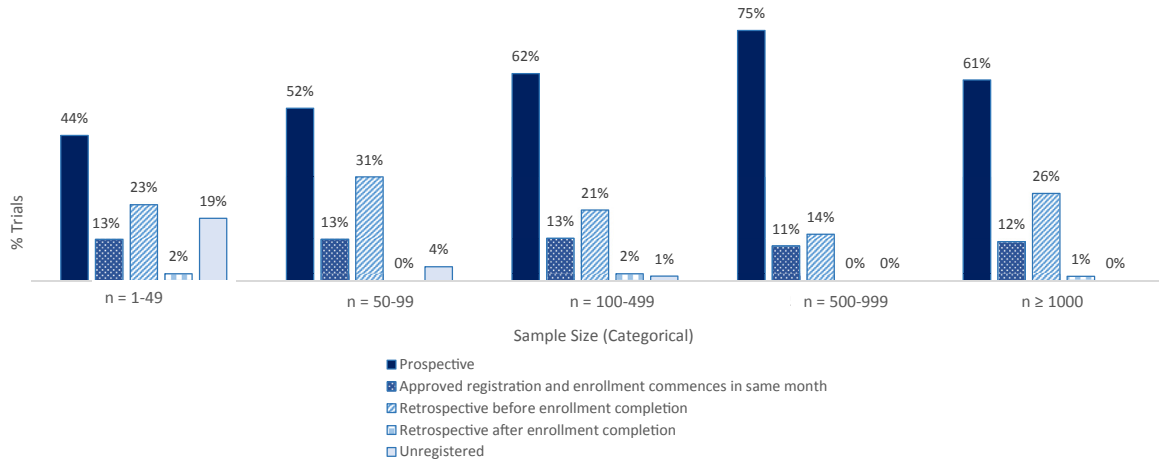

Fig. 3. Sample size and registration status.

Fig. 4. Risk of bias domains by registration timing.

treatment trials [10]. In the present study, we show that Farquhar et al.'s findings can be generalized beyond fertility treatment trials, by including a spectrum of general and specialty medicine journals [10]. Our study adds important information by demonstrating the role of registration timing in risk of bias. The later a trial was registered, the higher the probability for high risk of bias. This provides novel insight to the implications of only including prospectively registered trials in systematic reviews as proposed by Roberts et al. [11].

Registration rates differed across trial characteristics. If studies were excluded based on registration timing, some study types would be disproportionately excluded from systematic reviews. This may introduce new bias. For instance, primarily industry-funded trials were more likely to be registered than trials funded by other sources. If only prospectively registered studies were to be included in systematic reviews, primarily industry-funded trials would be more likely to be included than trials from other funding sources, yet these may have higher risk of bias in other domains. Previous studies have shown that industry-funded trials are more likely to be designed in a way that produces favorable results: the likelihood of an industry-funded study to find a positive result is two to four times higher than that of a non–industry-funded study [24–26]. Selectively including more industry-funded studies could thus introduce new bias toward more favorable results. Moreover, while there was an association between risk of bias and registration timing as predicted by Roberts et al., this association was not perfect [11]. Excluding unregistered or retrospectively registered studies would inevitably exclude some low risk of bias studies and include some prospectively registered high risk of bias studies.

Overall, this study shows that excluding all retrospectively registered and unregistered studies from systematic reviews would risk introducing new bias and excluding high-quality studies.

4.3. Alternatives to excluding retrospectively registered and unregistered studies

Based on our results, we suggest an alternative approach. The Cochrane Risk of Bias Tool offers a reliable method to assess risk of bias, which takes into account risk of selective reporting bias [18]. We advocate that systematic reviewers use the Cochrane tool to assess risk of bias on a case-by-case basis. They can then conduct sensitivity analyses excluding all high risk of bias trials assessed with a gold standard risk of bias tool instead of using the imperfect proxy of registration to predict risk of bias.

In the long term, we advocate for the implementation of mechanisms that further improve registration rates, to strive toward all trials being prospectively registered. This would make the debate of whether to include or exclude unregistered trials in systematic reviews redundant. Hunter et al. have recently shown that the greatest barrier to prospective registration is a lack of awareness and that 74% of retrospective registrants think that linking ethics to registration would have helped them to register prospectively [20]. We therefore urge registries and ethics committees to integrate their important services to reduce the administrative burden for researchers and improve prospective registration compliance.

4.5. Conclusion

This study gives a comprehensive overview of trial registration rates and their relationship to trial characteristics and risk of bias. Excluding all trials that do not comply with the prospective registration criterion from systematic reviews could introduce new bias because trial registration is an imperfect proxy for risk of bias. Instead, systematic reviewers should assess risk of bias on a case-by-case basis and conduct sensitivity analyses only including low risk of bias studies. Trial registration rates are on the rise, and mechanisms should be implemented for further improvement, to ultimately render this debate redundant.

CRediT authorship contribution statement

Aidan Christopher Tan: Data curation, Formal analysis, Writing - original draft, Writing - review & editing. **Ivy Jiang:** Data curation, Formal analysis, Writing - original draft, Writing - review & editing. **Lisa Askie:** Conceptualization, Writing - review & editing. **Kylie Hunter:** Conceptualization, Writing - original draft, Writing - review & editing. **Robert John Simes:** Writing - review & editing. **Anna Lene Seidler:** Conceptualization, Data curation, Formal analysis, Writing - original draft.

Acknowledgments

The authors thank Dr. Melina Willson, Managing Editor of the Cochrane Breast Cancer Group, NHMRC Clinical Trials Centre, University of Sydney, for her expert advice and support in applying the Cochrane Risk of Bias Tool.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclinepi.2019.05.009.

References

[1] Wille-Jorgensen P, Gluud C. Prospective registration of clinical trials. Colorectal Dis 2006;8(1):1.

[2] Abaid LN, Grimes DA, Schulz KF. Reducing publication bias of prospective clinical trials through trial registration. Contraception 2007;76(5):339−41.

[3] De Angelis C, Drazen JM, Frizelle FA, Haug C, Hoey J, Horton R, et al. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. N Engl J Med 2004;351:1250−1.

[4] Jones CW, Platts-Mills TF. Quality of registration for clinical trials published in emergency medicine journals. Ann Emerg Med 2012;60(4):458−464.e1.

[5] Huser V, Cimino JJ. Evaluating adherence to the International Committee of Medical Journal Editors' policy of mandatory, timely clinical trial registration. J Am Med Inform Assoc 2013;20:e169−74.

[6] van Lent M, IntHout J, Out HJ. Differences between information in registries and articles did not influence publication acceptance. J Clin Epidemiol 2015;68:1059−67.

[7] Reveiz L, Bonfill X, Glujovsky D, Pinzon CE, Asenjo-Lobos C, Cortes M, et al. Trial registration in Latin America and the Caribbean's: study of randomized trials published in 2010. J Clin Epidemiol 2012;65:482−7.

[8] Dal-Re R, Ross JS, Marusic A. Compliance with prospective trial registration guidance remained low in high-impact journals and has implications for primary end point reporting. J Clin Epidemiol 2016;75:100−7.

[9] Viergever RF, Li K. Trends in global clinical trial registration: an analysis of numbers of registered clinical trials in different parts of the world from 2004 to 2013. BMJ open 2015;5(9):e008932.

[10] Farquhar CM, Showell MG, Showell EA, Beetham P, Baak N, Mourad S, et al. Clinical trial registration was not an indicator for low risk of bias. J Clin Epidemiol 2017;84:47−53.

[11] Roberts I, Ker K, Edwards P, Beecher D, Manno D, Sydenham E. The knowledge system underpinning healthcare is not fit for purpose and must change. BMJ 2015;350:h2463.

[12] Dechartres A, Ravaud P, Atal I, Riveros C, Boutron I. Association between trial registration and treatment effect estimates: a meta-epidemiological study. BMC Med 2016;14(1):100.

[13] Liu JP, Han M, Li XX, Mu YJ, Lewith G, Wang YY, et al. Prospective registration, bias risk and outcome-reporting bias in randomised clinical trials of traditional Chinese medicine: an empirical methodological study. BMJ Open 2013;3(7):e002968.

[14] Scott A, Rucklidge JJ, Mulder RT. Is mandatory prospective trial registration working to prevent publication of unregistered trials and selective outcome reporting? An observational study of five psychiatry journals that mandate prospective clinical trial registration. PLoS One 2015;10:e0133718.

[15] Gates A, Hartling L, Vandermeer B, Caldwell P, Contopoulos-Ioannidis DG, Curtis S, et al. The conduct and reporting of child health research: an analysis of randomized controlled trials published in 2012 and evaluation of change over 5 years. J Pediatr 2018;193:237−244.e37.

[16] Mathieu S, Boutron I, Moher D, Altman DG, Ravaud P. Comparison of registered and published primary outcomes in randomized controlled trials.[Erratum appears in JAMA. 2009 Oct 14;302(14):1532]. JAMA 2009;302:977−84.

[17] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009;151:264−9.

[18] Higgins JPT, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343(7829):d5928.

[19] Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration; 2011. Available at www.handbook.cochrane.org. Accessed June 12, 2019.

[20] Hunter KE, Seidler AL, Askie LM. Prospective registration trends, reasons for retrospective registration and mechanisms to increase prospective registration compliance: descriptive analysis and survey. BMJ Open 2018;8(3):e019983.

[21] Hartling L, Hamm M, Milne A, Vandermeer B, Santaguida PL, Ansari M, et al. Validity and inter-rater reliability testing of quality assessment instruments. Rockville, MD: Agency for Healthcare Research and Quality (US); 2012.

[22] Loder E, Loder S, Cook S. Characteristics and publication fate of unregistered and retrospectively registered clinical trials submitted to the BMJ over 4 years. BMJ open 2018;8(2):e020037.

[23] Chan AW, Pello A, Kitchen J, Axentiev A, Virtanen JI, Liu A, et al. Association of trial registration with reporting of primary outcomes in protocols and publications. JAMA 2017;318:1709−11.

[24] Falk Delgado A. The association of funding source on effect size in randomized controlled trials: 2013-2015 - a cross-sectional survey and meta-analysis. Trials 2017;18(1):125.

[25] Every-Palmer S, Howick J. How evidence-based medicine is failing due to biased trials and selective publication. J Eval Clin Pract 2014;20:908−14.

[26] Perlis RH, Perlis CS, Wu Y, Hwang C, Joseph M, Nierenberg AA. Industry sponsorship and financial conflict of interest in the reporting of clinical trials in psychiatry. Am J Psychiatry 2005;162(10): 1957−60.