Journal of Clinical Epidemiology 68 (2015) 1059−1067

Journal of Clinical Epidemiology

Differences between information in registries and articles did not influence publication acceptance

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Accepted 24 November 2014; Published online 29 November 2014

Abstract

Objectives: To assess whether journals are more likely to reject manuscripts with differences between information in registries and articles. We compared differences by sponsorship and assessed whether selective reporting favored publication of significant outcomes.

Study Design and Setting: Drug trials submitted to eight journals (January 2010−April 2012) were included. Publication status, primary outcomes, enrollment, and sponsorship were extracted. Primary outcomes and enrollment in registries and registration timing were reviewed. Prospective registration included registration before study start. Consistency between registered and reported information was evaluated.

Results: For 226 submitted manuscripts, primary outcomes were specified in both article and registry. Sixty six of 226 (29.2%) had primary outcome differences; 14 of 66 manuscripts with differences (21.2%) and 46 of 160 without differences (28.8%) were accepted. Fifty manuscripts (22.4%) had sample size differences; 10 of 50 with differences (20.0%) and 49 of 173 without differences (28.3%) were accepted. Industry-sponsored trials had less differences and were more often prospectively registered. After adjustment for sponsorship, differences and/or retrospective registration were not associated with decreased chance of acceptance (odds ratio 0.56; 95% confidence interval: 0.27, 1.13). Primary outcome differences favored significant outcomes in 49% of manuscripts.

Conclusion: Differences between registered and reported information are not decisive for rejection. Editors should assess consistency between registries and articles to address selective reporting.

Keywords: Trial registration; Selective reporting; Drug trials; Editorial decision making; Peer review; Industry sponsorship

1. Introduction

Registration of clinical trials in public trial registries before patient enrollment has been introduced to increase transparency and accountability in the trial process and to address selective publication of study results [1,2]. Through trial registration, investigators should be able to identify all existing trials, whether published or not, and perform unbiased assessments of the available evidence for a medical intervention. The International Committee of Medical Journal Editors (ICMJE) enforced such registration in 2005 as a condition for publication of trial reports in their journals [2]. Several other medical journals have since adopted similar policies [3−6].

Although trial registration is now widely implemented, selective outcome reporting remains to be prevalent among adequately registered trials [7]. For a substantial proportion of randomized controlled trials (RCTs) published in high impact factor journals, evidence of differences between primary outcomes in trial registries, and peer-reviewed publications has been found [8−11]. The differences favored publication of statistically significant outcomes in several trials [8,9]. Differences have also been detected between registered and published secondary outcomes, eligibility criteria, and sample sizes [11−13].

These findings suggest that registered trial information is not sufficiently being considered during manuscript review by journals to identify changes to trial characteristics.

Funding: This research was supported by an unrestricted educational grant from MSD, The Netherlands (Dutch subsidiary of Merck & Co., Inc). The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Conflict of interest: H.J.O. is a paid employee from Teva Pharmaceuticals. M.v.L. and J.I.H. report no conflict of interests.

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http://dx.doi.org/10.1016/j.jclinepi.2014.11.019

What is new?

Key findings

- A substantial number of manuscripts had differences between registered and reported information and/or were retrospectively registered. These articles were not more likely to be rejected at initial screening or after peer review.
- Industry-sponsored trials less often had differences between registered and reported information than nonindustry and industry-supported trials. Industry-sponsored trials were also more often prospectively registered.
- For trials registered before completion, primary outcome differences favored statistically significant outcomes in almost 50% of the manuscripts.

What this adds to what was known?

- Previous studies found that selective reporting remains prevalent among registered trials. However, the role of registered information in editorial decision making has hardly been assessed. This study indicates that editors do not take full advantage of the possibilities provided by registration, as differences between registered and reported information were found among articles accepted for publication.

What is the implication and what should change now?

- Editors and reviewers have the opportunity to identify changes to trial characteristics and should routinely assess the consistency between information in registries and submitted articles to address selective reporting and improve the quality of the publication process.

Cross-checking of information in registries with data actually reported in articles, during initial editorial screening or peer review, could improve the quality of the publication process. A limited number of studies have evaluated the role of registered information in editorial processes. Wager and Williams [14] showed that only 55 of a sample of 200 journals publishing clinical trials required trial registration according to their instructions to authors, which was comparable to findings of studies with smaller samples of journals [3,5,6]. A survey among peer reviewers of clinical trials indicated that only one-third of the reviewers surveyed examined registered information [15]. However, it has not been investigated whether journals requiring registration are less likely to publish trials with unacknowledged differences between information in registries and submitted manuscripts.

Previously, we reported on publication bias in editorial decision making by evaluating the publication status of 472 drug trials submitted to eight medical journals in relation to the direction of results and sponsorship [16]. The aim of this study was to assess whether editors are more likely to reject submitted manuscripts at initial editorial screening or after peer review if there are differences between registered and reported information on the primary outcome or sample size, using the same set of manuscripts. In addition, the extent of differences between registries and manuscripts was compared by sponsor type, and we assessed whether selective outcome reporting favored publication of statistically significant outcomes.

2. Methods

2.1. Selection of journals and submitted manuscripts

Six major general medical journals were asked to provide access to submitted manuscripts and decisions on publication. BMJ agreed to participate, and the BMJ Group also provided access to data of BMJ specialty journals. In addition, other European specialty journals were asked to participate. All journals were selected based on (1) impact factor (journals indexed with the highest impact factors within subject categories, according to the Institute for Scientific Information Journal Citation Report 2011) and (2) the number of drug RCTs published in 2010–2011. As a result, manuscripts submitted to one general medical journal (BMJ, impact factor 2011 14.093) and seven specialty journals (Annals of the Rheumatic Diseases, 8.727; British Journal of Ophthalmology, 2.902; Gut, 10.111; Heart, 4.223; Thorax, 6.840 (all from the BMJ Group); Diabetologia, 6.814; and Journal of Hepatology, 9.264) were included. We selected manuscripts on RCTs submitted from January 2010–April 2012, if at least one study arm assessed the efficacy or safety of a drug intervention and a statistical test was used to evaluate treatment effects. This cohort of manuscripts has been described in detail previously [16]. In this study, post hoc and subgroup analyses of RCTs, follow-up studies of RCTs, and articles reporting results of >1 trial were excluded because these are not routinely and/or separately registered.

2.2. Data extraction manuscripts

The primary outcome was acceptance for publication. Full texts of submitted manuscripts and publication status were retrieved from manuscript submission systems or provided by journals. Manuscripts were outright rejected, rejected after peer review, or accepted for publication. For each manuscript, we reviewed the number of participants and the number and nature of reported primary outcomes. Primary outcomes were those explicitly reported as such

in the article. If none was reported, we used the outcome stated in the sample size calculation. If none was identified in the text or sample size calculation, the article was considered to have no primary outcome reported. Information on sponsorship was previously extracted from manuscripts and classified according to predefined criteria [17]. In short, trials were classified as nonindustry, industry-supported, or industry-sponsored. For nonindustry trials, no associations with pharmaceutical companies were reported. Studies reporting donation of study medication by a manufacturer, studies stating receipt of financial support from a pharmaceutical company, and studies with industry-affiliated authors were classified as industry-supported trials. For industry-sponsored trials, a pharmaceutical company was explicitly described as study sponsor or the company funding the trial participated in the design, data collection, analysis, and/or preparation of the manuscript [17].

2.3. Assessment of trial registration

For each manuscript, we assessed trial registration according to ICMJE requirements [18]. We checked whether authors reported registering their trial and whether a registration number was included in the article or submission system. When no registration number could be identified, the trial was considered not registered. All journals included in this study required trial registration in their instructions to authors. Journals published by the BMJ Group explicitly required that trials were prospectively registered, whereas Diabetologia and Journal of Hepatology both referred to ICMJE policy on registration [18], in which trial registration at or before the time of first patient enrollment is required.

2.4. Data extraction trial registers

For each registered trial, we reviewed the anticipated sample size and the number and nature of primary outcomes in the registry. Primary outcomes were outcomes explicitly reported as such in the registry. If none was identified, the primary outcome was considered not registered. To take into account any amendments after initial trial registration [19], when feasible, we checked changes to the protocol that were available using the history function (eg, ''History of Changes'' on ClinicalTrials.gov archive site). For each trial, the registration date, start date, and completion date reported in the registry were extracted. Trials were considered to be prospectively registered when they were registered before or at the reported start date of the study. As ClinicalTrials.gov only displays a month and year for start and completion dates, trials that were registered in the same month and year as the study start date were classified as prospectively registered. Trials registered after the start date (either before or after study completion) were classified as retrospectively registered. When it was unclear whether a trial was registered before the start of the study (ie, start and/or end date missing in registry), trials were considered to be retrospectively registered. If trials were registered in multiple registries, we extracted data from the registry in which trial information was most completely reported.

2.5. Definition of differences between registered and reported information

For manuscripts with primary outcomes specified in both the registry and the article (sample 1), we assessed the consistency between registered and reported primary outcomes and sample sizes. As in previous studies, we defined differences in primary outcomes according to a modified classification of Chan et al. [8,9,20]:

1. The registered primary outcome was defined as a nonprimary outcome in the submitted article.
2. The registered primary outcome was omitted in the submitted article.
3. A new primary outcome was introduced in the submitted article (ie, an outcome that does not appear in the registry is introduced as primary in the article).
4. The primary outcome in the submitted article was described as a secondary outcome in the registry.
5. The timing of assessment of the registered primary outcome and that reported in the submitted article was different.

If the registry contained multiple primary outcomes, this definition was applied for each primary outcome. If the sample size reported in the manuscript was smaller than 75% of the anticipated sample size specified in the registry, we scored it as a difference.

2.6. Definition of selective outcome reporting

To determine whether selective outcome reporting favored publication of significant outcomes, trials registered before completion were selected (sample 2). For trials registered after completion, it was not possible to evaluate the risk of outcome reporting bias. *P*-values were extracted from manuscripts for all registered primary outcomes and for all outcomes reported in the article. $P < 0.05$ was considered statistically significant. A difference was considered to favor statistically significant outcomes if [20]:

1. A new significant primary outcome supporting the efficacy of the test drug was introduced.
2. A nonsignificant primary outcome was omitted or defined as nonprimary in the article.
3. A new efficacy primary outcome was introduced for a noninferiority trial, and treatments were equivalent.

If a nonsignificant safety primary outcome (ie, the experimental drug had no more adverse effects than the

comparator) was reported as nonprimary in the article, this was not considered as a difference favoring significant outcomes. If the article contained no data for registered primary outcomes, the influence of differences could not be assessed.

2.7. Statistical analysis

Descriptive statistics were used to describe included manuscripts (data presented as frequencies and percentages). We used correlation and regression analyses (univariate and multivariate) to test the relation between manuscript rejection and differences between registered and reported trial information. First, the association between publication status and differences between registered and reported data and timing of registration was analyzed using Pearson chi-square tests, adjusted for sponsorship. Subsequently, the probability of publication was evaluated with logistic regression. As the sample of manuscripts with primary outcomes in both the registry and the article was relatively small ($n = 226$), of which 60 were published, the number of parameters that could be included in the logistic model was limited. The effects of the three parameters on acceptance status were similar; therefore, they were combined in the composite variable ''difference between registered and reported information (primary outcome or sample size) and/or retrospective registration'' in the regression model. We estimated associations between acceptance (vs. rejection) and trial characteristics with odds ratios (ORs) and 95% confidence intervals (CIs). To control for sponsor type, multivariate logistic regression was used and ORs were calculated. Interaction of the composite variable and sponsorship was evaluated. $P < 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS software (version 20; Chicago, Illinois).

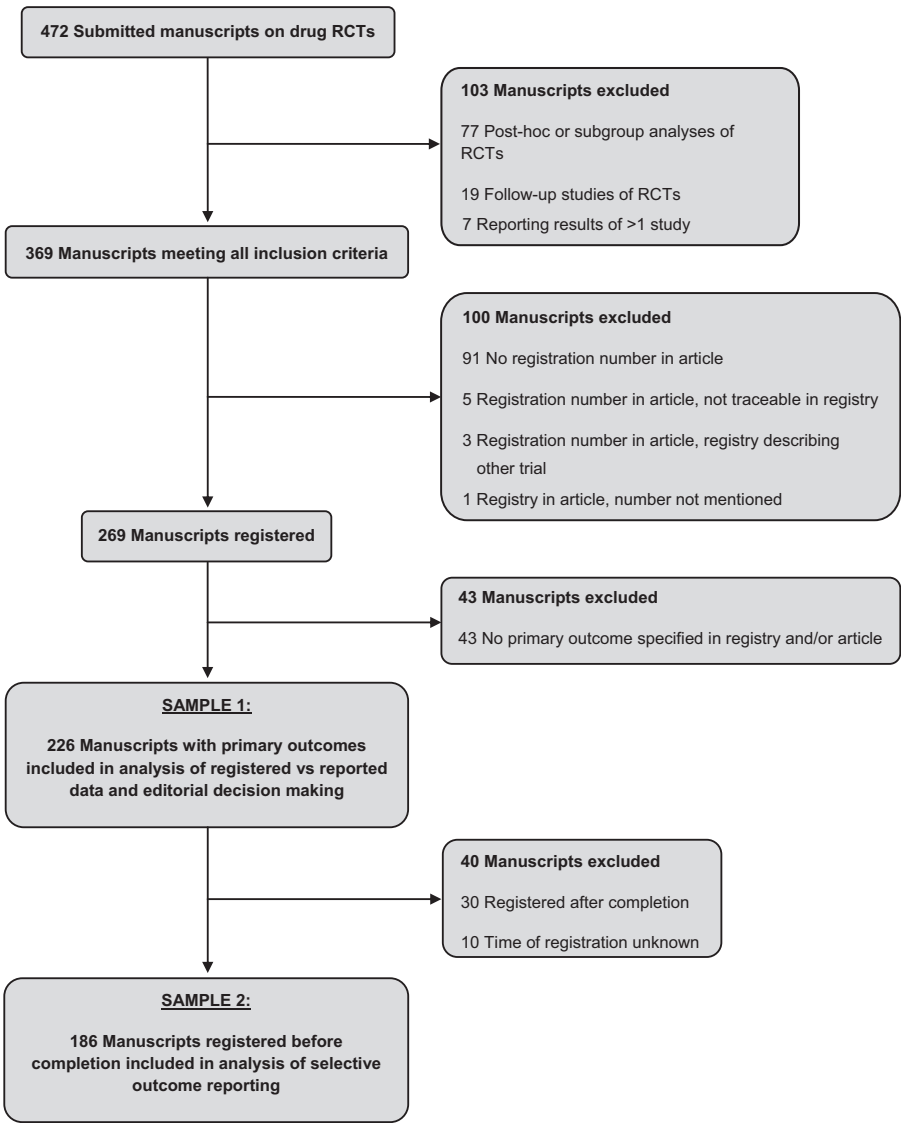

Fig. 1. Flowchart of trial registration and sample selection. RCT, randomized controlled trials.

3. Results

Of the 472 manuscripts on drug RCTs submitted from January 2010 through April 2012, 369 met all inclusion criteria (Fig. 1). Of these, 73 (19.8%) were submitted to BMJ, 36 (9.8%) to Annals of the Rheumatic Diseases, 19 (5.1%) to British Journals of Ophthalmology, 93 (25.2%) to Diabetologia, 59 (16.0%) to Gut, 21 (5.7%) to Heart, 37 (10.0%) to Journal of Hepatology, and 31 (8.4%) to Thorax. Of the 369 manuscripts, 269 (72.9%) were registered, and for 226 (61.2%), a primary outcome was reported in both the article and the registry (sample 1). Of these 226 trials, 186 (82.3%) were registered before trial completion (sample 2).

Of the 269 registered trials, most were registered at ClinicalTrials.gov (n = 178, 66.2%), followed by International Standard Randomized Controlled Trial Number Register (n = 27, 10.0%), Australian New Zealand Clinical Trials Registry (n = 16, 5.9%), and EU Clinical Trials Register (n = 16, 5.9%; Table 1). Most trials were registered before trial start (n = 107, 39.8%) or after the start date but before trial completion (n = 110, 40.9%). However, 40 (14.9%) were registered after completion, and timing of registration was unknown for 12 (4.5%) trials. One primary outcome was reported in the registry for 181 trials (67.3%), whereas 8 (3.0%) reported no primary outcome, 51 (19.0%) had two primary outcomes, and 29 (10.8%) had three to nine primary outcomes. The number of primary outcomes reported in articles varied from 0 to 7, with most trials (n = 188, 69.9%) reporting one primary outcome.

Table 1. Registration characteristics of manuscripts submitted to eight medical journals (n = 269)

Characteristic	Registered manuscripts, *n* (%)
Total manuscripts	269 (100)
Sponsor type	
Nonindustry	114 (42.4)
Industry-supported	85 (31.6)
Industry-sponsored	70 (26.0)
Trial registry	
ClinicalTrials.gov	178 (66.2)
ISRCTN	27 (10.0)
ANZCTR	16 (5.9)
EU-CTR	16 (5.9)
Other	32 (11.9)
Timing of registration	
Before start of trial	107 (39.8)
Before end of trial, after start date	110 (40.9)
After end of trial	40 (14.9)
Unknown (no dates in registry)	12 (4.5)
Number of primary outcomes registered	
0	8 (3.0)
1	181 (67.3)
2	51 (19.0)
3 to 9	29 (10.8)
Number of primary outcomes in article	
0	36 (13.4)
1	188 (69.9)
2	34 (12.6)
3 to 7	11 (4.1)

Abbreviations: ISRCTN, International Standard Randomized Controlled Trial Number Register; ANZCTR, Australian New Zealand Clinical Trials Registry; EU-CTR, EU Clinical Trials Register.

Of the 226 manuscripts with primary outcomes in both the registry and the article (sample 1), 66 (29.2%) had differences between registered and reported primary outcomes, whereas 160 (70.8%) did not (Table 2). Of these, 30 (45.5%) and 60 (37.5%) were outright rejected. Twenty-two manuscripts (33.3%) with primary outcome differences were rejected after peer review, compared with 54 (33.8%) without differences. Eventually, 14 manuscripts (21.2%) with primary outcome differences and 46 (28.8%) without differences were accepted. Overall, the pattern of editorial decisions was not significantly different for manuscripts with or without changed primary outcomes (P = 0.418). Differences between registered and reported sample sizes (ie, sample size in the manuscript smaller than 75% of the anticipated enrollment specified in the registry) were found for 50 manuscripts (22.4%), whereas 173 (77.6%) had no differences (Table 2). Of these, 19 (38.0%) and 71 (41.0%) were outright rejected. Twenty-one manuscripts (42.0%) with sample size differences were rejected after review, compared with 53 (30.6%) without differences. Ten (20.0%) manuscripts with sample size differences and 49 (28.3%) without differences were published. Overall publication status was not significantly different based on sample sizes differences (P = 0.271).

For 132 (58.4%) of 226 manuscripts, timing of registration was retrospective (ie, after trial start date) or unknown, whereas 94 (41.6%) were prospectively registered (Table 2). Of these, 59 (44.7%) and 31 (33.0%) were outright rejected. Forty-three retrospectively registered trials (32.6%) were rejected after review, compared with 33 prospectively registered trials (35.1%). Eventually, 30 (22.7%) retrospectively and 30 (31.9%) prospectively registered manuscripts were accepted. Overall publication status did not significantly differ by timing of registration (P = 0.154). With regard to the composite variable (“difference between registered and reported information and/or retrospective registration”), 175 trials (77.4%) had a discrepancy and/or were retrospectively registered, whereas 51 (22.6%) did not (Table 2). Of these, 75 (42.9%) and 15 (29.4%) were outright rejected. Sixty-one manuscripts (34.9%) with differences and/or retrospective registration were rejected after review, compared with 15 (29.4%) prospectively registered without differences; 39 (22.3%) and 21 (41.2%) manuscripts were eventually accepted, respectively. The overall publication status was significantly associated with the composite variable (P = 0.024).

Of the nonindustry trials (n = 89), 31 (34.8%) had primary outcome differences, compared with 23 (31.5%) of the trials that were supported by industry (n = 73) and 12 (18.8%) of the industry-sponsored trials (n = 64;

Table 2. Publication status of registered manuscripts in relation to differences between registered and reported trial information and timing of registration (n = 226)

		No differences prospective registration, *n* (%)				Differences retrospective registration, *n* (%)				
		N	Outright rejected	Rejected after peer review	Published	*N*	Outright rejected	Rejected after peer review	Published	*P*-value χ^2-test
Total manuscripts (n = 226)	Primary outcome	160	60 (37.5)	54 (33.8)	46 (28.8)	66	30 (45.5)	22 (33.3)	14 (21.2)	0.418
	Sample size[a]	173	71 (41.0)	53 (30.6)	49 (28.3)	50	19 (38.0)	21 (42.0)	10 (20.0)	0.271
	Timing of registration	94	31 (33.0)	33 (35.1)	30 (31.9)	132	59 (44.7)	43 (32.6)	30 (22.7)	0.154
	Composite variable[b]	51	15 (29.4)	15 (29.4)	21 (41.2)	175	75 (42.9)	61 (34.9)	39 (22.3)	0.024
Sponsor type										
Nonindustry (n = 89)	Primary outcome	58	27 (46.6)	20 (34.5)	11 (19.0)	31	17 (54.8)	11 (35.5)	3 (9.7)	
	Sample size[a]	68	35 (51.5)	23 (33.8)	10 (14.7)	19	9 (47.4)	6 (31.6)	4 (21.1)	
	Timing of registration	30	12 (40.0)	12 (40.0)	6 (20.0)	59	32 (54.2)	19 (32.2)	8 (13.6)	
	Composite variable	14	5 (35.7)	4 (28.6)	5 (35.7)	75	39 (52.0)	27 (36.0)	9 (12.0)	
Industry-supported (n = 73)	Primary outcome	50	22 (44.0)	20 (40.0)	8 (16.0)	23	9 (39.1)	8 (34.8)	6 (26.1)	
	Sample size	51	24 (47.1)	16 (31.4)	11 (21.6)	22	7 (31.8)	12 (54.5)	3 (13.6)	
	Timing of registration	28	11 (39.3)	13 (46.4)	4 (14.3)	45	20 (44.4)	15 (33.3)	10 (22.2)	
	Composite variable	13	5 (38.5)	7 (53.8)	1 (7.7)	60	26 (43.3)	21 (35.0)	13 (21.7)	
Industry-sponsored (n = 64)	Primary outcome	52	11 (21.2)	14 (26.9)	27 (51.9)	12	4 (33.3)	3 (25.0)	5 (41.7)	
	Sample size[a]	54	12 (22.2)	14 (25.9)	28 (51.9)	9	3 (33.3)	3 (33.3)	3 (33.3)	
	Timing of registration	36	8 (22.2)	8 (22.2)	20 (55.6)	28	7 (25.0)	9 (32.1)	12 (42.9)	
	Composite variable	24	5 (20.8)	4 (16.7)	15 (62.5)	40	10 (25.0)	13 (32.5)	17 (42.5)	

Abbreviation: *N*, number of submitted manuscripts.

P-values were calculated using Pearson chi-square tests adjusted for sponsor type.

[a] Three manuscripts (two nonindustry and one industry-sponsored) reported no sample size in the registry.

[b] The composite variable is defined as ''difference between registered and reported information and/or retrospective registration.''

Table 2). Sample size differences were found for 19 nonindustry trials (21.8%), 22 industry-supported trials (30.1%), and 9 industry-sponsored trials (14.3%). Industry-sponsored trials were less often retrospectively registered (43.8%) than industry-supported (61.6%) and nonindustry trials (66.3%).

In the univariate analysis, the effects found for primary outcome differences, sample size differences, and timing of registration were similar (Table 3). The composite variable ''difference between registered and reported information and/or retrospective registration'' was significantly associated with a decreased chance of acceptance (OR 0.41; 95% CI: 0.21, 0.79). After adjustment for sponsor type in the multivariate analysis, the composite variable was no longer significantly associated with publication, although the direction of the effect was equal to the univariate analysis (OR 0.56; 95% CI: 0.27, 1.13). There was no interaction of the composite variable and sponsor type (P = 0.122).

Among 66 of 226 manuscripts (29.2%) for which primary outcome differences were detected, 21 articles had two reasons for a difference in primary outcomes (Table 4). Differences most often consisted of a registered primary outcome that was reported as a nonprimary outcome in the article (34 of 226, 15.0%), followed by introduction of a new primary outcome in the article (22 of 226, 9.7%). Among 186 of 226 trials (82.3%) that were registered before completion (sample 2), 49 had primary outcome differences. Twenty-four of 49 manuscripts (49.0%) had differences that favored statistically significant outcomes.

4. Discussion

In this study, we focused on the role of registered trial information in editorial decision making and investigated whether differences between trial characteristics specified in registries and those reported in submitted manuscripts were associated with the chance of subsequent publication.

For almost 30% (66 of 226) of submitted manuscripts on drug RCTs, we found differences between primary outcomes in registries and articles. The chance of rejection after initial editorial screening or peer review was not substantially different between trials with or without primary outcome differences. Eventually, 21.2% of manuscripts with differences vs. 28.8% of those without differences were accepted. Interestingly, the proportion of submitted manuscripts with primary outcome differences was comparable to that found in previous studies, which included only published articles [8,10,11,13]. More than 20% (50 of 223) of the manuscripts reported sample sizes smaller than 75% of the enrollment specified in the registry. The influence of this difference on rejection rates after initial screening or peer review was modest. Acceptance rates for trials with and without sample size differences were 20.0% vs. 28.3%, respectively. For almost 60% (132 of 226) of the trials, timing of registration was retrospective or unknown. Publication status did not significantly differ by timing of registration, and 22.7% of the retrospectively registered trials vs. 31.9% of those registered prospectively were accepted. The univariate analysis indicated that the composite variable ''difference between registered and reported information and/or retrospective registration'' was

Table 3. Characteristics of registered manuscripts and their association with publication (accepted vs. all rejected) (n = 226)

Characteristic	Total n (%)	Published n (%[a])	OR (95% CI) univariate
Total manuscripts	226 (100)	60 (26.5)	
Different primary outcome in registry and article			
No	160 (70.8)	46 (28.8)	1.00
Yes	66 (29.2)	14 (21.2)	0.67 (0.34, 1.32)
Different sample size in registry and article[b]			
Sample size article ≥75% of registered sample size	173 (77.6)	49 (28.3)	1.00
Sample size article <75% of registered sample size	50 (22.4)	10 (20.0)	0.63 (0.29, 1.36)
Timing of registration			
Prospective	94 (41.6)	30 (31.9)	1.00
Retrospective or unknown	132 (58.4)	30 (22.7)	0.63 (0.35, 1.14)
Difference between registered and reported information and/or retrospective registration			
No	51 (22.6)	21 (41.2)	1.00
Yes	175 (77.4)	39 (22.3)	0.41 (0.21, 0.79)
Sponsor type			
Nonindustry	89 (39.4)	14 (15.7)	1.00
Industry-supported	73 (32.3)	14 (19.2)	1.27 (0.56, 2.87)
Industry-sponsored	64 (28.3)	32 (50.0)	5.36 (2.53, 11.37)
			OR (95% CI) Multivariate
Difference between registered and reported information and/or retrospective registration			
No			1.00
Yes			0.56 (0.27, 1.13)
Sponsor type			
Nonindustry			1.00
Industry-supported			1.26 (0.55, 2.85)
Industry-sponsored			4.80 (2.23, 10.31)

Abbreviations: OR, odds ratio; CI, confidence interval.

[a] Percentage of row category that was accepted for publication.

[b] Three manuscripts reported no sample size in the registry. ''Sponsor type'' and ''Difference between registered and reported information and/or retrospective registration'' were included in the multivariate model.

associated with a decreased chance of publication, although this association was not significant after adjusting for sponsor type.

Table 4. Type of differences between registered and reported primary outcomes (n = 226) and selective outcome reporting (n = 186)

	Registered manuscripts, n (%)
Total manuscripts	226 (100)
Different primary outcome in registry and article	66 (29.2)
Type of difference[a]	
Registered primary outcome defined as nonprimary outcome in article	34 (15.0)
Registered primary outcome omitted in article	14 (6.2)
New primary outcome introduced in article	22 (9.7)
Primary outcome in article described as secondary outcome in registry	12 (5.3)
Different timing of assessment of primary outcome	5 (2.2)
Total manuscripts registered before trial completion	186 (82.3)
Difference favoring statistically significant outcomes	49[b]
Yes	24 (49.0)
No	15 (30.6)
Impossible to conclude	10 (20.4)

[a] Twenty-one articles had two reasons for difference in primary outcome. Therefore, the total % of type of differences is >29.2%.

[b] Of 186 trials registered before completion, 49 had differences between registered and reported primary outcomes.

Industry-sponsored trials less often had primary outcome and sample size differences than nonindustry or industry-supported trials. This corresponds to findings of a recent study that examined trials submitted to a Dutch research ethics committee indicating that nonindustry trials had significantly more problems in recruiting the required number of subjects than studies initiated by pharmaceutical companies [21]. Trials not including the required number of subjects may have lower chances of meeting the study objectives, and subjects may be unnecessarily exposed to risks and burdens [21,22]. In contrast, we found that only 5.8% (13 of 223) of the manuscripts reported sample sizes larger than 125% of the enrollment specified in the registry.

For manuscripts that were registered before trial completion, we found that primary outcome differences favored statistically significant results in almost 50% (24 of 49) of the manuscripts. This number lies between the proportions reported in previous studies [8,9]. Our study sample was too small to determine whether selective outcome reporting in favor of significant outcomes was associated with sponsor type.

In agreement with previous studies, approximately a quarter of the trials were not registered [8,9,13,23]. Industry-sponsored and industry-supported trials were more often registered than nonindustry trials. Both the timing and quality of registration should be improved, as only 40% of

the trials were prospectively registered and primary outcomes or sample sizes were missing for several trials. Similar findings regarding the timing and accuracy of registration have previously been shown, and investigators have emphasized that without adequate registration, the potential to address selective publication is limited [24−26].

This study is strengthened by the inclusion of submitted manuscripts, instead of only published articles [8−13]. By including both rejected and accepted articles, we were able to evaluate the role of registered information in editorial decision making. Furthermore, as we selected manuscripts submitted from 2010 to 2012, the number of trials that started enrollment before the implementation date of the ICMJE policy on prospective registration (ie, July 1, 2005) was most likely lower than in previous studies including trials published in earlier years [8−11].

This study has some limitations. We determined trial registration by checking whether authors reported registering their trial and included a registration number. We have not contacted authors or searched registries to identify trial records if no registration number was reported. We compared registered and reported primary outcomes and sample sizes, although differences may also be common for other trial characteristics including secondary outcomes, eligibility criteria, and trial interventions [10,11] and for results and adverse events reported in the ClinicalTrials.gov results database [27,28]. In addition, it could be argued that sample size and primary outcome differences are not completely comparable. Differences between registered and reported sample sizes may reflect problematic recruitment and may not necessarily constitute a reporting quality issue as with changed primary outcomes.

Furthermore, trial protocol amendments that occur during the course of a trial, after initial registration, may not always be accurately reported in the registry. This may in part explain the observed difference among industry-sponsored trials and those with other funding sources regarding the extent of differences between registered and reported information. Through better administrative support, registered information may be more adequately updated for industry-sponsored trials in case of protocol amendments [19].

Finally, although all journals required trial registration, there may be variation among journals in how strictly this policy is being enforced. Some journals may insist that registered information and the timing of registration are verified as part of an initial check of submitted articles, whereas others may do little to assess whether authors comply with requirements [14]. Overall, we found that rejection rates for manuscripts that were retrospectively registered or had primary outcome or sample size differences were not substantially increased, but it was not possible to assess for individual journals whether they actually only considered prospectively registered manuscripts without unacknowledged differences between registered and reported information. A survey among editors may provide more insight.

Although introduction of the ICMJE requirement of prospective trial registration in 2005 led to a large increase in the number of trial registrations [29], our study and prior research indicate that editors and reviewers do not take full advantage of the possibilities provided by registration [8,9,14,15]. Although editors and reviewers who evaluated manuscripts included in this study had the opportunity to identify changes to trial characteristics and address selective outcome reporting, we found inconsistencies between registered and reported information among articles that were accepted for publication. The consistency between articles and registries should be routinely and thoroughly checked by journal staff to identify any changes. If necessary, editors should require explanations from authors which could be explicitly reported in published articles.

In conclusion, differences between trial information specified in registries and that reported in submitted manuscripts were not a decisive factor for rejection after initial editorial screening or after peer review. Editors should assess the consistency between registries and articles to address selective reporting and improve the quality of the publication process.

Acknowledgments

The authors thank BMJ, Annals of the Rheumatic Diseases, British Journal of Ophthalmology, Gut, Heart, Thorax, Diabetologia, and Journal of Hepatology for participating in this study. The authors are grateful to Gerard Rongen (Radboud University Medical Center) for reviewing and commenting on the content of this manuscript.

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