European Journal of Orthodontics, 2018, 1–6
doi:10.1093/ejo/cjy046

Original article

Outcome reporting discrepancies between trial entries and published final reports of orthodontic randomized controlled trials

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Summary

Background/Objectives: The aim of this study was to identify outcome-related discrepancies between registry trial entries and final published reports in orthodontic randomized controlled trials (RCTs). The percentage of registered orthodontic RCTs was also recorded.

Materials/Method: Five trial registries, ClinicalTrials.gov (https://clinicaltrials.gov/), International Standard Randomised Controlled Trial Number registry (http://www.isrctn.com/), European Union Clinical Trials Register (https://www.clinicaltrialsregister.eu/), Australia New Zealand Clinical Trials Registry (http://www.anzctr.org.au/) and Clinical Trials Registry of India (www.ctri.nic.in/) were searched up to April 2018 in order to identify completed orthodontic RCTs. The unique trial identifier, the title and authors name were used to search for publications based on entries within Google (https://www.google.com), Google Scholar (https://scholar.google.gr/) and MEDLINE via PubMed (https://www.ncbi.nlm.nih.gov/pubmed/). Outcome reporting discrepancies and a number of other entry/publication characteristics were recorded including timing of registration, type of journal/publication, significance of the primary outcome in the final report. The number of trials registered among the total number of published RCTs in orthodontics was recorded within the time span assessed.

Results: One hundred and twenty-four entries were identified for completed orthodontic RCTs, whereas 53 of those were related to published final reports. Outcome reporting discrepancies were ascertained for 47 per cent of publications (n = 2 5); discrepancies were more prevalent for non-primary outcomes (n = 21, 40 per cent). Only 16 per cent of the published orthodontic RCTs had been registered.

Limitations: Only a subset of trial entries were assessed as these were related to publication records.

Conclusions/Implications: Registration of clinical trials in orthodontics remains far from universal. A significant level of outcome reporting discrepancy was observed within this subset of registered trials.

Introduction

Reporting bias, an umbrella term for reporting 'misconduct', has been related to preferential presentation of research findings based on the direction of the results, making them more attractive for readers and journal editors and potentially promoting prompt and more certain publication (1, 2). Therefore, negative findings may be intentionally withheld from publication, whereas positive or statistically significant results are given priority. In addition, there is abundant evidence on the existence of discrepancies between pre-specified and published trial outcomes, selective publication of subgroup analyses or analyses based on specific time-points. The importance or priority of certain outcomes may also be downgraded or upgraded *post hoc* while others might be selectively promoted (3–9).

To overcome these problems, registration of clinical trials and pre-publication of trial protocols have been suggested. This approach ensures transparency and clarity of outcome reporting and identification of inconsistencies between initial trial entries or study protocols and final results (7, 8), in an attempt to promote transparency, reduce reporting bias and provide more valid evidence for clinical decision-making. Moreover, the International Committee of Medical Journal Editors has advocated trial pre-registration before considering a study for publication within the related member journals (10). Trial pre-registration is also known to mitigate against late publication or even non-publication of trials (11).

Two of the better known online trial repositories are ClinicalTrials.gov (https://clinicaltrials.gov/; US National Library of Medicine) and the International Standard Randomised Controlled Trial Number registry (ISRCTN; http://www.isrctn.com/) that allow entry of details such as specific study objectives including primary and secondary outcomes, information on patient enrolment, study design, eligibility criteria and others. Other lesser known registries include the EU Clinical Trials Register, the ANZCTR (Australia New Zealand Clinical Trials Registry) and the Clinical Trials Registry of India (CTRI). Entries may be updated to reflect progress including participant enrolment and protocol amendments.

Orthodontic research is not immune to reporting limitations (12, 13); however, the frequency of outcome reporting discrepancies within orthodontic trials has not yet been assessed. Therefore, the aim of this study was to identify final reports of registered and completed orthodontic randomized controlled trials (RCTs) and to assess the prevalence of reporting discrepancies between initial trial registry entries and related publications. In addition, the association between discrepancies and a number of trial characteristics including type of registry, study design, timing of registration and funding were assessed.

Materials and methods

Five trial registries were searched for completed registered RCTs in orthodontics up to April 2018: the ClinicalTrials.gov (https://clinicaltrials.gov/) by the US National Library of Medicine, ISRCTN (http://www.isrctn.com/), the EU Clinical Trials Register, the ANZCTR and the CTRI. The search term used for identification of trial entries was 'orthodontic'. Non-randomized or non-orthodontic trials were automatically excluded. Subsequently, the unique identifier assigned to each trial entry within the registry as well as the title and author's name were searched on an Internet search engine (https://www.google.com), google scholar (https://scholar.google.gr/) and using MEDLINE via PubMed (https://www.ncbi.nlm.nih.gov/pubmed/) for possible publication originating from the trial entries. Duplicate publications for one entry were considered as a single trial and no time restriction was set. Authors of unidentified published reports of trial protocols were contacted by email to ascertain any missed publications or to ask for unpublished results of their research.

Data from eligible studies were recorded independently by one author and confirmed by a second after initial calibration on 10 articles. Unweighted kappa statistic was conducted on 15 studies after initial calibration for identification of outcome discrepancies within both primary and non-primary outcomes. Disagreements were resolved through discussion or consultation with a third author. Bespoke pre-piloted and standardized data extraction forms were used. Information was obtained on the following: year of protocol/publication, timing of registration (i.e. prospective or retrospective), type of journal, number of authors, study design, funding and statistical significance of the primary outcome on the published report.

The main focus was to record whether discrepancies existed between trial entries and final reports with respect to primary or non-primary outcomes declared. Identification of outcome type was based on recording of outcomes within the trial repositories (primary, secondary/non-primary). Changes in outcomes including addition, removal/omission or change in definition of outcomes, downgrade and upgrade of outcomes from primary to secondary and *vice versa* were also recorded. In addition, discrepancies in sample sizes and participant enrolment were recorded. MEDLINE via PubMed was searched for published orthodontic RCTs using the terms '(orthodontic) AND (randomized OR randomised)' in an attempt to estimate the fraction of trials registered among the total number of published RCTs. The date of the first published and registered study was used as a lower time limit for the search.

Descriptive statistics were calculated for eligible studies on the variables of interest, namely the timing of registration, time lapse between registration and publication, type of journal/publication, study design, number of researchers involved, funding, significance of the primary outcome, and registry used. Data were recorded on reporting discrepancies of primary or non-primary outcomes along with the nature or type of discrepancy or sample sizes involved. Cross-tabulations were undertaken to investigate possible associations between outcome discrepancies and variables of interest. The level of statistical significance was pre-specified at $P < 0.05$. Statistical analyses were performed with STATA version 15.1 software (StataCorp, College Station, Texas, USA).

Results

The initial search yielded a total of 192 trial entries. Reliability assessment yielded an unweighted kappa of 0.76 for primary outcomes and 0.79 for non-primary, reflecting substantial agreement between the two investigators. In total, 124 entries for completed orthodontic RCTs were identified in all five registries (Supplementary Material). Of these, 53 were eligible for inclusion (43 per cent) as published final reports of the trials were identified (Figure 1). Four of these were retrieved after personal email contact with the authors. The results of efforts to gather information on initially unidentified published reports are displayed in Figure 2.

The majority of trials with retrieved final reports were registered on clinicaltrials.gov (n = 32, 60 per cent). The vast majority of these were retrospectively registered (n = 37, 70 per cent). Final reports of original entries were mostly found in orthodontic journals (n = 33, 62 per cent), whereas 5 (9 per cent) were published as theses, in isolation. A statistically significant result was reported for most of the studies in the final report (n = 36, 68 per cent), whereas the involvement of companies/industry in funding was seen in nearly a quarter of the trials (n = 11, 21 per cent%) (Table 1).

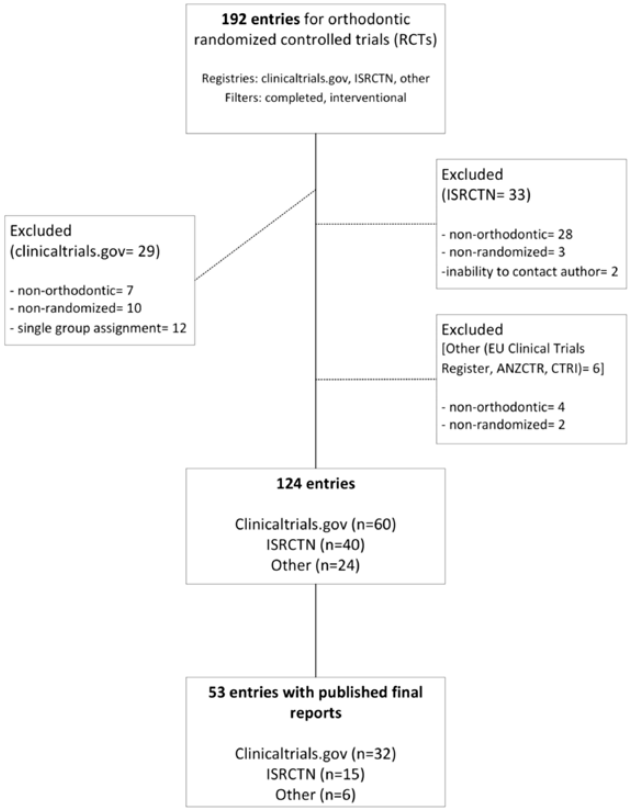

Figure 1. Flow chart of study selection.

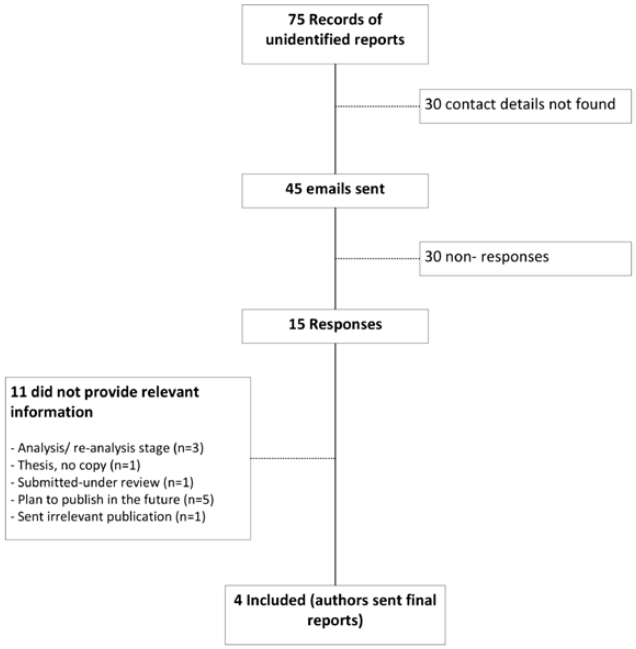

Figure 2. Diagram of authors' responses in unidentified publications of registered protocols after initial search.

The time lapse between registration and final publication commonly ranged from 1 to 4 years (n = 30, 57 per cent), whereas 21 per cent (n = 11) of publications required 4 or more years to appear in press. One-fifth of reports (n = 12, 22 per cent) revealed publication within a year or up to 4 years before registration denoting retrospective registration of the trials. Association between outcome reporting discrepancies or otherwise could be established only for the type of study design, with reporting discrepancies being more prevalent in parallel-group studies (n = 24/42, 57 per cent, P = 0.02); however, other designs were under-represented in our sample (Table 1).

Outcome reporting discrepancies for either primary or non-primary outcomes were identified for nearly half of the included studies (n = 25, 47 per cent) and the distribution of discrepancies was similar for both major repositories, namely the clinicaltrials.gov and the ISRCTN. Twenty-one per cent of the studies (n = 11) presented a discrepancy for the primary outcome, whereas a greater proportion (n = 21, 40 per cent) involved discrepancy in reporting of a non-primary outcome. Discrepancies in reporting of participant enrolment and final sample sizes were seen in 47 per cent (n = 25) of the reports (Table 2; Figure 3). The most frequent discrepancies related to primary outcomes were omission or downgrade to non-primary (n = 6, 55 per cent), and outcome addition or upgrade from non-primary to primary (n = 4, 36 per cent). Similarly, for the non-primary outcomes, type of discrepancies included outcome addition (n = 10, 48 per cent) or omission (n = 9, 43 per cent; Table 3).

Finally, the search for published orthodontic RCTs from 2000 onwards yielded a number of 2151 results. Of those, 336 were recorded as orthodontic RCTs. The percentage of registered orthodontic RCTs was only a small fraction of the actual number of trials published within the period examined (n = 53/336, 16 per cent).

Discussion

Previous research has shown a high prevalence of outcome reporting discrepancies within biomedical research and indeed among journals with high impact factor (4). A similar level of outcome reporting issues are highlighted in this study with almost half of orthodontic studies affected. Furthermore, in keeping with previous research, non-primary outcomes appear to be affected more commonly than primary outcomes in orthodontic research. Although registration of clinical trials is now common to most orthodontic journals and the concepts of research registration and selective reporting are better understood (5, 7), there is a need for practical improvement in these respects. An additional benefit stemming from the transparency offered by protocol trial registration is potential mitigation of publication bias emanating from preference given to positive outcomes by journal editors and reviewers.

The prevalence of selective reporting for primary and non-primary outcomes was 21 per cent and 40 per cent, respectively. The higher preponderance of selective reporting among non-primary outcomes is typical of research in other areas. Specifically, issues related to primary outcomes were observed within 18 per cent of studies in high-impact journals (4), while figures as high as 49 per cent have been recorded in surgical research for non-primary outcomes (7). This pattern reflects better handling of primary outcomes; notwithstanding this, the problem of undertaken additional unplanned secondary analyses, risking 'data dredging' and spurious positive outcomes is clear. As such, it is important that trial entries and protocols contain explicit description of both primary and non-primary outcomes (14). It is, however, accepted that legitimate changes to clinical trial outcomes may be made during the conduct of research; it is important that the rationale for any modification is outlined within the published report.

Table 1. Frequency distribution of study characteristics with respect to outcome reporting discrepancies (either primary or non-primary) between trial entries and published reports or otherwise (n = 53). International Standard Randomised Controlled Trial Number registry (ISRCTN), European Union (EU), Australia New Zealand Clinical Trials Registry (ANZCTR), Clinical Trials Registry of India (CTRI)

	Overall outcome discrepancy**						
	No		Yes		Total		*P* value
	N	%	*N*	%	*N*	%	
Type of registry							0.78#
clinicaltrials.gov	16	50	16	50	32	100	
ISRCTN	8	53	7	47	15	100	
EU Clinical Trials Register	0	0	0	0	0	0	
ANZCTR	2	50	2	50	4	100	
CTRI	2	100	0	0	2	100	
Timing of registration							0.79*
Prospectively	8	50	8	50	16	100	
Retrospectively	20	54	17	46	37	100	
Study design***							0.02#
Parallel	18	43	24	57	42	100	
Split mouth	5	100	0	0	5	100	
Crossover	4	80	1	20	5	100	
Factorial	1	100	0	0	1	100	
Type of publication							0.50#
Orthodontic journal†	16	48	17	52	33	100	
Other journal	10	67	5	33	15	100	
Thesis	2	40	3	60	5	100	
No. of authors							0.18#
1–3	7	78	2	22	9	100	
4–6	12	43	16	57	28	100	
Over 6	9	56	7	44	16	100	
Statistical significance							0.56*
No	8	47	9	53	17	100	
Yes	20	56	16	44	36	100	
Type of funding							0.32#
University	20	54	17	46	37	100	
Company	7	64	4	36	11	100	
None	1	20	4	80	5	100	
Total	28	53	25	47	53	100	

*chi-square test, # Fisher's exact test

**Discrepancy in either primary, non-primary or both

***The definitions of study designs are as follows: *Parallel:* a type of study where two groups of treatments, A and B are given, so that one group receives only A while another group receives only B; *Split-mouth*: a type of study where two groups of treatments, A and B, are given so that each side of mouth (or quadrant) receives only A while the other receives only B; *Crossover*: a type of study in which subjects receive a sequence of different treatments; *Factorial*: a type of study whose design consists of two or more factors (treatments), each with discrete possible levels and whose subjects take all possible combinations of these levels across all such factors.

†Orthodontic journals included are: Progress in Orthodontics, American Journal of Orthodontics and Dentofacial Orthopedics, The Journal of Indian Orthodontic Society, Seminars in Orthodontics, Journal of Orthodontics, European Journal of Orthodontics, Angle Orthodontist, Journal of Orofacial Orthopaedics, Orthodontics and Craniofacial Research.

Discrepancies between planned and final sample sizes were common with 47 per cent. Again, this figure reflects other biomedical areas, with discrepancies ranging from 45 per cent to 73 per cent in other studies (4, 5, 7). It is important that sample size calculations are present in trial reports and within trial protocols to ensure that sufficient power exists to support clinically meaningful differences by means of statistical analyses (15). It was interesting that the majority of published reports were retrospectively registered with a tangible amount being registered shortly before, or even after publication. This practice denotes a weakness of trial repositories to mitigate issues of selective outcome reporting or publication bias and efforts should be made to promote early and prospective registration of trial protocols in the future.

A possible antidote to issues around selection and reporting of outcomes is the adoption of agreed outcome sets which could be used as a minimum in clinical trials (core outcome sets). Core outcome set development has commenced in orthodontics and is likely to be established within 2–3 years (16). In theory, this practice should not only lead to the measurement of important outcomes but should also mitigate against selective reporting, by ensuring trials report on a minimum agreed group of outcomes. This may well increase the yield from clinical research and ultimately promote better yields from downstream research including systematic reviews. The latter would be of value in view of the pervasion of barren reviews, with just 27 per cent of orthodontic reviews involving meta-analysis and the majority of reviews adjudged to be of either low or very low quality according

Table 2. Breakdown of outcome related and sample size discrepancies between trial entries and final reports according to registry ($n = 53$). Only registries that included entries related to publications are presented. Not applicable (Na)

	Registry				
	Clinicaltrials.gov *N* (%)	ISRCTN *N* (%)	ANZCTR *N* (%)	CTRI *N* (%)	Total *N* (%)
Overall outcome discrepancy					
No	16 (50)	8 (53)	2 (50)	2 (100)	28 (53)
Yes	16 (50)	7 (47)	2 (50)	0 (0)	25 (47)
Primary outcome discrepancy					
No	25 (78)	11 (73)	4 (100)	2 (100)	42 (79)
Yes	7 (22)	4 (27)	0 (0)	0 (0)	11 (21)
Non-primary outcome discrepancy					
Na	8 (25)	8 (53)	0 (0)	1 (50)	17 (32)
No	9 (28)	3 (20)	2 (50)	1 (50)	15 (28)
Yes	15 (47)	4 (27)	2 (50)	0 (0)	21 (40)
Sample size discrepancy					
No	19 (59)	5 (33)	1 (25)	1 (50)	26 (49)
Yes	13 (41)	8 (53)	3 (75)	1 (50)	25 (47)
Unclear	0 (0)	2 (14)	0 (0)	0 (0)	2 (4)
Total	32 (100)	15 (100)	4 (100)	2 (100)	53 (100)

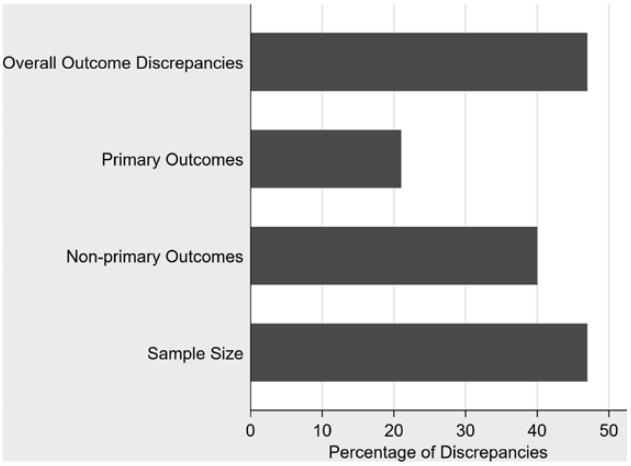

Figure 3. Percentage of discrepancies across registered parameters of randomized controlled trials (RCTs).

Table 3. Breakdown of outcome discrepancies (for both primary and non-primary) according to recorded type of discrepancy

Type of discrepancy	*N*	%
	Primary outcome	
Outcome added or upgraded from non-primary	4	36
Outcome omitted or downgraded to non-primary	6	55
Change in outcome definition	1	9
Total	11	100
	Non-primary outcome	
Outcome added	10	48
Outcome omitted	9	43
Outcome upgraded to primary	2	9
Total	21	100

to GRADE (Grading of Recommendations Assessment, Development and Evaluation) working group tool (17). An additional problem having an impact on the evidence is non-publication of all registered trials, which has actually been confirmed by a recent publication indicating that after 5 years of registration 28 per cent remain unpublished (18).

An inherent limitation of this study is that less than half of the retrieved entries were actually assessed, in view of the absence of publication records. However, this study was performed on five electronic online repositories, thereby attempting to portray a complete picture of registration status of randomized clinical trials in orthodontics. Moreover, the influence of peer review and editorial processes on the level of selective reporting was not recorded, as the final manuscript was only assessed. However, there is evidence that peer review itself possibly tends to have limited effect on the delineation of outcomes (19) with verification of outcomes reliant on the availability of registry entries or trial protocols to peer reviewers. Consequently, novel approaches to alleviate selective reporting may well be required. Journals and editors of major high-impact journals have already adopted submission and publication of protocols on-site and along with original trial reports and this will hopefully become common in a range of medical domains including dentistry in the years to come (20, 21). In addition, public availability and universal access to all protocol versions will facilitate the identification of outcome amendments across subsequent versions of the protocols and the final report (22).

Conclusions

On the basis of the present data, selective reporting appears to be common within orthodontic clinical trials with non-primary outcomes being particularly affected.

Supplementary Material

Supplementary material is available at *European Journal of Orthodontics* online.

Conflict of interest

None declared.

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