



HAL
open science

Nonpublication and Selective Outcome Reporting of Oral Health Trials

Hadrien Diakonoff, G. Khalil, Sébastien Jungo, Jean-Marc Treluyer, Hélène Fron Chabouis, Violaine Smaïl-Faugeron

► **To cite this version:**

Hadrien Diakonoff, G. Khalil, Sébastien Jungo, Jean-Marc Treluyer, Hélène Fron Chabouis, et al.. Nonpublication and Selective Outcome Reporting of Oral Health Trials. *Journal of Dental Research*, 2023, 102 (6), pp.599-607. 10.1177/00220345231158544 . hal-04136668

HAL Id: hal-04136668

<https://hal.science/hal-04136668>

Submitted on 21 Jun 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Nonpublication and Selective Outcome Reporting of Oral Health Trials

H. Diakonoff^{1,2}, G. Khalil³, S. Jungo^{1,4}, J.M. Treluyer^{3,5,6}, H. Fron-Chabouis^{7,8,9}, and V. Smail-Faugeron^{1,3,4}

Abstract

Less than one-quarter of oral health trials are registered in a public registry. However, no study has assessed the extent of study publication and selective outcome reporting bias in the field of oral health. We identified oral health trials registered between 2006 and 2016 in ClinicalTrials.gov. We assessed whether results of early discontinued trials, trials having an unknown status, and completed trials had been published and, among published trials, whether outcomes differed between the registered record and the corresponding publication. We included 1,399 trials, of which 81 (5.8%) were discontinued, 247 (17.7%) had an unknown status, and 1,071 (76.6%) were completed. The registration was prospective for 719 (51.9%) trials. Over half the registered trials were unpublished ($n = 793$, 56.7%). To explore the association between trials publication and characteristics of trials, we performed a multivariate logistic regression analysis. Trials conducted in the United States ($P = 0.003$) or Brazil ($P < 0.001$) were associated with increased odds of publication, whereas trials registered prospectively ($P = 0.001$) and industry-sponsored trials ($P = 0.02$) were associated with decreased odds. Among the 479 published trials with completed status, the primary outcomes of 215 (44.9%) articles differed from that registered. Major discrepancies consisted of the introduction of a new primary outcome in the published article (196 [91.2%]) and the transformation of a registered secondary outcome into a primary outcome (112 [52.1%]). In the remaining 264 (55.1%) trials, primary outcomes did not differ from that registered, but 141 (53.4%) had been registered retrospectively. Our study highlights the high rate of nonpublication and selective outcome reporting in the field of oral health. These results could alert sponsors, funders, authors of systematic reviews, and the oral health research community at large to combat the nondisclosure of trial results.

Keywords: clinical protocols, randomized controlled trial, publication bias, humans, registries, bias

Introduction

Meta-analyses of randomized controlled trials (RCTs) are considered the gold standard for making informed decisions about which treatment is best. They combine the findings of several RCTs and may overcome the limitations of individual RCTs (Egger et al. 2003). However, a vast number of RCTs remain unpublished, making the conclusions of a meta-analysis misleading (Song et al. 2010). Indeed, investigators, sponsors, or editors tend not to publish results of either full registered RCTs or specific outcomes only because of the direction, magnitude, or statistical significance of the results (Montori et al. 2008). Reporting bias, including nonpublication and selective outcome reporting (SOR), is a recognized cause of waste in biomedical research (Macleod et al. 2014). SOR is defined as the selection of a subset of the original variables recorded, on the basis of the results, for inclusion in publication of trials (Williamson et al. 2005). SOR often favors statistically significant results (Chan et al. 2004). Thus, SOR should compromise the validity of a trial and subsequent meta-analysis. Prospective registration of RCTs represents the best solution to reporting bias if journals or reviewers check registers before publication (Sim et al. 2006). Although trial registration does not ensure that all trial results will be published, it is a key factor in reducing reporting bias (Ioannidis et al. 2014). Thus, the International

Committee of Medical Journal Editors (ICMJE) required registration of all RCTs before enrollment of the first patient in September 2004 and asked for detailed information about trial design in 2005 (Trofimova and Bluemke 2022).

¹Université Paris Cité, Faculté de santé, UFR d'odontologie, Paris, France

²Institut droit et santé, INSERM UMR_S 1145, Université de Paris, Paris, France

³EA7323 Pediatric and Perinatal Drug Evaluation and Pharmacology, Université de Paris, Paris, France

⁴Dental Medicine Department, AP-HP, Bretonneau Hospital, Paris, France

⁵Pediatric Intensive Care Unit, Necker-Enfants malades Hospital, AP-HP, Paris, France

⁶Clinical Research Unit Paris Descartes—CIC P1419, Necker-Enfants malades Hospital, AP-HP, Paris, France

⁷Faculté d'odontologie, Université de Bordeaux 2, Bordeaux, France

⁸Laboratoire ICMCB, UMR5026 (CNRS), Pessac, France

⁹Service de médecine et chirurgie bucco-dentaire, hôpital Saint André, CHU, Bordeaux, France

A supplemental appendix to this article is available online.

Corresponding Author:

V. Smail-Faugeron, Dental Medicine Department, AP-HP, Bretonneau Hospital, 1 rue Maurice Arnoux, Paris, 75184, France.

Email: violaine.smail-faugeron@parisdescartes.fr

In a previous study, we found that only 23% of a sample of 317 RCTs with results published in oral health journals were registered in a public register, and among those, 91% were registered retrospectively (Smaïl-Faugeron et al. 2015). Moreover, studies in specific dental areas such as endodontics, orthodontics, and implantology found high rates of SOR (Koufatzidou et al. 2019; Sendyk et al. 2019; Tzanetakakis and Koletsi 2021). These results suggest that the risk of reporting bias is high in the field of oral health in general. However, no study has assessed the extent of study publication bias and SOR bias in the field of oral health in general.

Our objective was to assess 1) how many RCTs registered in ClinicalTrials.gov were discontinued early (i.e., before all intended participants were enrolled or before the study was completed), 2) how many RCTs registered in ClinicalTrials.gov were unpublished, and 3) among published results, how many RCTs showed discrepancies in the analyzed primary outcomes between registered records and published articles.

Methods

Selection of RCTs

We searched ClinicalTrials.gov because it is the largest register and comprises most oral health trial protocols (71%) (Zarin et al. 2011; Smaïl-Faugeron et al. 2015). We did not consider trials registered after 2016 to allow an elapsed time of at least 5 y for trial completion and publication (Ioannidis 1998). Trials recruiting patients before 2006 were excluded because the 2004 ICMJE statement had defined July 1, 2005, as a key date for prospective trial registration (Waldman et al. 2008). Two independent authors selected RCTs registered in the category “Mouth and Tooth Diseases” on ClinicalTrials.gov (searched on January 7, 2022). We read all records, included registered RCTs with a closed recruitment status, and excluded any ongoing RCTs. We selected trials if the “allocation” was “randomized” in the field “study design” of the register. Any disagreements were resolved by discussion.

Characteristics of RCTs

For each RCT, 2 authors independently and in duplicate assessed the following characteristics. First, we recorded the unique trial identifying number assigned by the register. Second, we assessed the dental specialty and the study design (i.e., parallel arm, cluster, crossover, or split mouth). Third, we assessed whether the registration was prospective or retrospective, that is, before or after the date of first enrollment. Prospective registration was defined as registration occurring before the date of first enrollment. We distinguished trials registered within 6 mo of the first enrollment from those registered afterward. Fourth, we assessed changes in the protocol by listing initial and current primary outcomes registered. Initial outcomes were outcomes registered on the date of trial registration. Current outcomes were the last outcomes accessible on the registry (modified from initial outcomes); for those, we

retrieved the date of modification. We also listed secondary outcomes registered. Fifth, we assessed the availability of outcome results on ClinicalTrials.gov.

Finally, we reported the planned sample size, included the date on which data collection was completed for all primary outcome measures, the type of investigator (investigator-initiated trial vs. industry-sponsored trial), and listed location countries where research was conducted.

Assessment of Early Discontinued RCTs

We defined a discontinued RCT in ClinicalTrials.gov if the current recruitment status was “terminated,” “suspended,” or “withdrawn.” We tried to contact investigators by email to inquire about the reason for a discontinued status—when there was no explanation on clinicaltrials.gov—and when the recruitment status was unknown. An email reminder was sent after 10 d.

Assessment of Unpublished RCTs

We assessed whether the results of early discontinued trials, trials having an unknown status, and completed trials had been published. We considered an RCT as published when a journal had published a peer-reviewed manuscript, either online or in print. To identify the publication of results, we checked each trial record on ClinicalTrials.gov for links to publications. Second, for register entries that did not include a link to the publication, we searched PubMed, Google Scholar, and Embase using trial registration numbers (Zarin et al. 2005). Third, for RCTs for which no published results were identified, we searched PubMed, Google Scholar, and Embase by using relevant keywords based on the title, authors’ names or participants, experimental intervention, and comparator (Grobler et al. 2008). If more than 1 publication corresponded to a trial, we selected the publication whose primary outcome matched the 1 recorded. When no publication was identified using the described search strategy, we attempted to contact investigators by email (with a reminder after 10 d). If the investigator indicated that the results were unpublished, we asked for the reason.

Assessment of SOR

Among published RCTs, we compared the number and the definition of primary outcomes between the registered record and the corresponding publication. We defined discrepancies according to the modified classification of Chan et al. (2004) (Appendix Table 1).

Primary outcomes were those that were explicitly reported as such in the published article. If none was explicitly reported, we used the outcome stated in the sample size estimation. If none was explicitly identified in the text or the sample size calculation, we used the first outcome reported in the results section. Two review authors independently collected the data in a data extraction form that had been pilot-tested with 50 articles and modified accordingly. Disagreements were resolved by discussion.

Data Synthesis and Analysis

Characteristics of trials were described using frequencies (percentages) for qualitative variables and median (interquartile range, minimum–maximum) for quantitative variables. When appropriate, the Mann–Whitney U test or Kruskal–Wallis test was used for quantitative variables and Fisher exact test for binary variables, to compare differences between published and unpublished trials registered in ClinicalTrials.gov. To explore the association between trial publication and trial characteristics, on the one hand, and SOR and trial characteristics, on the other hand, univariate and multivariate logistic regression analyses were performed. Variables with $P \leq 0.2$ in the univariate analysis were introduced into the multivariate logistic regression analysis. Then, backward stepwise procedures based on the Akaike Information Criterion (AIC) were performed to create reduced multivariate models. For each model, regression diagnostics plots are provided in Appendix Figures 1 to 4. Kaplan–Meier curves for the length of time after the completion date until modification of the initial primary outcome were presented for published and unpublished trials. Analyses involved the use of the R software (R Foundation for Statistical Computing).

Results

Characteristics of Included Studies

The initial search identified 2,046 trials, of which 1,399 were included in the final analysis ($\kappa=0.997$) (Fig. 1). Among the 1,399 included trials, 1,071 (76.6%) were completed, 81 (5.8%) were discontinued, and 247 (17.7%) had an unknown status. Details of characteristics are given in Table 1.

Early Discontinuation

Among the 81 discontinued trials, 48 (59.3%) were terminated, 31 (38.3%) were withdrawn, and 2 (2.5%) were suspended. The most common reasons for discontinuation were poor recruitment ($n=26$, 32.1%), lack of funding or sponsor issues ($n=17$, 20.9%), and termination due to negative interim results ($n=10$, 12.3%). Sixteen (19.8%) trials had team or protocol concerns, and 3 (3.7%) had not started.

Among the 247 trials with an unknown status, we identified contact email addresses for 161 (65.2%) and received replies from 42. The most common reason for this status was poor recruitment ($n=15$, 35.7%). Three (7.1%) trials had not started, 3 (7.1%) were completed but not published (without any reason given), and 6 (14.4%) had team or business concerns. In addition, 15 (35.7%) responded that they had published the results anyway.

Nonpublication

Of 81 discontinued trials and 247 trials with an unknown status, we identified 0 and 125 (50.6%), respectively, as published following searches on electronic databases. Combining

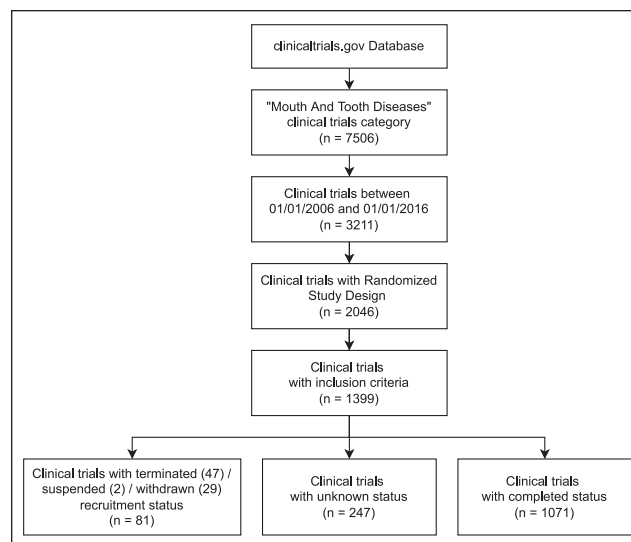


Figure 1. Flowchart of included clinical trials registered in ClinicalTrials.gov.

responses of contacted authors, 201 (61.3%) discontinued trials and trials with an unknown status were unpublished.

Of 1,071 completed trials, we initially identified 472 (44.1%) as published following searches on electronic databases: 162 (34.3%) were found by using the link to the publication provided on ClinicalTrials.gov, 212 (44.9%) by using trial registration numbers provided on ClinicalTrials.gov, and 240 (50.8%) by using relevant keywords. We sought contact email addresses for the remaining 599 (55.9%) unpublished trials, for which 358 email addresses were identified and contacted. Twenty-one (5.9%) replies were received, of which 8 (38%) gave the article reference. The responses identified a further 7 (33.3%) trials as unpublished, with reasons given by the authors. Last, 1 industrial promoter refused to give us the reasons for the nonpublication of 2 clinical trials. Combining these results with published studies found by manual search, we found a total of 592 (55.3%) unpublished completed trials.

In the multivariate analysis, trials conducted in the United States or Brazil were associated with increased odds of publication (1.89 [1.28–2.80] and 2.14 [1.44–3.19], respectively), whereas trials registered prospectively (0.66 [0.52–0.85]) and industry-sponsored trials (0.24 [0.07–0.74]) were associated with decreased odds (Table 2).

The median time from study completion to publication date was 27 mo (interquartile range, 17–44; minimum–maximum, 1–132).

Figure 2 shows that there was no significant difference in the probability of including the initial registered primary outcome between published and unpublished trials.

SOR

Among the 479 published RCTs with completed status, the primary outcomes of 215 articles (44.9%) differed from those

Table 1. Characteristics of Discontinued Trials, Completed Trials, and Trials with an Unknown Status Registered in ClinicalTrials.gov.

Characteristic	Overall Status (n = 1,399)	Discontinued Status (n = 81)	Completed Status (n = 1,071)	Unknown Status (n = 247)	P Value
Dental specialty					
Dental caries	271 (19.4)	11 (13.6)	206 (19.2)	54 (21.9)	<0.001 ^a
Oral diseases and surgery	214 (15.3)	18 (22.2)	156 (14.6)	40 (16.2)	
Oral pain	205 (14.7)	17 (21.0)	159 (14.8)	29 (11.7)	
Orthodontics	56 (4.0)	4 (4.9)	39 (3.6)	13 (5.3)	
Periodontal diseases	507 (36.2)	17 (21.0)	413 (38.6)	77 (31.2)	
Prosthetics	146 (10.4)	14 (17.3)	98 (9.2)	34 (13.8)	
Number of countries					
One country	1,313 (93.9)	81 (100)	1,002 (93.6)	230 (93.1)	0.03 ^b
More than 1 country	86 (6.2)		69 (6.4)	17 (6.9)	
Country					
United States (alone or not)	339 (24.2)	31 (38.3)	289 (27.0)	19 (7.7)	<0.001 ^a
Brazil (alone or not)	181 (12.9)	3 (3.7)	131 (12.2)	47 (19.0)	
Other countries	600 (42.9)	26 (32.1)	442 (41.3)	132 (53.4)	
Not provided	279 (19.9)	21 (25.9)	209 (19.5)	49 (19.8)	
Study design					
Crossover	146 (10.5)	11 (13.9)	113 (10.6)	22 (8.9)	<0.001 ^b
Factorial	33 (2.4)		25 (2.3)	8 (3.3)	
Parallel	1,162 (83.2)	63 (79.7)	893 (83.4)	206 (83.7)	
Single group	15 (1.1)	5 (6.3)		10 (4.1)	
Split mouth	40 (2.9)		40 (3.7)		
Investigator type					
Federal	2 (0.1)		1 (0.1)	1 (0.4)	<0.001 ^b
Individual	2 (0.1)		1 (0.1)	1 (0.4)	
Industry	326 (23.3)	24 (29.6)	281 (26.2)	21 (8.5)	
Network	6 (0.4)		5 (0.5)	1 (0.4)	
National Institutes of Health	3 (0.21)	2 (2.5)	1 (0.1)		
Universities, community-based organizations	1,043 (74.5)	52 (64.2)	773 (72.2)	218 (88.3)	
Government	17 (1.2)	3 (3.7)	9 (0.8)	5 (2.0)	
Enrollment					
>50 participants	641 (47.0)	13 (16.0)	512 (49.4)	116 (47.2)	<0.001 ^a
<50 participants	723 (53.0)	68 (84.0)	525 (50.6)	130 (52.8)	
Results available on ClinicalTrials.gov					
No/not provided	1,097 (78.4)	81 (100)	769 (71.8)	247 (100)	<0.001 ^b
Yes	302 (21.6)		302 (28.2)		
Registration					
Prospectively	720 (51.9)	52 (72.2)	507 (47.3)	161 (66.3)	<0.001 ^a
Retrospectively	666 (48.1)	20 (27.8)	564 (52.7)	82 (33.7)	
Original primary outcome					
Not modified	926 (66.2)	47 (58)	660 (62)	219 (89)	<0.001 ^a
Modified	473 (33.8)	34 (42)	411 (38)	28 (11)	

Data are n (%).

^aP values comparing status are from χ^2 test.

^bP values comparing status are from Fisher's exact test.

registered. Of these articles, 161 (74.9%) had 2 or more reasons for differences in primary outcomes (Appendix Table 2). The discrepancies consisted of the introduction of a new primary outcome in the publication (i.e., a secondary outcome or an absent outcome in the registry that becomes a primary outcome; 196 [91.2%]), omission of the registered primary outcome in the publication (76 [35.3%]), published primary outcome registered as a secondary outcome (112 [52.1%]), a registered primary outcome reported as a secondary outcome in the publication (48 [22.3%]), and timing of assessment that differed between publication and registration (83 [17%]). The sample size differed from that registered for 102 articles (21%). The median number of primary outcomes did not differ from

that registered (median number, 1; minimum–maximum, 0–68 for those registered and 1–11 for those published). The number of published primary outcomes was the same as those registered for 388 RCTs (81%); it was higher for 75 (15.7%) RCTs and smaller for 16 (3.3%) RCTs. There were more discrepancies in outcomes when the initial primary outcome was not modified than when it was (143 [49%] vs. 72 [39%]). Details are given in Table 3. Ninety-two (19%) of published RCTs were prospectively registered and used the initial registered primary outcome as such in the final publication. Outcome modification was more frequent with prospective registration than with retrospective registration (115 [62%] vs. 71 [38%]) (Appendix Table 3).

Table 2. Characteristics of Published and Unpublished Trials Registered with ClinicalTrials.gov.

Characteristic	Overall Status (n = 1,399), n (%)	Nonpublication (n = 795), n (%)	Publication (n = 604), n (%)	P Value	Multivariate OR (95% CI, P Value)	Multivariate OR (95% CI, P Value) ^a
Status						
Discontinued	81 (5.8)	81 (10.2)	0	<0.001	2.76E-08 (0–∞, P=0.97)	0.00 (0–0.25, P=0.97)
Completed	1,071 (76.6)	592 (74.5)	479 (79.3)		0.88 (0.65–1.18, P=0.40)	0.84 (0.62–1.14, P=0.27)
Unknown	247 (17.7)	122 (15.3)	125 (20.7)		—	—
Dental specialty						
Dental caries	271 (19.4)	153 (19.2)	118 (19.5)	0.1	0.82 (0.53–1.27, P=0.37)	
Oral diseases and surgery	214 (15.3)	109 (13.7)	105 (17.4)		1.31 (0.83–2.09, P=0.24)	
Oral pain	205 (14.7)	134 (16.9)	71 (11.8)		0.83 (0.52–1.33, P=0.45)	
Orthodontics	56 (4)	31 (3.9)	25 (4.1)		0.91 (0.47–1.77, P=0.80)	
Periodontal diseases	507 (36.2)	287 (36.1)	220 (36.4)		0.84 (0.56–1.25, P=0.39)	
Prosthetics	146 (10.4)	81 (10.2)	65 (10.8)		—	
Study design						
Crossover	146 (10.5)	94 (11.9)	52 (8.6)	0.36		
Factorial	33 (2.4)	19 (2.4)	14 (2.3)			
Parallel	1,162 (83.2)	647 (81.7)	515 (85.3)			
Single group	15 (1.1)	8 (1.0)	7 (1.2)			
Split mouth	40 (2.9)	24 (3.0)	16 (2.7)			
Registration						
Prospectively	720 (51.5)	447 (57.1)	272 (45.1)	<0.001	0.67 (0.53–0.86, P=0.001)	0.66 (0.52–0.85, P=0.001)
Retrospectively	666 (47.6)	335 (42.8)	331 (54.9)		—	—
Investigator type						
Federal	2 (0.1)	2 (0.3)	0	<0.001	1.40E-08 (0–∞, P=0.99)	0.00 (0–∞, P=0.99)
Individual	2 (0.1)	1 (0.1)	1 (0.2)		0.69 (0.03–13.84, P=0.81)	0.61 (0.02–17.80, P=0.74)
Industry	326 (23.3)	239 (30.1)	87 (14.4)		0.26 (0.08–0.84, P=0.02)	0.24 (0.07–0.74, P=0.02)
Network	6 (0.4)	3 (0.4)	3 (0.5)		0.62 (0.09–4.54, P=0.64)	0.59 (0.08–4.38, P=0.60)
National Institutes of Health	3 (0.2)	3 (0.4)	0 (0)		8.57E-08 (0–∞, P=0.99)	0.00-08 (0–∞, P=0.99)
Universities, community-based organizations	1,043 (74.6)	539 (67.8)	504 (83.4)		0.67 (0.22–2.05, P=0.48)	0.60 (0.18–1.79, P=0.38)
Government	17 (1.2)	8 (1.0)	9 (1.5)		—	—
Enrollment						
>50 participants	641 (47)	360 (46.1)	281 (48.2)	0.44		
<50 participants	723 (53.0)	421 (53.9)	302 (51.8)			
Results available on ClinicalTrials.gov						
No/not provided	1,097 (78.4)	623 (78.4)	474 (78.5)	1		
Yes	302 (21.6)	172 (21.6)	130 (21.5)			
Country						
United States (alone or not)	339 (24.2)	221 (27.8)	118 (19.5)	<0.001	1.82 (1.23–2.70, P=0.003)	1.89 (1.28–2.80, P=0.001)
Brazil (alone or not)	181 (12.9)	80 (10.1)	101 (16.7)		2.17 (1.45–3.24, P<0.001)	2.14 (1.44–3.19, P<0.001)
Other countries	600 (42.9)	315 (39.6)	285 (47.2)		1.87 (1.37–2.57, P<0.0001)	1.92 (1.40–2.63, P<0.0001)
Not provided	279 (19.9)	179 (22.5)	100 (16.6)		—	—
AIC					1,757.928	1,756.780

AIC, XXX; CI, confidence interval; OR, odds ratio; —, reference group.

^aVariable selection after backward stepwise procedure based on AIC criteria.

Table 3. Discrepancies between Primary Outcomes in Trial Registration and in Published Article According to Modification of Original Primary Outcome.

Characteristic	Overall (n=479)	Original Primary Outcome Not Modified (n=293)	Original Primary Outcome Modified (Current Outcome) (n=186)	P Value
Discrepancies in outcomes				
No	264 (55)	150 (51)	114 (61)	0.03
Yes	215 (45)	143 (49)	72 (39)	
Introduction of a new primary outcome				
No	283 (59)	161 (55)	122 (66)	0.021
Yes	196 (41)	132 (45)	64 (34)	
Registered primary outcome reported as a secondary outcome				
No	431 (90)	263 (90)	168 (90)	0.84
Yes	48 (10)	30 (10)	18 (10)	
Omission of the registered primary outcome				
No	403 (84)	245 (84)	158 (85)	0.70
Yes	76 (13)	48 (16)	28 (15)	
Published primary outcome registered as a secondary outcome				
No	367 (77)	218 (74)	149 (80)	0.015
Yes	112 (23)	75 (26)	37 (20)	
Absent outcome in the register as primary outcome in the article				
No	307 (64)	173 (59)	134 (72)	0.004
Yes	172 (36)	120 (41)	52 (28)	
Timing of assessment differs				
No	396 (83)	240 (82)	156 (84)	0.58
Yes	83 (17)	53 (18)	30 (16)	
Enrollment size differs				
No	377 (79)	226 (77)	151 (81)	0.29
Yes	102 (21)	67 (23)	35 (19)	

Data are n (%). P values comparing status are from the χ^2 test.

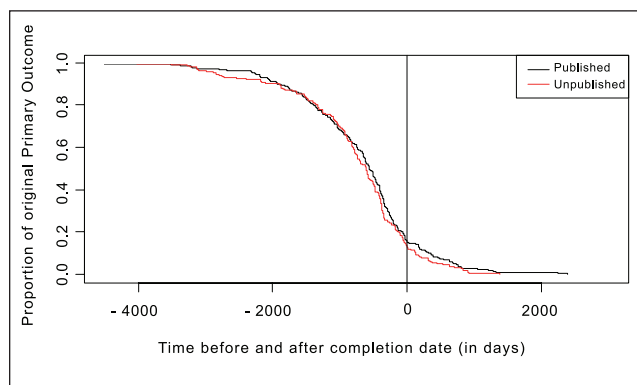


Figure 2. Kaplan–Meier estimate of cumulative original primary outcome percentage by time elapsed from trial completion to modification of original primary outcome among published and unpublished trials.

In the multivariate analysis, industry-sponsored trials were associated with decreased odds of SOR (0.38 [0.22–0.66]) (Appendix Table 4).

Discussion

Our large study assessed nonpublication and SOR of all 1,399 oral health RCTs registered in ClinicalTrials.gov.

Discontinuation

Out of 1,399 registered oral health trials, 5.8% were discontinued. In medicine, trial discontinuation reached 30%. In both specialties, poor recruitment was the main discontinuation cause. The higher the sample size, the harder the recruitment. In this aspect, lesser trial discontinuation in oral health may be explained by smaller sample sizes (median 53 in our oral health registered RCTs and 250 in medical RCTs) (Speich et al. 2022).

Nonpublication

Trials registered prospectively had decreased odds of publication (odds ratio [OR], 0.67 [0.53–0.86]). A possible explanation is an increased risk of early discontinuation for prospectively registered trials, which is consistent with Table 1 showing that 72.2% of early discontinued trials were registered prospectively.

Over half of the registered oral health RCTs were unpublished. Nonpublication in dentistry seems to be higher than in medicine. It seems 20% to 50% of medical trials remain unpublished (Jones et al. 2013; Speich et al. 2022). Small and nonpharmaceutical medical trials seem to convey a higher risk for nonpublication, which could partly explain the high nonpublication rate observed in oral health. The other reasons could be searched, as more publications would help in enhancing research results dissemination.

Nonpublication and country. We found that trials conducted in the United States or Brazil were associated with increased odds of publication. These results are consistent with those of recent bibliometric analyses evaluating the publications in the field of dentistry, which indicate that the United States is the most productive country, followed by Brazil (Yahya Asiri et al. 2020; Jiang et al. 2021). These results are also consistent with other bibliometric analyses of general biomedical publications (Bornmann et al. 2018; Web of Science Group 2019).

Nonpublication and industry funding. We found that nonpublication is more common among trials that received industry funding. See Appendix Table 5.

Nonpublication and registration. In our previous study published in 2014, we found that 77% of published oral health RCTs were not registered in a public registry (Smaïl-Faugeron and Esposito 2014), compared to 6% to 7% in medicine (Loder et al. 2018; Speich et al. 2022). Since 2014, trial registration has hopefully improved in oral health.

In medicine, only 2% of published randomized trials were not registered, while 21% of nonpublished trials were not registered (Speich et al. 2022). This means nonpublication is more frequent in unregistered trials, and our high rate of nonpublication in oral health (56.7%) is probably underestimated.

Publication and retrospective registration. In medicine, retrospective registration of RCTs published in 2013 could be as high as 67%, mostly before publication submission (Harriman and Patel 2016). Of the RCTs submitted for publication in the *BMJ* in the period 2013–2017, 89 were retrospectively registered and rejected as such but subsequently published in another journal (Loder et al. 2018). ICMJE guidelines paid off as 41.7% of RCTs published in 2018 complied with prospective registration (Al-Durra et al. 2020).

We found a 57% rate of retrospective registration among oral health published RCTs registered between 2006 and 2016. This is consistent with the rates observed in other medical specialties and hopefully a sign of progress in prospective registration of trials, although we could not find any publication in the oral health field to check if there was a trend toward prospective registration.

Among all registered RCTs, we found 47.6% were retrospectively registered, which means there is more retrospective registration in published trials than in unpublished ones. This confirms Harriman and Patel's (2016) findings: many RCTs are registered retrospectively, before publication, to conform with journals' guidelines for submission. More precisely, most RCTs are registered retrospectively within a year of submission for publication (Al-Durra et al. 2020).

The Indian register has been insisting on prospective registration since 2018 (Birajdar et al. 2019). In Australia and New Zealand, prospective registration increased from 48% in 2006 to 63% in 2012 and plateaued afterward, with investigators citing a lack of awareness as a reason for not registering their study prospectively (Hunter et al. 2018). To enforce prospective registration, ethics committees could require registration

for final trial approval. Journals publishing retrospectively registered trials could require that the authors give a transparent rationale as to why their study was not registered (Gray and Mackay 2020).

SOR

Most trials had only 1 primary outcome (median number, 1; minimum–maximum, 0–68), which means most investigators now conform with this CONSORT recommendation in oral health. Among oral health published RCTs, we found that almost half had primary outcomes differing from that registered (44.9%). This rate is consistent with SOR rates in endodontics (36.4%) (Tzanetakis and Koletsi 2021), implantology (55%) (Sendyk et al. 2019), and orthodontics (47%) (Koufatzidou et al. 2019). Similar SOR rates were found in medicine (Dwan et al. 2011) and when authors compared systematic reviews to protocols (45.4%) (Pandis et al. 2015).

This rate is probably underestimated, as 57% of published trials were registered retrospectively and change in outcomes is less probable in the latter cases. After correction for retrospective registration, the “real” rate of SOR could be as high as 74.3% ($n=356$). In medicine, SOR rates seem lower: 12% in oncology, 14% in psychopharmacotherapy, 8% to 18% in the leading journals in 2012–2015, 37% in obesity, 39% in anesthesia and pain, and 76% in neuro-otology.

Despite the fact that SOR often favors statistically significant results (Fleming et al. 2015; Raghav et al. 2015; Bonnot et al. 2016; Rankin et al. 2017; Zhang et al. 2017; van Beurden et al. 2021; Lancee et al. 2022), our results did not show this trend. However, industry-sponsored trials were associated with decreased odds of SOR; such a trend has been reported in other medical specialties (Lancee et al. 2022), but an opposite trend has been observed for dental implants (Sendyk et al. 2019) and in medicine (Rankin et al. 2017).

Limitations

First, our search strategy may have failed to identify some trials, either due to unidentified registers or publication further delayed after registration. Second, our study had difficulties in tracing trial investigators: contact information on registration records is often scarce, and investigators can change their surnames, email addresses, or institution. Finally, we chose to focus on primary outcomes and did not address the problem of unreported secondary outcomes.

In conclusion, our study highlights the high rate of nonpublication and SOR in the field of oral health. These results could alert the oral health research community at large. Transparency in oral health research is the responsibility of researchers as well as journal editors and ethics committees. Ethics committees could condition approval to trial registration; this would theoretically enforce prospective registration. Moreover, any changes to the protocol should be submitted to an ethics committee and explained in the trial report. Journal editors or reviewers should systematically assess reporting bias; they should check that the registration identification number is

mentioned, check that registration was prospective, and compare reported to registered outcomes. Editors should not reject nonsignificant results and maybe hide numbers in the manuscript to prevent reviewer bias. Trial results publication, at least in the registry, should be mandatory. We need to combat the nondisclosure of trial results to prevent the waste of biomedical research.

Author Contributions

H. Diakonoff, contributed to conception, data acquisition, analysis, and interpretation, drafted the manuscript; G. Khalil, contributed to acquisition and data interpretation, critically revised the manuscript; S. Jungo, contributed to design, data acquisition, analysis, and interpretation, critically revised the manuscript; J.M. Treluyer, H. Fron-Chabouis, contributed to data interpretation, drafted and critically revised the manuscript; V. Smail-Faugeron, contributed to conception and design, data acquisition and interpretation, edited and critically revised the manuscript. All authors gave final approval and agreed to be accountable for all aspects of the work.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

H. Diakonoff  <https://orcid.org/0000-0003-1089-3386>

References

- Al-Durra M, Nolan RP, Seto E, Cafazzo JA. 2020. Prospective registration and reporting of trial number in randomised clinical trials: global cross sectional study of the adoption of ICMJE and declaration of Helsinki recommendations. *BMJ*. 369:m982.
- Birajdar AR, Bose D, Nishandar TB, Shende AA, Thatte UM, Gogtay NJ. 2019. An audit of studies registered retrospectively with the clinical trials registry of India: a one year analysis. *Perspect Clin Res*. 10(1):26–30.
- Bonnot B, Yavchitz A, Mantz J, Paugam-Burtz C, Boutron I. 2016. Selective primary outcome reporting in high-impact journals of anaesthesia and pain. *Br J Anaesth*. 117(4):542–543.
- Bornmann L, Wagner C, Leydesdorff L. 2018. The geography of references in elite articles: which countries contribute to the archives of knowledge? *PLoS One*. 13(3):e0194805.
- Chan AW, Hróbjartsson A, Haahr MT, Gøtzsche PC, Altman DG. 2004. Empirical evidence for selective reporting of outcomes in randomized trials: comparison of protocols to published articles. *JAMA*. 291(20):2457–2465.
- Dwan K, Altman DG, Cresswell L, Blundell M, Gamble CL, Williamson PR. 2011. Comparison of protocols and registry entries to published reports for randomised controlled trials. *Cochrane Database Syst Rev*. 2011(1):MR000031.
- Egger M, Smith GD, Altman DG. 2003. *Systematic reviews in health care: meta-analysis in context*. London: BMJ Books.
- Fleming PS, Koletsi D, Dwan K, Pandis N. 2015. Outcome discrepancies and selective reporting: impacting the leading journals? *PLoS One*. 10(5):e0127495.
- Gray R, Mackay B. 2020. A review of prospective registration of randomized controlled trials published in the journal of advanced nursing in 2019. *J Adv Nurs*. 76(7):1491–1493.
- Grobler L, Siegfried N, Askie L, Hooft L, Tharyan P, Antes G. 2008. National and multinational prospective trial registers. *Lancet*. 372(9645):1201–1202.
- Harriman SL, Patel J. 2016. When are clinical trials registered? An analysis of prospective versus retrospective registration. *Trials*. 17:187.
- Hunter KE, Seidler AL, Askie LM. 2018. Prospective registration trends, reasons for retrospective registration and mechanisms to increase prospective registration compliance: descriptive analysis and survey. *BMJ Open*. 8(3):e019983.
- Ioannidis JP. 1998. Effect of the statistical significance of results on the time to completion and publication of randomized efficacy trials. *JAMA*. 279(4):281–286.
- Ioannidis JP, Greenland S, Hlatky MA, Khoury MJ, Macleod MR, Moher D, Schulz KF, Tibshirani R. 2014. Increasing value and reducing waste in research design, conduct, and analysis. *Lancet*. 383(9912):166–175.
- Jiang CM, Lee GHM, Lo ECM, Chu CH, Wong MCM. 2021. Randomized controlled trials in dental journals on children and adolescents: a bibliometric analysis. *J Evid Based Dent Pract*. 21(4):101621.
- Jones CW, Handler L, Crowell KE, Keil LG, Weaver MA, Platts-Mills TF. 2013. Non-publication of large randomized clinical trials: cross sectional analysis. *BMJ*. 347:f6104.
- Koufatzidou M, Koletsi D, Fleming PS, Polychronopoulou A, Pandis N. 2019. Outcome reporting discrepancies between trial entries and published final reports of orthodontic randomized controlled trials. *Eur J Orthod*. 41(3):225–230.
- Lancee M, Schuring M, Tijdink JK, Chan AW, Vinkers CH, Luyck JJ. 2022. Selective outcome reporting across psychopharmacotherapy randomized controlled trials. *Int J Methods Psychiatr Res*. 31(1):e1900.
- Loder E, Loder S, Cook S. 2018. Characteristics and publication fate of unregistered and retrospectively registered clinical trials submitted to the BMJ over 4 years. *BMJ Open*. 8(2):e020037.
- Macleod MR, Michie S, Roberts I, Dirnagl U, Chalmers I, Ioannidis JP, Al-Shahi Salman R, Chan AW, Glasziou P. 2014. Biomedical research: increasing value, reducing waste. *Lancet*. 383(9912):101–104.
- Montori V, Ioannidis J, Guyatt G. 2008. Reporting bias. In: Guyatt G, Rennie D, Meade M, Cook D, editors. *User's guide to the medical literature: a manual for evidence-based clinical practice*. New York: McGraw-Hill. p. 543–554.
- Pandis N, Fleming PS, Worthington H, Dwan K, Salanti G. 2015. Discrepancies in outcome reporting exist between protocols and published oral health Cochrane Systematic Reviews. *PLoS One*. 10(9):e0137667.
- Raghav KP, Mahajan S, Yao JC, Hobbs BP, Berry DA, Pentz RD, Tam A, Hong WK, Ellis LM, Abbruzzese J, et al. 2015. From protocols to publications: a study in selective reporting of outcomes in randomized trials in oncology. *J Clin Oncol*. 33(31):3583–3590.
- Rankin J, Ross A, Baker J, O'Brien M, Scheckel C, Vassar M. 2017. Selective outcome reporting in obesity clinical trials: a cross-sectional review. *Clin Obes*. 7(4):245–254.
- Sendyk DI, Rovai ES, Souza NV, Deboni MCZ, Pannuti CM. 2019. Selective outcome reporting in randomized clinical trials of dental implants. *J Clin Periodontol*. 46(7):758–765.
- Sim I, Chan AW, Gülmezoglu AM, Evans T, Pang T. 2006. Clinical trial registration: transparency is the watchword. *Lancet*. 367(9523):1631–1633.
- Smail-Faugeron V, Esposito M. 2014. Should all clinical trials of oral health be registered? *Eur J Oral Implantol*. 7(4):327–328.
- Smail-Faugeron V, Fron-Chabouis H, Durieux P. 2015. Clinical trial registration in oral health journals. *J Dent Res*. 94(3 Suppl):8S–13S.
- Song F, Parekh S, Hooper L, Loke YK, Ryder J, Sutton AJ, Hing C, Kwok CS, Pang C, Harvey I. 2010. Dissemination and publication of research findings: an updated review of related biases. *Health Technol Assess*. 14(8):iii, ix–xi, 1–193.
- Speich B, Gryaznov D, Busse JW, Gloy VL, Lohner S, Klatt K, Taji Heravi A, Ghosh N, Lee H, Mansouri A, et al. 2022. Nonregistration, discontinuation, and nonpublication of randomized trials: a repeated meta-research analysis. *PLoS Med*. 19(4):e1003980.
- Trofimova AV, Bluemke DA. 2022. Prospective clinical trial registration: a prerequisite for publishing your results. *Radiology*. 302(1):1–2.
- Tzanetakakis GN, Koletsi D. 2021. Trial registration and selective outcome reporting in endodontic research: evidence over a 5-year period. *Int Endod J*. 54(10):1794–1803.
- van Beurden I, van de Beek MJ, van Heteren JAA, Smit AL, Stegeman I. 2021. Selective reporting of outcomes in tinnitus trials: comparison of trial registries with corresponding publications. *Front Neurol*. 12:669501.
- Waldman HB, Perlman SP, Wong A. 2008. Providing dental care for the patient with autism. *J Calif Dent Assoc*. 36(9):662–670.
- Web of Science Group. 2019. Research in Brazil: funding excellence. Analysis prepared on behalf of CAPES by the Web of Science Group [accessed 2022

- Apr 1]. https://jornal.usp.br/wp-content/uploads/2019/09/ClarivateReport_2013-2018.pdf.
- Williamson PR, Gamble C, Altman DG, Hutton JL. 2005. Outcome selection bias in meta-analysis. *Stat Methods Med Res.* 14(5):515–524.
- Yahya Asiri F, Kruger E, Tennant M. 2020. Global dental publications in PubMed databases between 2009 and 2019—a bibliometric analysis. *Molecules.* 25(20):4747.
- Zarin DA, Tse T, Ide NC. 2005. Trial registration at ClinicalTrials.gov between May and October 2005. *N Engl J Med.* 353(26):2779–2787.
- Zarin DA, Tse T, Williams RJ, Califf RM, Ide NC. 2011. The ClinicalTrials.gov results database—update and key issues. *N Engl J Med.* 364(9):852–860.
- Zhang S, Liang F, Li W. 2017. Comparison between publicly accessible publications, registries, and protocols of phase III trials indicated persistence of selective outcome reporting. *J Clin Epidemiol.* 91:87–94.