Selective Outcome Reporting Bias Is Highly Prevalent in Randomized Clinical Trials of Periodontology

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Abstract

Objectives: This study aimed to investigate the prevalence of a type of bias named Selective Outcome Reporting (SOR) in publications of RCTs on non-surgical periodontal therapy (NSPT) and verify its associated factors.

Materials and Methods: The protocols were searched and selected on the www.clinicaltrials.gov platform up to January 16, 2022. Corresponding publications were identified, and data extraction and discrepancy analysis were performed. The risk of bias was assessed according to the RoB2 tool.

Results: One hundred forty-five studies (174 publications) were included. The prevalence of SOR was 49.7% and was unclear in nearly one third of studies (27.6%). Only 31.7% of the primary outcomes were completely described in the publications. The overall risk of bias was high in 60% of the included studies. SOR was associated with statistical significance ($p < .001$), and multiple publications of the same study ($p = .005$).

Conclusions: Our study demonstrated the high prevalence of SOR, highlighting the need to improve the quality of reporting of RCTs on NSPT studies.

Clinical relevance: SOR is a concerning bias that can affect clinical practice as it increases the effect of the intervention, emphasizing positive results. The incidence of SOR can be reduced by the prospective registry of the study protocol and the complete definition of the outcome. Journal editors could instruct reviewers to check discrepancies between the protocol and the manuscript whenever such information is available.

Introduction

Evidence-based practice (EBP) consists of health care decision-making based on integrating clinical experience, patient values, and the best scientific evidence available [1, 2]. When it comes to decisions about clinical treatment, the randomized clinical trial (RCT) is the study that provides the highest level of scientific evidence about the efficacy of interventions [3]. However, the validity of the evidence can be threatened when biases are incorporated into the planning, conduct, and reporting of clinical trials [4, 5].

A specific form of bias that may be present in clinical trial publications is selective outcome reporting (SOR) [6]. SOR occurs when the primary outcome of a study protocol is changed or omitted, when a new outcome is added, or when the time point of the primary outcome is altered in the final publication [7, 8]. SOR directly affects EBP and may distort the effect of interventions, affecting clinical decision-making and public health policies [7, 8]. Furthermore, it may overestimate the effect of a treatment in the meta-analyses of systematic reviews [9, 10]. For these reasons, it is essential to identify the prevalence of SOR in RCTs in a given area of knowledge, and the factors that lead authors to introduce SOR in their publications.

The incomplete specification of outcomes can also compromise the transparency of clinical trial results [11, 12]. An outcome is completely specified when it is described in five levels: (a) domain, (b) specific measure, (c) specific metric, (d) aggregation method, and (e) time point [11, 13]. The incomplete specification of outcomes in the protocol or publication creates opportunities for authors to choose specific measures, metrics, and time points that were statistically significant [13].

Considering the important consequences of the occurrence of SOR, studies in the medical field have evaluated its prevalence with estimates ranging between 14% and 100% [14]. In dentistry, a previous study by our group identified SOR in 40.9% of the root coverage trials. Further, we observed an association of SOR with statistically significant results and the incomplete specification of outcomes [12].

Non-surgical periodontal therapy (NSPT) has been extensively studied for decades. Several therapies and adjuncts have been tested, and many outcomes have been used to measure the efficacy of these interventions [15]. However, it is necessary to investigate discrepancies between registered protocols and their respective publications regarding these outcomes.

So far, there is no information on the prevalence of SOR in clinical trials of NSPT. Therefore, this study aimed to assess outcomes discrepancies between protocols and publications in RCTs of NSPT and the variables associated to SOR.

Material And Methods

Search strategy and eligibility criteria

We searched www.clinicaltrials.gov up to January 16, 2022 to identify RCT protocols in which one of the interventions consisted of NSPT. We used the keywords "periodontal" and "periodontitis" in the search and applied the filter "interventional (clinical trial)" to exclude observational studies at this stage of selection. We included the protocol if: a) the study was an RCT of patients diagnosed with periodontitis who have undergone NSPT with ultrasonic, manual instrumentation, or both, associated or not with adjunct therapies (e.g., laser, systemic antibiotics, local antimicrobials, etc.); b) at least one outcome in the registry was a clinical periodontal parameter such as probing depth (PD), clinical attachment level (CAL), or bleeding on probing (BOP), among others; c) at least one article related to the protocol was published in a peer-reviewed scientific journal. We excluded protocols in which NSPT was not evaluated, for example, studies of periodontal medicine, whose primary or secondary outcomes did not involve any periodontal parameter.

Selection of the protocols

Two reviewers (N.V.S. and A.C.N.) independently searched the protocols registered on the www.clinicaltrials.gov platform. When a protocol met the eligibility criteria, the same reviewers searched for publication references in the registry to identify any associated published articles. If publication

references were unavailable in the registry, the reviewers searched the PubMed and Google Scholar databases, using the protocol identification provided by www.clinicaltrials.gov (NCT number), the principal investigator's name, and protocol-related keywords.

When two or more publications regarding the same protocol were identified, all data were collected and organized under the same NCT number. When no article returned from the search, the reviewers contacted the study's principal investigator by email. The study was not included when there were no responses after two contacts. All disagreements in study selection were solved by two experienced reviewers (J.C. and C.M.P.).

Data extraction

The data were extracted independently by the same reviewers (N.V.S. and A.C.N.) using a previously described extraction form [16] that addressed the protocol, the corresponding publication, and any discrepancies between them. Briefly, we extracted data about NCT number, principal investigator's name, country, and presence of industry funding for each protocol. In addition, we collected the protocol publication date and the start date of the study. To identify changes in the protocol after the initial record, a specific tool of www.clinicaltrials.gov called "history of changes" was used. We collected data regarding the original registration using this tool. According to the time of registration, the protocol was identified as prospectively or retrospectively registered. We considered that a study was prospectively registered if information about the registration was recorded before the inclusion of the first study subject. We also extracted information about the RCT design (parallel, split-mouth, factorial), blinding, number of arms, sample size, and follow-up period. The evaluation period of the results (time-points) for each protocol was collected. Data referring to primary and secondary outcomes were extracted according to protocol registration.

The following information of the corresponding publications was collected: the number of articles published related to the protocol, the name of the journal(s), their respective impact factor(s), and study start date (as published in the article). Furthermore, we verified if the authors reported the study registration, if the NCT number was available, and if any change in protocol was mentioned in the publication. Moreover, we extracted the number of arms and the tested interventions, follow-up period, industry funding, sample size, and sample size calculation. We also annotated the number of primary outcomes and if analysis of the primary and secondary outcome(s) was statistically significant ($p < 0.05$).

In cases where no outcome was identified as primary in the publication, we considered the outcome used to calculate the sample size as the primary. We considered the primary outcome unclear if it was not identified in the publication and if sample size calculation was not mentioned.

Analysis of discrepancies

We followed the criteria of Chan *et al*. [8], as modified by Mathieu *et al*. [7], to define SOR. Thus, we considered SOR to be present if a) an outcome recorded as primary in the protocol was reported as

secondary in the publication; b) a secondary outcome in the protocol was reported as primary in the publication; c) a new primary outcome, which had not been described in the protocol, was introduced in the publication; d) a primary outcome of the protocol omitted in the publication; or e) there were discrepancies between protocol and publication(s) regarding primary outcome time-points.

We determined that SOR favored statistically significant results when: a) a secondary outcome in the protocol was upgraded to primary and reported as statistically significant in the publication, b) when a new primary outcome was reported as statistically significant in the publication, or c) when a primary outcome in the protocol was omitted or downgraded to secondary and reported as non-significant in the publication.

In addition, we assessed if there were other discrepancies regarding the study start date, presence or absence of industry funding, study design, number of arms, sample size, follow-up period, or presence of a new secondary outcome and its statistical significance.

Outcome specification levels

We performed an analysis of the complete outcome definition of each reported primary outcome to identify a possible association between SOR and the complete specification of the outcome. For this analysis, the primary outcomes were defined using five levels of specification: domain, specific measurement, specific metric, aggregation method, and time point [11, 13]. We also analyzed the specification in four levels, without the aggregation method, since in many protocols researchers only define the statistical analysis after verifying normality and homoscedasticity [11].

Risk of bias

We performed the risk of bias analysis to verify whether there was an association between SOR and bias related to study design, conduct, and reporting of results. The risk of bias was assessed in duplicate (N.V.S. and I.N.R.R.) according to the Risk of Bias 2 (RoB2) tool [17]. Disagreements were solved by two experienced reviewers (C.M.P. and J.C.).

In domain five, "bias in the selection of the reported result", if SOR was found in our first analysis, we classified the study automatically with a high risk of bias for this domain. In addition, retrospectively recorded protocols were automatically judged to have "some concerns".

Statistical analyses

For the main analyses, the statistical unit was the study. Secondary analysis of the outcome complete description was performed, in which the statistical unit was the outcome. Regarding the study characteristics, frequency distributions for qualitative variables and means and standard deviations for quantitative variables were calculated. The presence or absence of SOR (dependent variable) was tested for possible association with the following independent variables: time of registration (prospective versus retrospective), industry funding (yes versus no), the significance of the primary study outcome ($p \leq .05$ versus $p > .05$), number of publications resulting from the same protocol (one publication versus more

than one publication), journal impact factor (smaller versus larger, using the median impact factor of the included journals as the cutoff point), risk of bias analysis (high versus low risk of bias or some concerns); complete definition of the primary outcome in the publication and in the protocol (studies in which the primary outcomes were defined entirely versus uncertain definition at one or more levels, except for the aggregation method). The chi-square test was used to test associations between independent variables and SOR. Statistical analyses were performed using the JAMOVI software (www.jamovi.org) and alpha was set at 5% for all tests.

Results

Initially, we collected 1742 RCT protocols resulting from the search performed on www.clinicaltrials.gov on January 16, 2022 (Fig. 1). In the first screening phase, we excluded 1381 protocols after removing duplicates and protocols not meeting the eligibility criteria. We included 331 protocols in the second screening phase. Of these, we ultimately selected 145 protocols which resulted in 174 publications.

Characteristics of protocols and publications

The characteristics of the protocols are shown in Table 1. The majority of the studies were conducted in Asia (34.5%), Europe (28.3%), and South America (23.4%). According to the " history of changes " function, most protocols (78.6%) had no changes. Registration was performed retrospectively in 91.7% of cases, and only five studies (3.4%) reported the presence of industry funding. More than half of the studies had more than one primary outcome (55.2%), ranging between two and 16 outcomes. The study's primary outcome was unclear in one protocol (0.7%).

Table 1
Characteristics of the protocols of the included studies

Characteristics	Studies (n = 145)
Region of principal investigator - n (%)	50 (34.5)
Asia	41 (28.3)
Europe	34 (23.4)
South America	11 (7.6)
North America	9 (6.2)
Africa	
Protocol changes - n (%)	31 (21.4)
Yes	114 (78.6)
No	
Timing of registration - n (%)	12 (8.3)
Prospective	133 (91.7)
Retrospective	
Industry funding - n (%)	5 (3.4)
Yes	140 (96.6)
No	
Study design as reported in the protocol - n (%)	124 (85.6)
Paralell	11 (7.6)
Split-mouth	5 (3.4)
Crossover	5 (3.4)
Factorial	
Number of arms reported in the protocol - n (%)	2–10
Min-max	104 (71.6)
Two	30 (20.7)
Three	10 (7.0)
Four or more	1 (0.7)
Unclear	

Characteristics	Studies (n = 145)
Sample size - n	11–816
Min-max	72.0 (94.3.2)
Mean (SD)	
Period of follow-up (months)	48 hours – 60 months
Min-max	7.45 (8.5)
Mean (SD)	
Number of primary outcomes in the protocol - n (%)	1–16
Min-max	64 (44.1)
One	80 (55.2)
More than one	1 (0.7)
Unclear	

Table 2 shows the characteristics of the 174 publications resulting from the 145 study protocols selected. Most studies (n = 132; 91%) resulted in a single publication. The remaining studies (n = 13; 9%) resulted in more than one publication, ranging from two to ten publications. The majority of the studies identified the protocol number in the publication (84.8%). In addition, no publication reported changes in the research protocol.

Many studies identified the primary outcome in the publication (81.4%). Approximately a third (32.4%) reported having only one primary outcome. In comparison, in 12.5% of studies, more than one primary outcome was reported, ranging from two to nine primary outcomes. The primary outcome was statistically significant in approximately half of the studies (n = 74; 51.1%).

Table 2: Characteristics of the publications of the included studies

Characteristics	Studies (n = 145)
Number of publications related to the same protocol - n (%)	132(91.0)
One	7 (4.8)
Two	2 (1.4)
Three	3 (2.1)
Four	1 (0.7)
Ten	
NCT number identified in the publication - n (%)	123 (84.8)
Yes	22 (15.2)
No	
Protocol change reported in publication - n (%)	0 (0.0)
Yes	145(100.0)
No	
Industry-funded study reported in publication - n (%)	11 (7.6)
Yes	127 (87.6)
No	7 (4.8)
Unclear	
Study design as reported in the publication - n (%)	113 (77.9)
Paralell	25 (17.2)
Split-mouth	1 (0.7)
Crossover	2 (1.4)
Factorial	4 (2.8)
Unclear	
Number of arms reported in the publication – n (%)	2–8
Min-max	106 (73.1)
Two	29 (20.0)
Three	10 (6.9)
Four or more	
Sample size calculation reported in the publication - n (%)	118 (81.4)
Yes	21 (14.5)

No	6 (4.1)
Unclear	
Sample size - n	5-823
Min-max	67 (92.5)
Mean (SD)	
Period of follow-up (months)	1h-60 months
Min-max	6.48 (7.75)
Mean (SD)	
Number of primary outcomes in publication - n (%)	47 (32.4)
One	18 (12.5)
More than one	80 (55.1)
Unclear	
Primary outcome identified in the publication - n (%)	118 (81.4)
Yes	27 (18.6)
Primary outcome statistically significant - n (%)	74 (51.1)
Yes	45 (31.0)
No	26 (17.9)
Unclear	

Analysis of the complete definition of the outcome in protocols and publications

The distribution of primary outcomes in the protocols according to the three most frequent definition levels (domain, specific measure, specific metric, aggregation method, and time point) is shown in Online Resource 1.

We analyzed 250 primary outcomes. The most used domains were CAL (23.6%), PD (23.2%), and biochemical parameters (14.4%). In half of the cases (50.8%), the specific measure was not informed. However, when they were reported, the most frequent specific measures were: reduction in the depth of the bone defect (4.4%), C-reactive protein (CRP) (4%), and HbA1c (3.6%). Change from baseline was the most used specific metric, being reported in 58% of cases. The vast majority of protocols (91.2%) did not specify the aggregation method used. Assessment times varied widely between protocols, with 3-month and 6-month time points being the most common, occurring in 24.4% and 18% of cases, respectively.

Of the 250 outcomes presented, only 14 (5.6%) were completely defined at their five levels in the protocol (Online Resource 2). However, when we excluded the aggregation method level from the analysis, the proportion of protocols with a completely defined outcome was 29.6% (Online Resource 3). Despite this, the number of incompletely defined outcomes was predominant and occurred in 70.4% of the studies (Online Resource 3).

Online Resource 4 shows the analysis of the definition of the 186 primary outcomes in the publications. The most frequently used domain in publications was CAL (25.2%). More than a third of the publications (38.1%) did not specify the specific measure used, but when described, the most frequent specific measure was "CAL in all teeth," reported 21 times (11.3%). The most common specific metric was "change from baseline" (e.g., CAL gain, PD reduction, etc.), occurring in more than half of the publications (55.4%). However, this information was unclear in a high proportion of publications (27.9%). Mean was the most frequent aggregation method (65%). Most primary outcomes were presented with time points at three months (17.2%) or six months (8.6%), although this information was unavailable in 45.2% of cases. Figure 2 shows the two most used primary outcomes in publications of NSPT trials and their definitions.

Number of outcomes related to CAL and PD domains. The specification of the primary outcome was described in five levels (Mayo-Wilson *et al.* 2009), namely: o domain specific measure specific metric aggregation method time-point.

Online Resource 5 presents the definition of the primary outcome at five levels, as presented in the publication. Of the 186 primary outcomes analyzed, only approximately a third (31.7%) carried out the complete outcome definition, with all five levels well defined in the publication. When excluding the aggregation method from the analysis, complete outcome definition occurred in 35.5% (Online Resource 6).

Risk of bias analysis of included studies

We performed the risk of bias analysis in all included studies (n = 145) (Online Resource 7). Most of these studies (n = 87; 60%) had a high overall risk of bias (Fig. 3). Only one study (0.7%) was classified as having a low risk of bias, and in the remaining 39.3% of cases (n = 57), the studies had some concerns. Information on the risk of bias in each domain and their respective frequencies are presented in Online Resource 7.

Discrepancies in the primary outcome identified between the research protocol and the corresponding publication

We identified selective outcome reporting in 49.7% of publications (n = 72; Table 3). In 27.6% of the publications, SOR was unclear because the primary outcome was inadequately reported in the

publication or the registry.

Table 3
Discrepancies identified between protocol and publication

Characteristics	Studies (n = 145)
Studies with Selective Outcome Reporting *	72 (49.7)
Yes	33 (22.7)
No	40 (27.6)
Unclear	
Primary outcome in the protocol described as secondary in the publication	36 (24.8)
Yes	77 (53.1)
No	32 (22.1)
Unclear	
Secondary outcome in the protocol described as primary in the publication	19 (13.1)
Yes	98 (67.6)
No	28 (19.3)
Unclear	
Protocol primary outcome not reported in publication	12 (8.3)
Yes	131 (90.3)
No	2 (1.4)
Unclear	
New primary outcome introduced in publication	16 (11.0)
Yes	111 (76.6)
No	18 (12.4)
Unclear	
Discrepancy in primary outcome time point	31 (21.4)
Yes	56 (38.6)
No	58 (40.0)
Unclear	

All variables were described as n (%). * According to the criteria established by Chan et al. (2004), modified by Mathieu et al. (2009).

Characteristics	Studies (n = 145)
Selective outcome reporting favored statistical significance	56 (38.6)
Yes	48 (33.1)
No	41 (28.3)
Unclear	
New secondary outcome	87 (60.0)
Yes	57 (39.3)
No	1 (0.7)
Unclear	
New secondary outcome statistically significant in publication	71 (49.0)
Yes	72 (49.6)
No	2 (1.4)
Unclear	
New outcome	18 (12.4)
Yes	127 (87.6)
No	
New outcome statistically significant in publication	
Yes	12 (8.3)
No	131(90.3)
Unclear	2 (1.4)
All variables were described as n (%). * According to the criteria established by Chan et al. (2004), modified by Mathieu et al. (2009).	

The discrepancies that led to SOR were: primary outcome of the protocol described as secondary in the publication (n = 36; 24.8%); secondary outcome in the protocol reported as primary in the publication (n = 19; 13.1%); omission of the protocol's primary outcome at publication (n = 12; 8.3%); a new primary outcome that was not reported in the protocol identified in the publication (n = 16; 11%); and discrepancies in assessment time-points of the primary outcome (n = 31; 21.4%). In addition, SOR clearly favored statistical significance in more than a third of the studies (n = 56; 38.6%), while this information was unclear in a further 28.3% of studies.

Other discrepancies between the study protocol and publication were in relation to: sample size (n = 66; 45.5%); study start date (n = 54; 37.2%); follow-up period (n = 25; 17.2%); study design (n = 14; 9.7%); number of arms (n = 10; 6.9%); and presence of industry funding (n = 7; 4.8%).

No statistically significant associations were found between SOR and risk of bias in the analyzed studies (in its four domains), industry funding, journal impact factor, study size, protocol changes, time of study registration, or with the incomplete definition of the primary outcome at both five and four levels ($p > 0.05$). However, SOR showed a significant association with statistical significance ($p < 0.001$), and more than one publication related to the same protocol ($p < 0.005$) (Table 4).

Table 4
Association between selective outcome reporting (SOR) and study characteristics

	SOR			Total (141)	p-value
Characteristics	Yes	No	Unclear		
Timing of registration, per protocol	67 (50.4)	29 (21.8)	37 (27.8)	133 (100.0)	0.656
Retrospective	5	4 (33.3)	3	12	
Prospective	(41.7)		(25.0)	(100.0)	
Industry funding, per protocol	2 (40.)	2 (40.0)	1 (20.0)	5 (100.0)	0.644
Yes	70 (50.0)	31 (22.1)	39 (27.9)	140 (100.0)	
No					
Statistical significance in the publication	56 (100.0)	0 (0.0)	0 (0.0)	56 (100.0)	**< 0.001***
Yes	12 (25.0)	33 (68.8)	3 (6.2)	48 (100.0)	
No	4 (9.8)	0 (0.0)	37 (90.2)	41(100.0)	
Unclear					
Journal impact factor	38 (56.7)	17 (25.4)	12 (17.9)	67 (100.0)	0.054
≥ 1	34 (43.6)	16 (20.5)	28 (35.9)	78 (100.0)	
< 1					
Protocol changes	21 (67.7)	6 (19.4)	4 (12.9)	31 (100.0)	0.053
Yes	51 (44.7)	27 (23.7)	36 (31.6)	114 (100.0)	
No					
Study Size	38 (52.1)	13 (17.8)	22 (30.1)	73 (100.0)	0.350
Small	34 (47.2)	20(27.8)	18 (25.0)	72 (100.0)	
Large					
Number of primary outcomes	28 (43.8)	21 (32.8)	15 (23.4)	64 (100.0)	0.060
One	44 (55.0)	12 (15.0)	24 (30.0)	80 (100.0)	
More than one	0 (0.0)	0 (0.0)	1 (100.0)	1 (100.0)	
Unclear					

	SOR			Total (141)	p-value
Number of publications referring to the protocol	60 (45.5)	33 (25.0)	39 (29.5)	132 (100.0)	**0.005***
One	12 (92.3)	0 (0.0)	1 (7.7)	13 (100.0)	
More than one					
Definition of the primary outcome(s) in the protocol	59 (56.2)	23 (21.0)	25 (22.8)	105 (100.0)	0.067
Unclear definition of outcome(s) at one level or more	13 (32.5)	10 (27.5)	15 (40.0)	40 (100.0)	
Completely defined outcome(s) in 4 levels (aggregation method not included)					
Definition of the primary outcome(s) in the publication	48 (49.5)	19 (19.6)	30 (30.9)	97 (100.0)	0.289
Unclear definition of outcome(s) at one level or more	24 (50.0)	14 (29.2)	10 (20.8)	48(100.0)	
Completely defined outcome(s) in 4 levels (aggregation method not included)					

All variables were described as n (%)

* Significant association according to the chi-square test.

Discussion

We identified a high prevalence of SOR (n = 72; 49.7%) in NSPT trials. Further, our results showed an association of SOR with statistical significance of the primary outcome in the publication, and more than one publication resulting from the same study.

The high prevalence of SOR in the NSPT trials is similar to those observed in the medical field: 62% in the study by Chan *et al*. [8] and 49% both in surgical trials [18] and hematology publications [19]. In Dentistry, the prevalence was also high: 47% in the orthodontics field [20], 55.1% in dental implant studies [16], and 40.9% in root coverage trials [12]. Despite this high rate, the prevalence of SOR may have been underestimated for two reasons: 1) SOR was unclear in almost a third of the studies (n = 40; 27.6%) because authors did not specify the primary outcome in the publication; 2) we only used the www.clinicaltrials.gov platform to identify the protocols. Therefore, extending the search to other platforms could have increased SOR occurrence.

Most of the analyzed protocols (91.7%) were retrospectively recorded. This is a concerning result because late registration allows authors to change their outcomes once they have analyzed data. Retrospective registration creates room for publication bias and changes in the pre-specified primary outcome [21]. The

rates of retrospective registration range from 46.9–79% in studies from the medical and dental fields [12, 16, 21, 22]. Study registration alone is not enough to increase transparency in reporting; it must be carried out prospectively before the inclusion of the first study participant [21, 23, 24].

Our study identified the primary outcome in 81.4% of the analyzed publications. A systematic review examining periodontal trials' primary outcomes between 2018 and 2020 showed that only half of the publications (54%) identified the primary outcome [25]. The low number of publications that identified the primary outcome is worrisome, since this oversight may increase the probability of authors selecting positive results, or omitting inconvenient results [26].

We analyzed the complete definition of the primary outcome both in the protocols and in their associated publications. According to the five specification levels, only 5.6% of the protocols had a completely specified outcome. A recent medical study also observed that the primary outcome was completely defined in only 3.3% of the trials, considering the five specification levels [27]. This percentage rose to 29.6% when we disregarded the aggregation method of the analysis. We carried out both analyses because in many studies, researchers only define the aggregation method in the statistical analysis after obtaining data and checking for normality and homoscedasticity [11]. On the other hand, we observed that almost a third (31.7%) of the publications presented the complete specification of the outcome when considering the five levels. After excluding the aggregation method from the analysis, this number increased to 35.5%. In a previous publication [12] we also observed a low rate (22.7%) of completely defined outcomes.

We did not identify an association between SOR and incomplete specification of the primary outcome in protocol and publication ($p > 0.05$). In contrast, Sendyk *et al*. [12] showed an association of SOR with an unclear definition of the primary outcome in the publication. Although no significant association was observed, it is worth noting observationally that there was SOR in 56.2% of the studies with an unclear definition of the outcome, as compared to 32.5% of the studies with a completely defined outcome. A possible explanation for this trend is that incomplete definition of the outcome can lead to cherry-picking, i.e., the investigator can perform multiple statistical analyses and select only the specific measures, metrics, or time points of the outcome that are statistically significant [13, 26]. These results emphasize the need to improve the description of the outcome, both in the protocol and in the publication.

Of the 145 included studies, 13 resulted in more than one publication referring to the same research protocol. Of these, 92.3% presented SOR. We observed SOR in the companion papers of these studies (i.e., from the second publication onwards). In these cases, the authors often 1) included a new primary outcome, 2) promoted the protocol's secondary outcome to the primary, or 3) omitted the protocol's primary outcome, recalculating the sample size for the outcome of interest. As a result, we observed a significant association between multiple publications and SOR. To prevent SOR and ensure transparency, authors must select *a priori* one primary outcome for the study and register this outcome in a publicly accessible registry. All resulting publications should mention the same original outcome as the primary [25], even in cases of companion papers that emphasize secondary outcomes.

SOR was associated with statistical significance, supporting previous findings [7, 8, 12, 19, 21, 28, 29]. The intention to select significant results to increase the chances of publication may be one of the reasons for the occurrence of SOR [8, 28, 30]. Furthermore, studies that interviewed authors to identify the reasons for the occurrence of SOR showed that the main justifications were a) lack of clinical importance, b) lack of statistical significance and c) space restrictions in the publication [8, 31, 32]. These findings corroborate Smyth *et al*. [33], who also demonstrated that there is misinformation by the authors, who do not understand the importance and consequences of not reporting all results in building the body of evidence. Omitting a non-significant finding or introducing a significant result can lead to overestimating the effectiveness of treatments and interfering with clinical practice [9, 10, 28, 34].

One of the limitations of this investigation is that the protocol search strategy was restricted to the www.clinicaltrials.gov platform, which may have compromised the external validity of our research. On the other hand, other registration platforms do not have the "history of changes" tool that identifies any changes made to the research protocol after its registration. Therefore, we chose to use www.clinicaltrials.gov because of the possibility of analyzing these changes.

Some measures can improve reporting transparency and reduce the incidence of SOR, such as 1) prospective registration of the study before the inclusion of the first research patient; 2) the complete definition of the primary outcome both in the research protocol and in the final publication; 3) changes in the planning and conduct of the ECR informed appropriately and transparently. In addition, journal editors should instruct reviewers to check for discrepancies between the protocol and the manuscript whenever such information is available. These efforts can increase the transparency of clinical trials, strengthening evidence-based practice in Periodontology and other fields of dentistry.

Conclusion

We observed a high prevalence of SOR in RCTs concerning non-surgical periodontal therapy. SOR was associated with statistical significance, and the number of publications referring to the same study.

Declarations

Authors contributions

N.V.S.: Contributed to conception, design, data acquisition and interpretation, drafted and critically revised the manuscript. A.C.N. and I.N.R.R. contributed to data acquisition and interpretation, and critically revised the manuscript. D.I.S. and J.C. contributed to conception, design, and critically revised the manuscript. C.M.P.: Contributed to conception, design, performed all statistical analyses, drafted, and critically revised the manuscript. All authors gave final approval and agreed to be accountable for all aspects of the work.

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Conflict of Interest: The authors declare that they have no conflict of interest.

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Figures

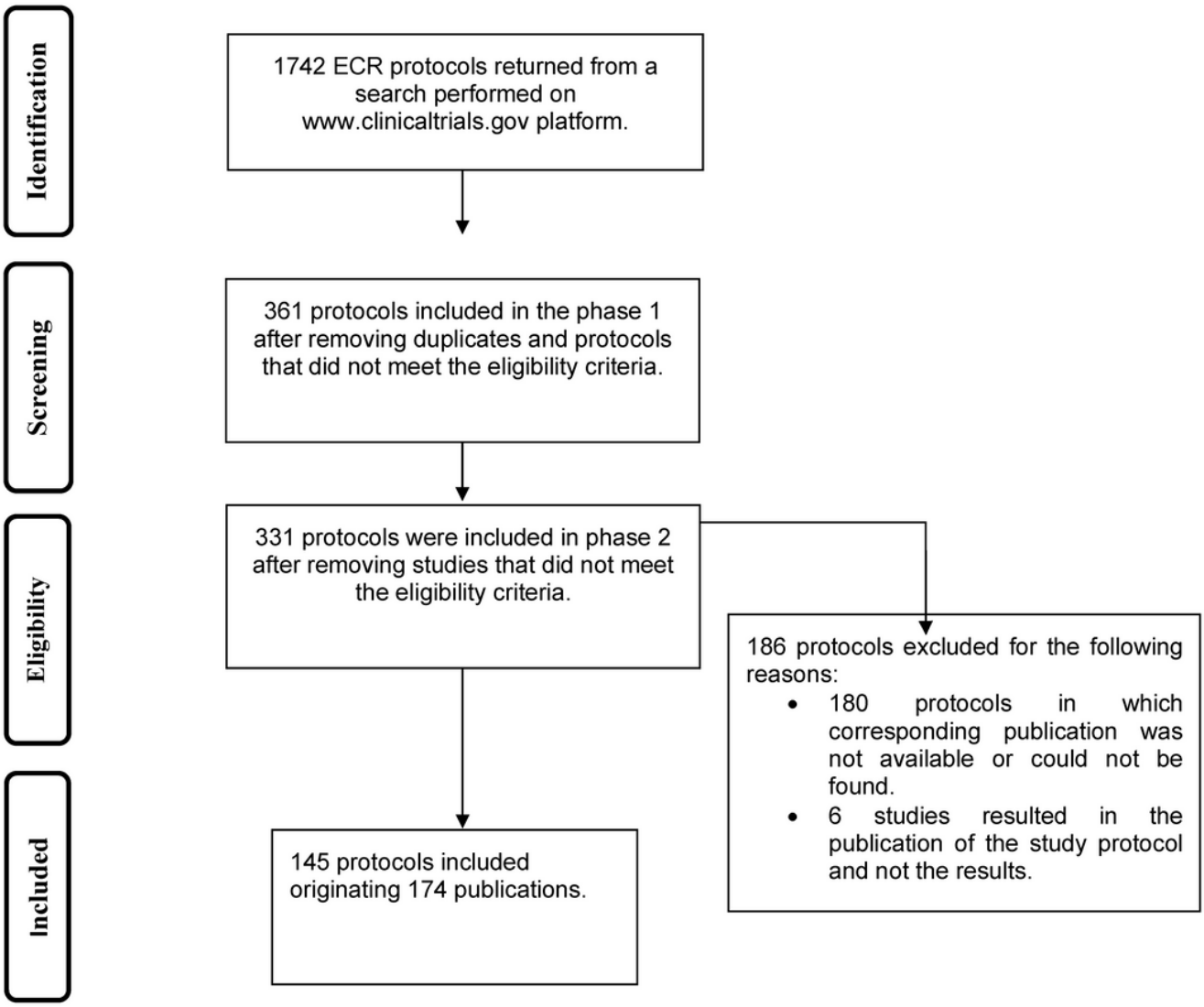
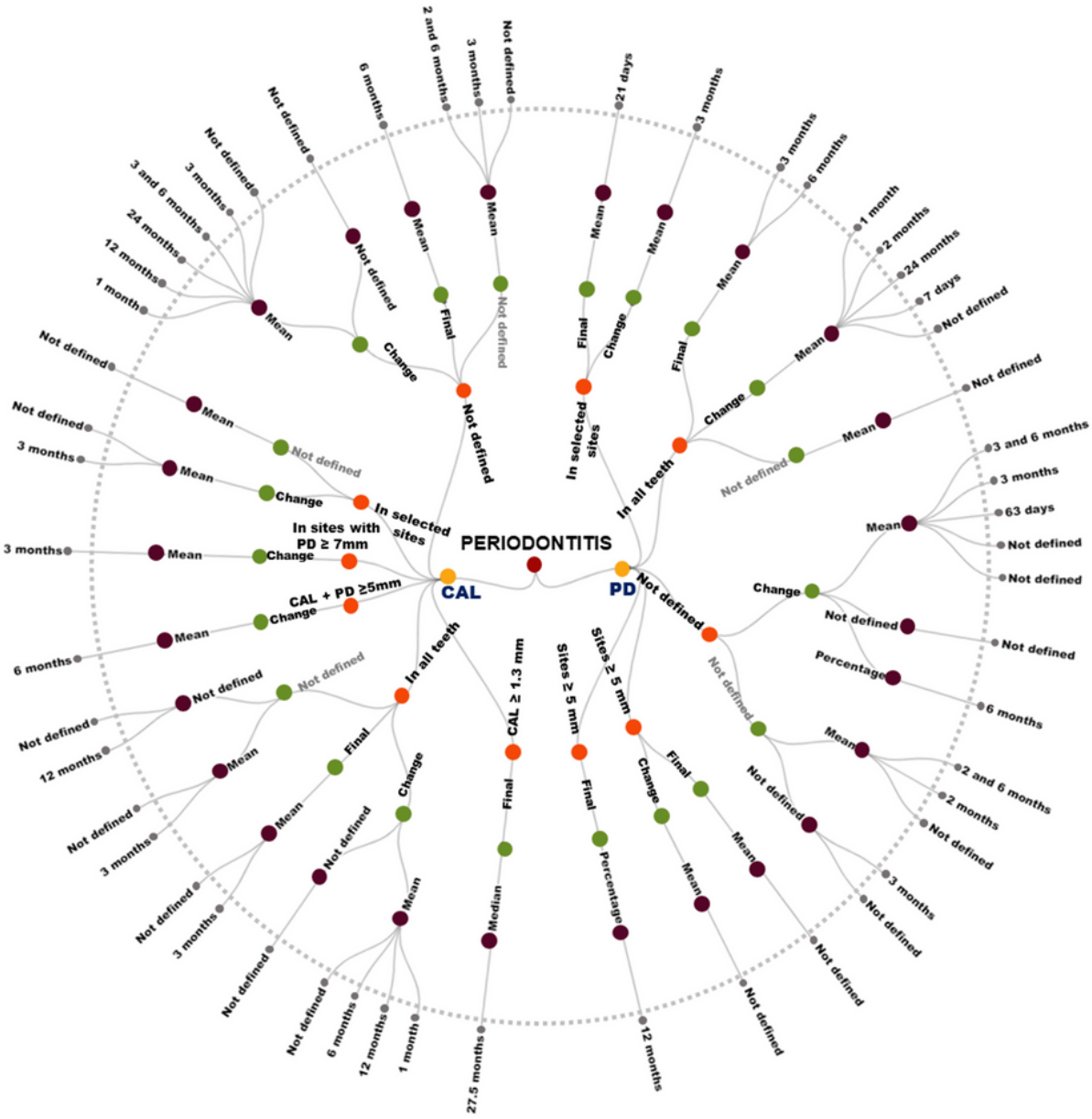


Figure 1

Study Flowchart.



Number of outcomes related to CAL and PD domains. The specification of the primary outcome was described in five levels (Mayo-Wilson *et al.* 2009), namely: domain specific measure specific metric aggregation method time-point.

Figure 2

The two most used primary outcomes in publications of NSPT trials and their definitions

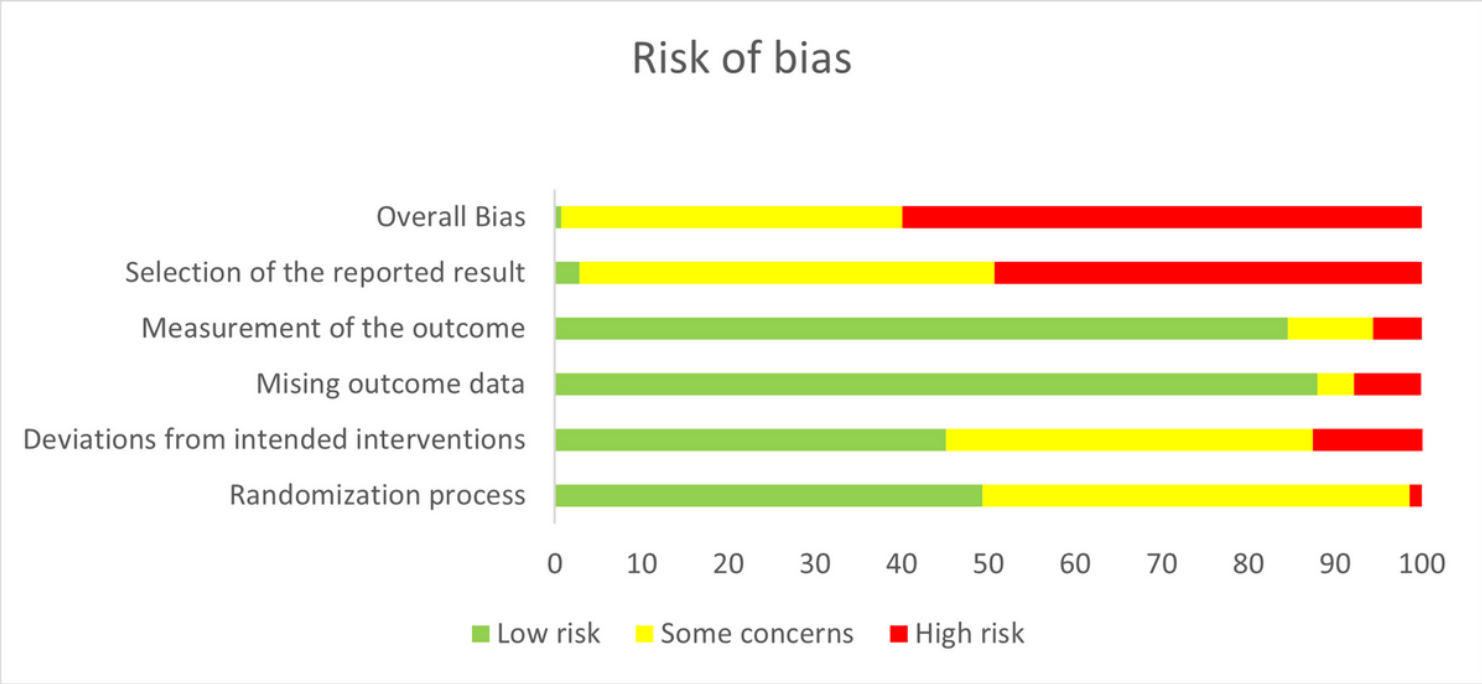


Figure 3

Risk of bias

Supplementary Files

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