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Meta-Research Of Periodontal Clinical Trials

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Meta-Research Of Periodontal Clinical Trials

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Dedicated to my family for their endless support, love, and encouragement.

I thank them, my faculty, my friends, and my co-residents for giving me strength to chase my dreams

“Life isn’t about waiting for the storm to pass; its about learning to dance in the rain”

Vivian Greene

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Introduction

Periodontitis is defined as a chronic inflammatory disease of the periodontal tissues. Inflammatory host response triggered by the accumulation of the bacterial biofilm causes gradual destruction of the alveolar bone, and connective tissue loss [1, 2]. Therefore, a perturbation in the microbial ecology is instrumental in causation of periodontal disease, in addition to dysregulation of local and systemic inflammatory response which can accentuate the disease [1].

Periodontal disease was recorded in Guinness World Records in 2001 as the common disease of mankind. Severe periodontitis reached the sixth most prevalent condition affecting 743 million people aged 15–99 years old worldwide. With an overall prevalence of 11.2%, the global cost of lost productivity for severe periodontitis has been estimated to be 54 billion USD/year [3-8].

Randomized controlled trials (RCTs) are considered the gold standard because they provided the strongest evidence for efficacy of clinical interventions which are a critical role in healthcare decision making [9, 10]. The characteristics of RCTs such as randomization, prevents bias during the different steps of conducting clinical studies [11]. However, they are not always feasible or ethical to conduct.

Absence of registration and protocol submission, in addition to poor documentation in biomedical studies can produce bias threats, inefficient knowledge building, misleading results and waste valuable resources [12-14]. Other parts of concern related to RCTs are bias, secondary publications, registration, and spinning the results. Bias in its several forms promotes in-efficacy in knowledge building and over estimating false results [15].

A recent systematic review showed that dental journals characterized by suboptimal reporting and quality [16, 17]. In biomedicine 50% of research reports were poor and unusable, therefore

high amount of waste mandates research to improve reporting [18, 19]. The validity and reliability of trial results are largely dependent on the study design and methodology. In 1996, the authors of the Consolidated Standards of Reporting Trials (CONSORT) statement issued specific guidelines intended to standardize and improve the quality of reporting of RCTs [20].

In addition, international Committee of Medical Journal Editors (ICMJE) in 2005 recommended registration of RCT protocols in a public register [21]. The importance of RCT registration is to decrease selective reporting of positive finding. Studies showed that only ½ of biomedical journals adhered to ICMJE requirement [22]. This illustrates the lack in the transparency of the periodontal clinical research [23].

Therefore, good quality randomized clinical trials are still needed to develop clinical guidelines for periodontal management of patients with systemic condition.

This research project touches two of the most published RCTs in Periodontology, including the association between cardiovascular diseases and chronic periodontitis, and the use of adjuncts along with periodontal therapy to improve clinical outcomes of periodontitis.

Reporting quality and spin in abstracts of randomized clinical trials of periodontal therapy and cardiovascular disease outcomes.

Introduction:

The abstract of randomized clinical trials (RCT) provides the reader with the first account of the trial objectives, methodology and results. Therefore, reporting accuracy, clarity and quality have a critical role during the initial assessment of the trial and affects the decision to read the full text [24]. Furthermore, in many geographic locations, RCT abstracts are often the only section of an RCT freely accessible to clinicians [25].

In recognition of the importance of RCT abstracts, the Consolidated Standards of Reporting Trials (CONSORT) for abstracts guidelines [26] were developed as an extension to the original CONSORT addressing clarity, completeness and transparency and ensuring that key trial elements are properly reported. Hence, poor reporting refers to omitting important information in abstracts as required by the well-defined CONSORT items [25].

Furthermore, spin, otherwise known as propaganda, is defined as failure to accurately and faithfully report the findings of a scientific study in a manner that would affect the reader's perception of the outcomes [27]. The tool for spin assessment in publication abstracts [27] identifies reporting practices that constitute an intentional or unintentional attempt to spin the results and/or conclusions leading to misreporting and bias. Despite the development of reporting and spin guidelines, abstracts in biomedical literature are often characterized by poor reporting quality and biased finding interpretation [28-32].

The impact of poor reporting and spin on the public and professional perception of research findings is discernible. In fact, abstracts with high levels of spin were found to be more frequently read compared to abstracts of the same trial after being edited to omit spin, and were also more

likely to mislead clinicians to accept a clinical intervention as being beneficial despite a non-significant primary outcome [24]. Moreover, spin in abstracts percolates into media coverage and press releases, which in turn generates greater public attention [33]. Paradoxically, articles that received greater media attention showed improved citation metrics in subsequent publications [34], creating what resembles of a vicious circle of public and scientific misinformation.

Ever since the publication of the earliest studies indicating a correlation between cardiovascular (CVD) disease and periodontitis [35, 36], the findings have received considerable professional and public interest. To test causal relationships, several RCTs explored the effect of periodontal therapy on CVD outcomes. Subsequently, the topic has sparked intense debates between researchers, caused wide-scale media coverage and public interest, and prompted involved professional organizations to issue official statements [37, 38].

Although multiple periodontal-CVD RCTs have been published, the adherence to the CONSORT guidelines and the incidence of spin have not been studied. Therefore, the aim of this study was to evaluate the reporting quality and the incidence of spin in abstracts of RCTs investigating the effect of periodontal therapy on CVD disease outcomes.

Materials and Methods:

Search methods and study selection:

Studies were retrieved from PubMed, Scopus based on search strategy shown below. In addition, we crosschecked 17 trial registration platforms included in the World Health Organization International Clinical Trials Registry Platform (ICTRP, www.who.int/trialsearch/) to confirm trial registration status and information (Appendix Table 1). The search was conducted for all registers on 01/01/2018.

Search keywords and limitations or filters for each database were as follows:

a. Pubmed: ("Lipids"[Mesh] OR "Acute-Phase Proteins"[Mesh] OR "Blood Pressure"[Mesh] OR "Arterial Pressure"[Mesh] OR "Hypertension"[Mesh] OR "Hypotension"[Mesh] OR "Cholesterol"[Mesh] OR "Cholesterol, LDL"[Mesh] OR "Cholesterol, HDL"[Mesh] OR "Cholesterol Esters"[Mesh] OR "Embolism, Cholesterol"[Mesh] OR "Cholesterol, VLDL"[Mesh] OR "Cardiovascular System"[Mesh] OR "Cardiovascular Infections"[Mesh] OR "Cardiovascular Abnormalities"[Mesh] OR "Cardiovascular Diseases"[Mesh] OR "Cardiovascular Physiological Phenomena"[Mesh] OR "Endothelium"[Mesh] OR "Endothelial Cells"[Mesh]) AND ("Periodontal Debridement"[Mesh] OR "Periodontal Diseases"[Mesh] OR "Periodontal Pocket"[Mesh] OR "Alveolar Bone Loss"[Mesh] OR "Dental Scaling"[Mesh] OR "Periodontitis"[Mesh] OR "Dental Prophylaxis"[Mesh] OR "Periodontal Attachment Loss"[Mesh]) filter: clinical trial
b. Scopus: TITLE-ABS-KEY (("Lipids" OR " Proteins*" OR "Pressure*" OR "Hypertension" OR "Hypotension" OR "Cholesterol" OR "Cardiovascular*" OR "Endothelium" OR "Endothelial*") AND ("Periodontal*" OR "Alveolar Bone Loss" OR "Dental*" OR "Periodontitis") AND "clinical trial") AND (LIMIT-TO (DOCTYPE , "ar"))
c. 17 trial registration platforms (Appendix a) were searched. Since these platforms were limited to one or two keywords, “periodont*” was used as a main keyword, then records were scanned for eligible studies.

The retrieved articles were hand-screened for identification of additional RCT reports (Figure 1), and then duplicates were excluded.

RCT report inclusion criteria:

1. Study Design:

   Only publications of periodontal-CVD RCTs. Cohort, non-randomized trials or observational trials were excluded. RCT publications in languages other than English were excluded.

2. Participants:

   Targeted populations included adult patients with no systemic diseases other than CVD diseases. Studies were included if the participants were diagnosed with chronic periodontitis only. Studies with participants diagnosed with aggressive periodontitis, gingivitis, or peri-implantitis were excluded.

3. Intervention:

   The tested intervention included either subgingival scaling and root planing (SRP) or SRP with adjunctive therapy. Interventional studies employing adjuncts alone, supragingival scaling alone or surgical therapy were excluded.

4. Outcomes:

   True or surrogate CVD outcomes were included. For descriptive purposes, outcomes were segregated into two groups [39]:

   a. CVD true events; such as angina, myocardial infarction, stroke, and CVD end points; such as CVD related-death.
   b. Surrogate outcomes; such as blood pressure, lipids, blood tests, C-reactive protein (hs-CRP), lipoproteins, and blood cell count.

Additional selection criteria for spin assessment:

Only studies with a clearly defined primary outcome were included in the spin analysis. To fulfill this condition, the primary outcome should be either explicitly stated in the abstract or the full text, or, in the case that the primary outcome was not explicitly reported, we considered the outcome

stated in the sample size calculations. If no outcome was stated in the sample size calculation, we deduced a primary outcome based on the stated objectives of the study. If no primary outcome could be identified, the study was excluded. In addition, studies with multiple primary outcomes were excluded.

Data extraction and compilation:

1. Selection of studies was carried out according to the inclusion criteria. Titles and abstracts of the search results were initially screened to look for possible eligible studies. Then, full texts were retrieved and assessed to further assess eligibility. In cases of multiple published reports associated with the same trial registration number, the primary publication focusing on the RCT results was selected.
2. Data extraction: Two authors (MS, KA) independently reviewed the abstracts -and the full texts, when needed- of the included RCT reports, and applied the CONSORT for abstracts and the SPIN checklist [24]. Disagreements were resolved by a third author (EI). Two items of the CONSORT abstracts guidelines were excluded because they only apply to unpublished studies or conference abstracts.
3. Characteristics of each RCT abstract and the respective publishing journal were extracted:
    a. Abstract word count
    b. Number of citations as shown on Scopus [40].
    c. Trial registration number, trial registration date was determined based on the information provided by the trial registry.
    d. Trial funding source, number of authors, geographic location,
    e. Trial's intervention and outcomes.
    f. Journal's 5 years-impact factor, impact factor without self-citation, influence factor as reported on Thomson-Reuters/Clarivate Analytics 2018 [41].

4. A decision-making guide was used to assist calibration and review process [42]. An Overall CONSORT Score for reporting quality (OCS) and Overall Spin Score (OSS) were calculated for each RCT report based on the CONSORT and Spin checklist.

Statistical Analysis

Cohen's Kappa test will be used to assess inter-rater agreement. For the descriptive analysis non-parametric categorical variables were expressed as proportion percent. For the exploratory bivariate association between OCS and related variables, we applied a Spearman correlation model. The limited sample size did not allow for a further multivariate regression model to assess predictors of reporting quality. Statistical analysis was performed with SPSS software (SPSS Inc).

Results:

1. *General findings:*

Twenty-four RCT reports were deemed eligible and entered the analysis (figure 1). Among them, one study was a secondary analysis publication (Bizzaro 2017). The PAVE study had multiple publications, and according to our inclusion criteria we included only the results publication (Offenbacher 2009).

For each trial, journal and article metrics are presented in Table 1. An overview of other outcomes of the included articles is shown Table 2.

Generally, all RCTs explored surrogate outcomes and none looked into CVD events (Table 2). Only 3 abstracts had explicitly stated primary outcome, while for the rest of the RCTs, we had to identify and extract the primary outcome from the full text (Table 2). RCTs with more than one outcome in the objectives were excluded from spin analysis as primary outcome identification was impossible.

Table 2 shows that SRP alone was used in 58.3% of the included RCTs, while SRP and adjuncts were used in 41.7%. Most o RCTs reported that they were funded (83.3%). Among them, 58% were funded intramurally, 46% by foundations, 29% by federal agencies, and 25% by industry. 60% of the funded RCTs had multiple funding sources.

Abstract word count for each trial is presented in Table 1, and was categorized into 3 groups according to CONSORT findings [26], which is presented in Table 2. 66.7% of the abstracts had <250-word count, 25% had word count from 250-300, and 8.3% had word count >300 [26].

2. CONSORT checklist findings

Following the RCT abstract assessment, OCS ranged from 2 to 9 out of 15. Table 3 presents the frequency of each CONSORT item fulfillment. Specifically, only 50% of the included RCTs reported that they were actually randomized clinical trials in the title.

Only 3 of the studies (13%) included the design of the study in the abstracts (i.e. parallel group, crossover, superiority, etc.).

2.a. Assessment of methods reporting:

Three items in the methods section lacked reporting in any of the RCTs, including the item “participants”, which lacked information about the location of the study and the detailed description of the participants that were included, and the item “randomization”, were all of the studies did not report the randomization method that was used, and the item “blinding”, were studies did not report the level blinding. The item “intervention” mostly lacked the necessary description of the intervention, therefore, only 54% of the RCTs fulfilled this item.

Most of the study abstracts (92%) included the objectives of the study. Interestingly, only 3 abstracts (18.5%) explicitly stated the primary outcome.

2.b. Assessment of results reporting:

Although 83% of the abstracts included the numbers of randomized populations, only 17% included the numbers of analyzed populations as part of the abstract materials and methods rather than the results section violating the CONSORT recommendations. Only 1 RCT indicated the harms in the abstracts (4%).

2.c. Assessment of conclusion, registration and funding reporting:

Only 13% discussed the results and conclusion of the primary outcome. Trial registration was reported in only 3 abstracts (13%). When the registration record was looked up in the public registry websites using the registration number included in the study, it was found that 4 RCTs registered retrospectively after the study was initiated and the first subject was recruited.

3. Spin analysis findings

After applying the exclusion criteria as outlined in the methodology, 14 out of the 26 RCT reports were included in the spin analysis. The prevalence and type of spin for the included articles is outlined in Table 4.

Some form of spin in both of the results and conclusions sections was detected in the majority of the RCTs (86%). Given that 79% of the included studies failed indicate the primary or secondary outcomes in the abstracts, we considered that these studies employed diverse strategies of spin.

In the results section, all items showed some form of spinning. 64% of the studies focused on statistically significant secondary outcomes, and on statistically significant within- and between-group comparisons of secondary outcomes.

In the conclusion sections, half of the included RCTs (50%) made hyped statements with 43% focusing only on significant results regardless if they corresponded to the primary outcome, 7%

focusing on another objective, and 7% making treatment recommendations. 64% acknowledged statistically non-significant results for the primary outcome yet emphasized the beneficial effect of treatment and emphasized other statistically significant results.

4. *Bivariate Correlation Analyses:*

The OCS ranged between 2-9 out of 15, which means some articles only had 2 items fulfilled from the whole checklist. The maximum number of items that have been fulfilled in one study is 9 out of 15 (figure 2). The OSS ranged between 1-13, which means some papers had only 1 item that included some sort of spin, and some articles had 13 items that were spun (figure 3).

Within the limitations of the study, there was no bivariate correlation between the OCS and the other variables (P-value >0.05), with the exception of the positive correlation between OCS and funding source reporting (correlation coefficient 0.416, P-value: 0.043). In addition, we observed a significant correlation between OCS and registration reporting in the abstract (correlation coefficient 0.518, P-value: 0.009). In summary, we observed that abstracts that included trial registration and funding information were characterized by high reporting quality.

OSS showed a marginal negative correlation with OCS (correlation coefficient -0.517, P-value: 0.059), which means the higher the reporting quality in the abstract, the lower the spin. OSS showed negative correlation with funding and registration; however, it wasn't significant. OSS showed marginal negative correlation with the number of authors (correlation coefficient of -0.509, P-value of 0.063).

Discussion:

Our study evaluated the reporting quality and incidence of spin in the abstracts of 24 RCT publications assessing the impact of periodontal interventions on CVD outcomes. To our knowledge, this is the first paper that evaluated both reporting quality and spin in abstracts of such publications. The overall reporting quality of the included abstracts was deemed to be generally poor. Overall, we found that the RCT objectives and numbers of randomized subjects were the only most adequately reported items (92% and 83% respectively). All other CONSORT items were adequately reported in almost less than 50% of the abstracts. Notably, we found limited RCT abstracts with adequate reporting on the exact trial design (17%), method of randomization (0%), blinding (0%), number of subjects analyzed (17%), harms (4%), outcomes in both trial arms (13%), as well as the interpretation of the results in the conclusions (13%). Our findings were in agreement with other studies in the medical and dental literature confirming inadequate reporting according to CONSORT guidelines [29, 43-45]. Surprisingly, even after dental journals adhered to the CONSORT for abstracts guidelines [45], those guidelines were not systematically reinforced. Therefore, RCT abstracts were still characterized by inadequate reporting quality.

Consistent with other reports, the CONSORT items most adequately reported in the RCT abstracts in our study were items related to objectives and numbers randomized. [44, 45]. Journal and article characteristics including impact factor or citation metrics were unreliable in predicting reporting quality, as confirmed in other studies [46]. The lack of significance in this correlation could be also related to the small number of included publications.

In regard to the spin analysis, it is noteworthy, that 10 of 24 the originally included RCT publications were excluded due the lack of an explicitly defined single primary outcome. The use of multiple primary outcomes in RCTs might allow researchers to find significance but in the absence of adequate power analysis for multiple outcomes, the risk of bias remains high.

The spin analysis according to the Boutron et al criteria [27] showed that various strategies of spin were adapted in the included abstracts (n=14). Specifically, spin phenomena in either the result or conclusion section of the abstracts were detected in the majority of the studies. Half of the abstracts presented a tendency for hyped conclusions. One third of the RCT abstracts presented the trial results in a before-after therapy manner focusing on within group analysis, highlighting statistical significance and ignoring the between group comparisons as directed by the study objectives. More than half of the RCT abstracts emphasized significance in secondary outcomes, a commonly used spin strategy, when the primary outcome results were not significant (Boutron et al.)

Our results agreed with other studies in the medical literature that investigated spin strategies and misrepresentation of RCT results with various methodologies [27, 46-49].

Our study has several strengths. We applied strict inclusion criteria and only included RCT publications examining the impact of periodontal intervention on CVD outcomes [50]. We standardized the data extraction methodology utilizing well defined decision guide and calibration between assessors. Therefore, we have demonstrated a high rate of inter-rater agreement with any differences resolved by a third evaluator to ensure greatest accuracy in our analysis. Although our study focused on RCT abstracts alone and not the full text of the included publications, these considerable reporting shortages and/or misrepresentations were a cause for concern given the wide attention abstracts receive within the healthcare and media communities.

Our study also has some inherent limitations. Although the spin assessment is characterized by subjectivity, two independent and calibrated reviewers per abstract conducted the data extraction and determined the spin strategies. With this method, we aimed to control the magnitude of subjectivity. We employed spin analysis previously used by other groups [24, 27, 31, 49]. Therefore, our analysis was focused on abstract sections and might have missed additional spin strategies present in the full text.

It is important to emphasize that although poor reporting quality might not imply poor study design [51], it certainly indicates lack of transparency and prevents replication of the experiment [52]. Therefore, reporting quality is necessary for the advancement of science [53]. Low quality reporting and introduction of spin might be contributing to continued controversy in this field of research [54], flawed professional and public perception of research findings [24, 33] and continued ill-advised expenditure of valuable time and resources [13]. The responsibility to improve reporting of RCTs and avoidance of misrepresentations falls on multiple parties. Journal editors and peer reviewers as gatekeepers could reinforce strict practices to ensure adherence to CONSORT or other reporting guidelines, and to require trial registration prior to the commencement of the trial as recommended by the ICMJE [55]. An additional effort by academic institutions, professional organizations, and scientific communities should be exerted to raise awareness among the general scientific audience on proper reporting practices and spin strategies. The scientific community should embrace post-publication appraisal and critique with a goal to improve reporting quality and minimize the incidence of spin.

Conclusions: Poor adherence to the CONSORT for abstracts guidelines and high levels of data “spin” were found in the abstracts of RCTs examining the effect of periodontal therapy on CVD outcomes. Our findings indicate that journal editors and reviewers should demand strict adherence to proper reporting guidelines by researchers and article authors to improve quality and reduce spin of results.

Tables and graphs:

Table 1: Characteristics of included articles and publishing journal:

RCT	Year	Journal metrices					Article metrices					
		Journal	5 years impact	Impact factor without self-citation	Eigenfactor	Influence factor	Abstract Word	Authors #	Citations	Registration	Geographic location	Funding
Bizzaro	2017	JCP	4.62	3.34	0.011	1.15	208	5	3	Yes	The Netherlands	Yes
Bokhari	2012	JCP	4.62	3.34	0.011	1.15	193	7	20	Yes	Pakistan	Yes
Carallo	2015	Medicine	2.19	1.89	0.05	0.59	237	11	132	No	Italy	No
Caula	2014	JCP	4.62	3.34	0.011	1.15	174	4	198	No	Brazil	Yes
Cortelli	2015	JP	3.52	3.02	0.011	0.86	266	5	113	Yes	Brazil	Yes
D'Auito	2005	J Dent Res	5.72	5.07	0.02	1.55	160	5	40	No	UK	Yes
D'Auito	2006	Am Heart Jour	4.63	4.08	0.04	2.11	346	6	27	No	UK	Yes
Fu	2016	Clin Oral Invest	2.55	2.23	0.011	0.68	240	5	682	No	China	Yes

Gul Oz	2007	Southern Medical Journal	0.96	0.81	0.002	0.32	145	7	36	No	Turkey	No
Gunupatti	2011	JP	3.52	3.02	0.011	0.86	239	3	12	No	India	No
Hada	2015	JP	3.52	3.02	0.011	0.86	277	4	1	Yes	India	No
Ide	2003	JCP	4.62	3.34	0.011	1.15	174	6	27	No	UK	Yes
Javed	2016	Lasers in Surgery and Medicine	2.74	2.49	0.004	0.59	249	8	16	No	Saudi Arabia	Yes
Kamil	2011	J perio Res	2.71	2.70	0.004	0.63	253	5	1	No	Jordan	Yes
Kapellas	2014	Hypertension	6.74	6.16	0.04	2.19	254	13	40	Yes	Australia	Yes
Li	2011	JCP	4.62	3.34	0.011	1.15	192	5	1	Yes	China	Yes
Lopez	2012	JP	3.52	3.02	0.011	0.86	310	6	88	No	Chile	Yes
Offenbacher	2009	JP	3.52	3.02	0.011	0.86	241	17	13	Yes	USA	Yes
Taylor	2010	Eur J Oral Sci	1.91	1.57	0.003	0.56	177	11	24	No	Australia	Yes

Tonetti	2007	NEJM	67.51	78.54	0.70	29.45	255	10	8	No	UK	Yes
Tüter	2007	JCP	4.62	3.34	0.011	1.15	201	12	240	No	Turkey	Yes
Ushida	2008	JCP	4.62	3.34	0.011	1.15	189	9	16	No	Japan	Yes
Vidal	2009	JP	3.52	3.02	0.011	0.86	228	4	5	No	Brazil	Yes
Zhou	2017	JP	3.52	3.02	0.011	0.86	252	10	25	Yes	China	Yes

Table 2: Other data which were collected

	CHARACTERISTIC	N=24	%
1	Nature of primary outcome		
	CV event	0	0
	Surrogate outcome	24	100
2	Identification of primary outcome		
	Explicitly stated in abstracts	3	13%
	Explicitly stated in full texts	3	13%
	From sample size calculation	7	29%
	Implied from objectives	8*	33%
4	Intervention		
	SRP alone	14	58.3%
	SRP + adjunct	10	41.7%
6	Source of funding		
	Foundation	11	46%
	Industry	6	25%
	Federal	7	29%
	Institution	14	58%
7	Word count		
	<250	16	66.7%
	250-300	6	25%
	>300	2	8.3%

- Had more than one primary outcome, they weren't included in the spin analysis

Table (3): % of fulfillment of CONSORT items across all RCTs:

CONSORT FOR ABSTRACT CHECK LIST	(NUMBER) PERCENTAGE
TITLE	12 (50%)
TRIAL DESIGN	3 (13%)
METHODS	
PARTICIPANTS	0.0%
INTERVENTIONS	13 (54%)
OBJECTIVE	22 (92%)
OUTCOME	3 (13%)
RANDOMIZATION (METHOD)	0 (0%)
BLINDING (MASKING)	0 (0%)
RESULTS	
NUMBERS RANDOMIZED	20 (83%)
NUMBERS ANALYZED	4 (17%)
OUTCOME	3 (13%)
HARMS	1 (4%)
CONCLUSIONS	3 (13%)
TRIAL REGISTRATION	3 (13%)
FUNDING	8 (33%)

Table 4: % of fulfillment of SPIN items across all RCTs:

TYPE OF SPIN	(NUMBER) PERCENTAGE
1) SPIN IN THE RESULT	
FOCUS ON STATISTICALLY SIGNIFICANT WITHIN-GROUP COMPARISON	3 (21%)
FOCUS ON STATISTICALLY SIGNIFICANT SECONDARY OUTCOMES	9 (64%)
FOCUS ON STATISTICALLY SIGNIFICANT SUBGROUP ANALYSES	2 (14%)
FOCUS ON STATISTICALLY SIGNIFICANT MODIFIED POPULATION OF ANALYSES (EG, PER-PROTOCOL ANALYSES)	4 (29%)
FOCUS ON STATISTICALLY SIGNIFICANT WITHIN- AND BETWEEN-GROUP COMPARISONS FOR SECONDARY OUTCOMES	9 (64%)
OTHER SPIN: NO DEFINITION OF PRIMARY OR SECONDARY OUTCOMES	11 (79%)
2) SPIN IN THE CONCLUSIONS	
FOCUS ONLY ON TREATMENT EFFECTIVENESS:	
1. CLAIMING EQUIVALENCE FOR STATISTICALLY NONSIGNIFICANT RESULTS	0 (0%)
2. CLAIMING EFFICACY WITH NO CONSIDERATION OF THE STATISTICALLY NONSIGNIFICANT PRIMARY OUTCOME	9 (64%)
3. FOCUSING ONLY ON STATISTICALLY SIGNIFICANT RESULTS	6 (43%)
ACKNOWLEDGE STATISTICALLY NONSIGNIFICANT RESULTS FOR THE PRIMARY OUTCOME BUT EMPHASIZE THE BENEFICIAL EFFECT OF TREATMENT	9 (64%)
ACKNOWLEDGE STATISTICALLY NONSIGNIFICANT RESULTS FOR THE PRIMARY OUTCOME BUT EMPHASIZE OTHER STATISTICALLY SIGNIFICANT RESULTS	9 (64%)
OTHER SPIN IN CONCLUSIONS SECTION:	
1. CONCLUSION RULING OUT AN ADVERSE EVENT ON STATISTICALLY NONSIGNIFICANT RESULTS	0 (0%)
2. CONCLUSION FOCUSING ON WITHIN-GROUP ASSESSMENT (BOTH TREATMENTS ARE EFFECTIVE/TREATMENT ADMINISTERED IN BOTH GROUPS IS EFFECTIVE (EG, ADD-ON STUDIES)	2 (14%)
3. RECOMMENDATION TO USE THE TREATMENT	1 (7%)
4. FOCUS ON ANOTHER OBJECTIVE	1 (7%)

5. COMPARISON WITH PLACEBO GROUP OF ANOTHER TRIAL	0 (0%)
6. STATISTICALLY NONSIGNIFICANT SUBGROUP RESULTS REPORTED AS BENEFICIAL	0 (0%)
OTHERS: INADEQUATE EXTRAPOLATION TO LARGER POPULATION, INTERVENTION OR OUTCOME	12 (86%)
HYPE	7 (50%)
3) SPIN IN BOTH RESULTS AND CONCLUSIONS	12 (86%)

Figure 1: Diagram of search results

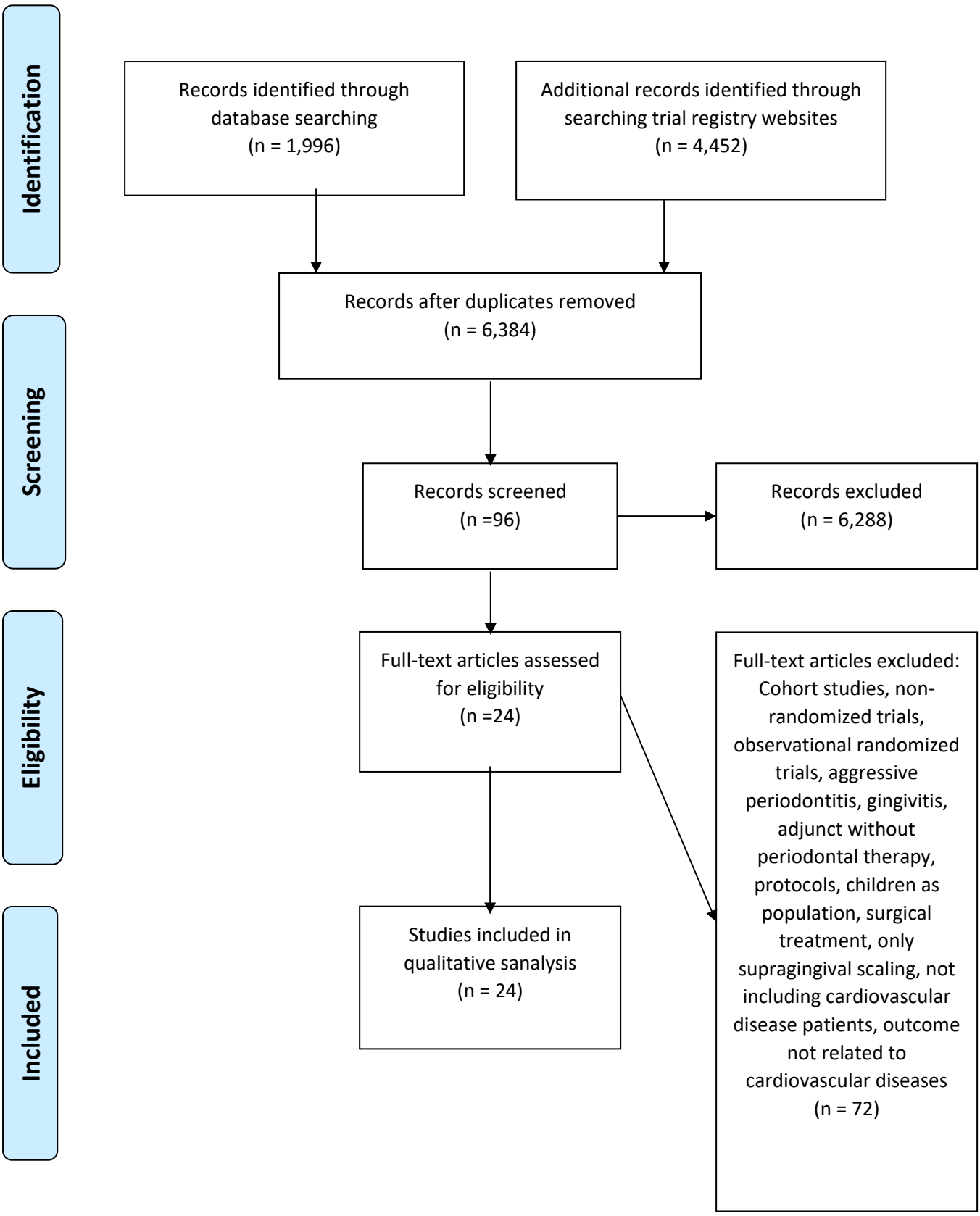


Figure 2: Overall Consort score (OCS) for each article

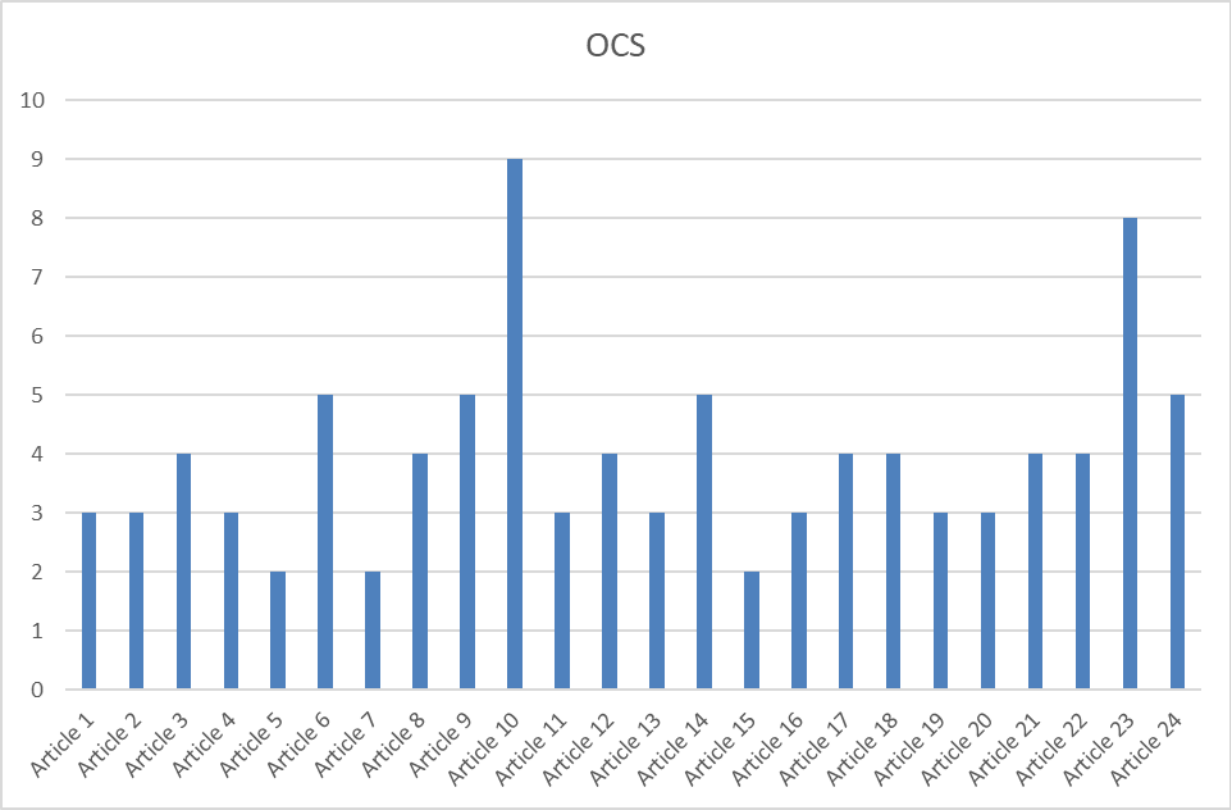
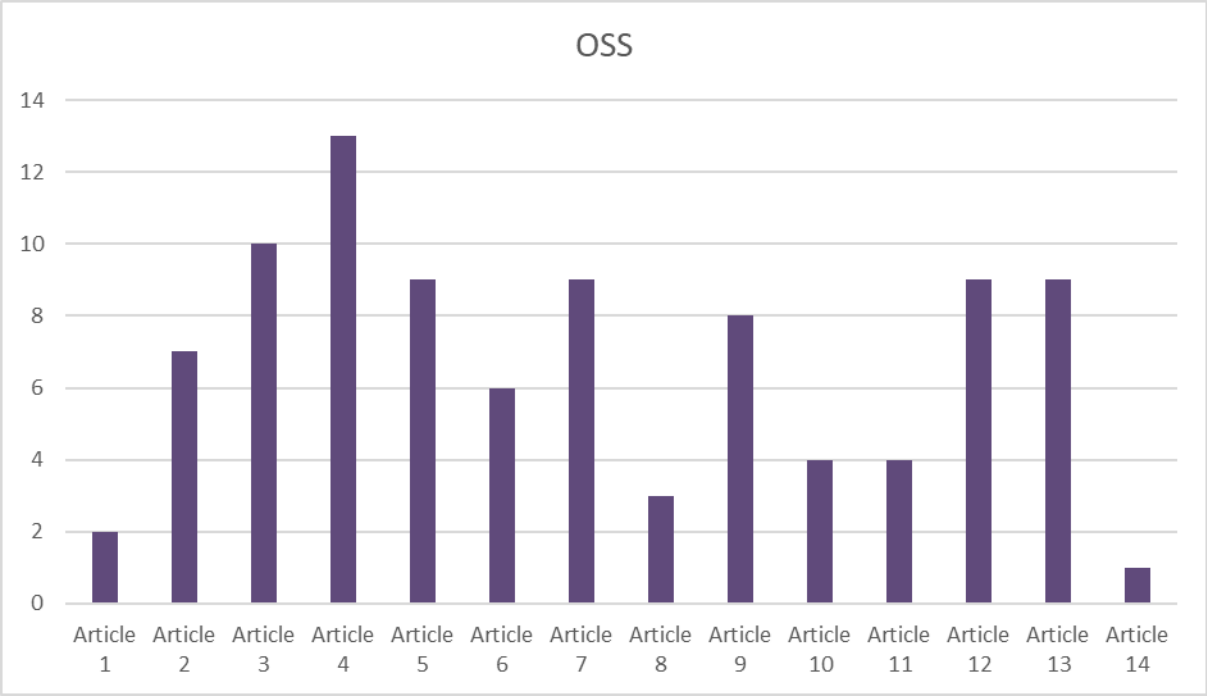


Figure 3: Overall Spin score (OSS) for each article



Appendix

Table 1: List of the trials register that were used to identify eligible studies

Australian new zealand clinical trials registry (anzctr)
Brazilian clinical trials registry (rebec)
Chinese clinical trial register (chictr)
Clinical research information service (cris), republic of korea
Clinicaltrials.gov
Clinical trials registry – india (ctri)
Eu clinical trials register (eu-ctr)
German clinical trials register (drks)
Iranian registry of clinical trials (irct)
Isrctn.org
Japan primary registries network (jprn)
Sri lanka clinical trials registry (slctr)
The netherlands national trial register (ntr)
Cuban public registry of clinical trials (rpcec)
Thai clinical trials registry (tctr)
Pan african clinical trial registry (pactr)
Peruvian clinical trial registry (repec)

Unusual Findings In A Group Of Studies Evaluating Agents Adjunctive To Scaling And Root Planning: Quality Assessment

Introduction

Scaling and root planing (SRP) is the first mode of therapy for periodontitis and is centered on the mechanical removal of supragingival and subgingival bacterial deposits with the objective of reducing periodontal inflammation, reducing periodontal probing depths and improving clinical attachment levels around the teeth [56-59].

The clinical impact of combining SRP with various adjunctive agents has been tested with the aim of improving therapeutic outcomes [60-64]. In 2015 the Council on Scientific Affairs of the American Dental Association published a systematic review on the effect of different adjuncts on clinical attachment level (CAL) as the primary outcome in randomized clinical trials (RCT) [63].

Results of this systematic review showed that the quality of evidence is only moderate [63]. The meta-analysis showed a modest effect size of adjuncts in combination with SRP. However, a single research group published a relatively large number of clinical trials on this subject (n=34, approximately 4 trials per year) and showed consistent large effect sizes of the various adjunctive agents tested and these results haven't been reproduced. Recent evidence has suggested that phase 2 and 3 RCTs require at least on average 2 years to publish [65-69], revealing the demanding requirements for RCT publication particularly in high impact journals. A recent systematic review and meta-analysis evaluating the adjunctive effects of statins to SRP showed promising large effect sizes but warned that the same research group mentioned above produced almost all the trials included. A companion report (ref) compared the results of a meta-analysis of the results of this single research group to the most recent ADA meta-analysis to identify possible causes for the observed difference in effect sizes.

Adequate and complete reporting of RCT's is crucial in evaluating outcomes and allowing the replication of these trials. Hence, the aim of this study is to identify RCT reports on SRP adjuncts published by the same group within the last 8 years, and to assess the reporting quality of the selected RCTs and trial registration discrepancies.

Materials and Methods:

1. *RCT search methods and identification*

Research was registered in a public registry website: Open Science Framework, https://osf.io/4meyd/. To identify the groups of authors with the most frequently published RCTs in the field of adjuncts with periodontal therapy, a search was run in Scopus from 2010-2017. Simple keywords were used to include most of the RCTs that are related to this topic, and to generate the results of this first step: ("periodont*" AND "adjunct*" AND "clinical trial*"). After assessing the names of the authors with the most frequently published RCTs. It was shown that these authors belong to one group. The names of the authors were hand searched in Scopus and Pubmed to retrieve all the RCTs that were published under their names. Duplicates were then excluded.

2. *RCT report inclusion criteria:*

a. Study Design:

Only randomized controlled trials (including cluster trials and cross-over studies, non-inferiority design and superiority designs) were included. Cohort, non-randomized trials or observational trials were excluded. RCT reports in languages other than English were excluded. Studies that did not report baseline or did not have a minimum follow-up period of 6 months were excluded.

b. Population and disease:

No distinction in term of patients and the type of periodontitis. RCTs that included gingivitis, sensitivity, and peri-implantitis were excluded.

c. Intervention:

Only RCTs related to periodontal therapy with SRP and adjuncts were included. RCTs that looked into furcation defects were excluded. Adjuncts such as lasers, photodynamic therapy, platelet fibrin were excluded. RCTs that included treatments other than SRP were excluded.

d. Outcomes:

All possible periodontal parameters; change in probing depth (PD), clinical attachment level (CAL), radiographic bone fill, plaque score, and bleeding on probing.

3. Data extraction and compilation:

A data extraction sheet based on the Cochrane Handbook for Systematic Reviews of Interventions guidelines was developed. Two authors (KA, MS) independently extracted the data from the studies that were included. Disagreements were resolved by consensus or in consultation with a third reviewer (EI). Cohen's Kappa test will be used to assess inter-rater agreement.

From each study, the following information were extracted:

(1) Quality characteristics of the study (example, registration, population, type of intervention, type of periodontal disease, primary and secondary outcomes, inclusion criteria of the sites, sample size and sample size calculation, baseline and 6 months results. and sample size). If trial was registered, the registry number was used to extract the following additional information from the online registration data:

A. Data from registry website was cross-matched with the data that was extracted from the article.

B. Determine whether there was pre-study power analysis and identification of primary and secondary outcome.

(2) Characteristics of the journal (year of starting and ending the trial, year of submission, follow-up period, impact factor). Subsequently, the following variables were defined:

A. X: The interval between trial initiation and termination

B. Y: The trial follow-up period per protocol.

C. When X>Y, trial reporting was deemed realistic. If X=Y, then trial reporting signifies an unrealistic process since it implies that all participants were recruited, enrolled, and randomized at the first day of the trial, and all interventions completed and the follow-up examinations done within the “X” interval. If Y>X, trial reporting was deemed realistic.

(3) RCT Outcomes to conduct a meta-analysis (to be published in the second part of this study).

The consolidated standards on reporting trials (CONSORT) statement guidelines were applied to assess reporting quality of each RCT. The Analysis of the “abstract” item according to CONSORT was excluded since this study focuses on the full text, and considering that abstracts have their own CONSORT reporting guidelines.

Extracted data were entered into a pre-formatted database spreadsheet using Microsoft Excel Software (Version 1707, Microsoft).

Descriptive analysis per CONSORT item. Specifically, every CONSORT item will be scored as fulfilled or not fulfilled (each item will be treated categorically), and therefore, analyzed with non-parametric statistics. For the inter-rater agreement, 0.7 will be used to conclude that there was high agreement between the two reviewers.

Results:

1. *General findings:*

Thirty-four were deemed eligible (Figure 1).

Table 1 shows the general data that was retrieved from each RCT. Table 1. A represents the bibliometric information of published trials, and Table 1. B represents the chronological comparisons between per protocol and published trial.

One paper didn't include the baseline data

2 RCTs reported outcome data in abstracts and not in in the results section. All of the RCTs included part of the demographic data in the materials and methods rather than the results section.

2. *CONSORT checklist findings:*

Table 2 represents the frequency of each CONSORT item fulfillment. The overall CONSORT score for the RCTs ranged from 4-12 out of 36.

Some items were scored as not fulfilled since there were no information were found in the RCTs, including: Important changes to methods after trial commencement, any changes to trial outcomes after the trial commenced, why the trial ended or was stopped, and binary outcomes analysis.

Introduction and objectives:

The term "Randomization" was included in the title in 94% of the RCTs.

The item "Scientific background and explanation of rationale" was only fulfilled in 5.9% of the RCTs, because most of the RCTs lacked a comprehensive and explanatory literature about the chosen adjunct. Phase 1 human clinical trials to assess the safety of the dosages where not cited or conducted.

47% of the RCTs had a specific objective or hypothesis, the objective/ hypothesis in the rest of the RCTs didn't include a specific outcome, population, or intervention so this item wasn't fulfilled.

Study design and intervention:

Trial design had 0% fulfillment because at least one of the design aspects was missing. The CONSORT items "Blinding level", "the number of study's arms", and "the allocation ratio" weren't reported in most of the studies.

Although the outcomes and methods in some trials were either inconsistent with the registration or were inconsistent throughout the study, none of the trials reported any changes, and therefore, the CONSORT item "changes to methods after commencement of study" scored 0%.

The CONSORT item "participants' eligibility criteria" scored a fulfillment score of 0% because none of those criteria were reported but rather the included participants' criteria were reported in the materials and methods, and only the sites' eligibility criteria were included in the methods section.

All articles reported the location where the study took place, however, the dates of recruitment or procedures or the follow up were missing, and therefore the CONSORT item "setting and location" wasn't fulfilled.

67.6% of the RCTs fulfilled the CONSORT item "interventions", Studies that failed to report the details of the intervention in manner allowing its replication were considered not to fulfill this item.

Only 50% of the RCTs had pre-defined primary and secondary outcomes, the rest did not specify which items were primary or secondary, and none of them had the primary outcome included in sample size and power analyses. Although some of the RCTs included the primary outcome for the sample size analysis, some of the analysis aspects were missing to finalize the sample size, such as standard deviation, effect size, and attrition percentages, therefore the CONSORT item "specified primary and secondary outcomes" scored as 0 for all the RCTs.

None of the RCTs reported any changes to trial outcomes after the trial commenced or gave reasons for the change. This item was going to be removed from the checklist since from the initial RCTs analysis, none of the RCTs showed any changes in the trail, however after discrepancies in the online registry were found this item was kept in the checklist and scored 0.

Randomization and blinding:

None of the RCTs reported the type/level of randomization, however, 41.2% of the RCTs reported the randomization method.

Only 11.8 of the RCTs reported the mechanism of allocation concealment, the rest of the RCTs did not even include it in the methods section.

Randomization was only implemented in 8.8%. This means most of the RCTs did not fully- report the information about who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions.

Blinding was only fulfilled in 14.7% of the RCTs. Most of the RCTs did not report the level of blinding. In some of the RCTS, although the level of blinding was reported, there was a discrepancy between the level of blinding that was reported, and the blinded arms.

Outcomes:

97.1% reported the analysis test that was used to compare the outcomes between the groups, and additional analysis was only reported in 23.5% of the RCTs.

The item “Participant flow” was fulfilled in 29.4% of the RCTs, because only the randomized number of participants were included, rather than the randomized number of sites, specially in studies that had the analysis on a site level and not on a participant level.

Only 17.6% of the studies gave reasons why the patients were lost for follow-up.

The analyzed RCTs included per-protocol follow-up period, but not the initial and the end dates of the follow-up period.

8.8% of the studies reported baseline demographic and clinical characteristics for each group, the other RCTs did not fulfill this item because none reported the groups' baseline demographic data.

All RCTs followed "per protocol" analysis, and none followed the intent to treat analysis, therefore, none of the RCTs fulfilled this item.

The item "outcome and estimation" scored 0 because none of the trials reported the effect size of the results.

Discussion:

76.5% of the RCTs reported any harms or adverse effects of the adjuncts in the results section.

Only 1 trial discussed the limitation of the study, none of other RCTs talked about the study's limitations or any potential bias.

The item "generalizability" only 5.9% of the RCTs fulfilled it, which means only 5.9% of the studies did not generalize its results to the overall population, however, the rest of the RCTs did.

The item "interpretation" in the discussion part scored 0, because all RCTs didn't discuss the harms and benefits of the adjunct. In addition, most of the discussion did not include the findings in other literature rather the studies that were included were the ones published by the same group.

Only 20.6% of the trials reported registration number.

None of the trials reported a pre-published protocol.

Only 70.6% reported whether the study was funded or not, and the source of funding.

3. *Comparison between the published articles and the pre-registered records:*

The 7 RCTs that were registered, were compared to the information that were registered online.

None of the trials were pre-registered although pre-registration is recommended by international committee of medical journal editors (ICMJE).

Although RCTs didn't mention any change of the trial design in the published manuscripts, differences between the published papers and the registration information were found.

Table 3 shows the comparison between the published articles and the pre-registered records. Table 3 A shows the data recovered from the published trials, and Table 3 B shows the data recovered from clinicaltrials.gov.

In one RCT, the follow up period in the published paper did not match the registry. In the same registry, the period listed was different in each paragraph.

The Funding source of all the published RCTs did not match with the funding source that was reported in the online registry.

Two of the RCTs had different inclusion criteria in the published trials compared to the online registry.

Only 2 of the published RCTs had reported the same blinding level as in the online registry, the rest had a different blinding level.

One of the RCTs' online registry had different trial initiation and termination dates compared to the same published RCT.

Three of the trials had different sample enrolment reported in the online registry compared to the published trial.

One trial included participants that were younger in age compared to the age range that was proposed in the online registry.

Three of the trials reported a follow-up period in the published trial that was different compared to the online registry.

One trial did not report the primary outcome in the published RCT but it was reported in the online registry. Two trials had different primary outcome reported in the published RCTs compared to the online registry.

4. *Trial period and follow-up period.*

According to our variables' definition in the materials and methods section, were grouped all the included RCTs into three categories in Table 4.

29% of the RCTs their reported dates of initiation and termination of the trial compared to per protocol follow-up period is unreliable or problematic, which means the last day of the follow-up period wasn't achieved or the dates that were reported were not reported correctly. 29% of the RCTs' initiation and termination dates deemed un-realistic. Only 38% of the RCTs' initiation and termination dates deemed realistic.

Publication period was defined as the time between the RCTs' termination date and submission date

Discussion:

Quality reporting of RCT's is considered essential to allow for an accurate and through appraisal of a clinical trial [70, 71]. The identification of bias and poor methodology is only possible with complete and transparent reporting practices, which would in turn allow the decision-maker to assess the quality of the trial [71]. The CONSORT statement was developed to standardize the reporting of RCT's and includes items to assess the risk of bias and proper study methodology [70]. Our study found that the large number of RCT's published by Pradeep et al on therapeutic pharmaceutical agents adjunctive to SRP suffer from poor reporting quality according to the CONSORT guidelines. Significantly, items that are important in assessing risk of bias such as randomization, blinding and allocation concealment [72-74] were very poorly reported (8.8%, 11.8 and 14.7% respectively).

Public trial registries were introduced and trial pre-registration was either mandated or encouraged by journal editors to minimize bias [75]. It is intended to discourage researchers from

changing study protocols such as the outcomes being assessed, trial size, or follow up time, all of which are believed to introduce bias towards significant results and subsequent publication bias [76-78]. Only 7 of the 32 RCT's examined in this study were pre-registered online, and among those registered trials, various protocol discrepancies exist between the manuscript and the online trial registration record. The detected changes were not reported as is expected in good scientific reporting and required by CONSORT guidelines.

Assessment of the reported length of the RCT relative to the follow up period, almost 60% were considered either problematic

Tables and graphs:

Table 1: A. Bibliometric information of published trials

Title	Journal	Journal impact factor*	Journal ICMJE adherence	Journal pre-registration requirement	Journal CONSORT adherence	IRB requirement
Pradeep AR-16 2016	Journal of periodontology	3.392	Yes ₸	Required starting Jan 1, 2016	Y	Y
Pradeep AR-5 2013	Journal of the International Academy of Periodontology	Not listed	Not reported	Not reported	N	Y
Pradeep AR-1 2016	Journal of periodontology	3.392	Yes ₸	Required starting Jan 1, 2016	Y	Y
Pradeep AR-6 2015	Journal of the International Academy of Periodontology	Not listed	Not reported	Not reported	N	Y
Pradeep AR-7 2014	Journal of Investigative and Clinical Dentistry	Not listed	Not reported	Encourages	Y	Y
Martande SS-1 2014	Journal of Investigative and Clinical Dentistry	Not listed	Not reported	Encourages	Y	Y
Priyanka N-1 2015	Contemporary Clinical Dentistry	Not listed	Yes 5/29/18	Encourages	Y	Y
Martande SS-2 2015	American Journal of Dentistry	0.76	Not reported	Not reported	Y	N
Sharma A-1 2012	Journal of periodontology	3.392	Yes ₸	Required starting Jan 1, 2016	Y	Y
Sharma A-2 2012 AG	Journal of periodontology	3.392	Yes ₸	Required starting Jan 1, 2016	Y	Y
Priyanka N-3 2017 AG	The international journal of perio and resto dentistry	Not listed	Not reported	Not reported	N	N
Pradeep AR-14 2013	Journal of periodontology	3.392	Yes ₸	Required starting Jan 1, 2016	Y	Y
Martande S-1 2017	Journal of Dental Research, Dental Clinics, Dental Prospects	Not listed	Yes 9/14/16	Require reg # but no pre-registration requirement	N	Y
Pradeep AR-9 2016	Journal of Investigative and Clinical Dentistry	Not listed	Not reported	Encourages	Y	Y
Pradeep AR-12 2017	Journal of periodontology	3.392	Yes ₸	Required starting Jan 1, 2016	Y	Y
Agarwal E-1 2012	Journal of periodontology	3.392	Yes ₸	Required starting Jan 1, 2016	Y	Y
Pradeep AR-15 2015	Journal of periodontology	3.392	Yes ₸	Required starting Jan 1, 2016	Y	Y
Pradeep AR-11 2016	Journal of Investigative and Clinical Dentistry	Not listed	Not reported	Encourages	Y	Y
Kumari M-1 2016	Journal of periodontology	3.392	Yes ₸	Required starting Jan 1, 2016	Y	Y
Priyanka N-2 2015	Journal of the International Academy of Periodontology	Not listed	Not reported	Not reported	N	Y
Pradeep AR-13 2013	Journal of periodontology	3.392	Yes ₸	Required starting Jan 1, 2016	Y	Y
Pradeep AR-10 2013	Journal of periodontology	3.392	Yes ₸	Required starting Jan 1, 2016	Y	Y
Kathariya R-1 2014	Journal of Investigative and Clinical Dentistry	Not listed	Not reported	Encourages	Y	Y
Pradeep AR-2 2013	Australian Dental Journal	1.494	Not reported	Not reported	Y	Y
Pradeep AR-8 2012	Journal of periodontology	3.392	Yes ₸	Required starting Jan 1, 2016	Y	Y
Agarwal E-2 2012	Journal of periodontology	3.392	Yes ₸	Required starting Jan 1, 2016	Y	Y
Bajaj P-1 2012	Journal of Investigative and Clinical Dentistry	Not listed	Not reported	Encourages	Y	Y
Rao NS-1 2013	Journal of periodontology	3.392	Yes ₸	Required starting Jan 1, 2016	Y	Y

Sharma A-3 2017	Journal of applied oral science	1.709	Not reported	Required starting Jan 1, 2016	Y	Y
Rao NS-1 2016	Australian Dental Journal	1.494	Not reported	Not reported	Y	Y
Kumari M-2 2016	Journal of Investigative and Clinical Dentistry	Not listed	Not reported	Encourages	Y	Y
Pradeep AR-3 2012	Journal of periodontology	3.392	Yes ₸	Required starting Jan 1, 2016	Y	Y
Pradeep AR-4 2011	Archives of Oral biology	2.05	Not reported	Not reported	N	N
Kanoriya R-2 2017	Journal of Investigative and Clinical Dentistry	Not listed	Not reported	Encourages	Y	Y

*According to Thomson Reuters 2017

₸ No date was listed

Table 1: B. Chronological comparisons between per protocol and published trial

Title	Initiation date	Termination dates	Submission date	Publication date	Interval between initiation and termination	Interval between termination and publication	Per protocol follow-up
Pradeep AR-16 2016	Sep-14	Jun-15	Dec-15	Jul-16	9.1	13.2	9
Pradeep AR-5 2013	Jun-11	Nov-11	-	Apr-13	5.1	-	6
Pradeep AR-1 2016	Jun-14	Dec-14	Mar-15	Mar-16	6.1	11.8	6
Pradeep AR-6 2015	Feb-12	Sep-12	-	Jul-14	7.1	-	6
Pradeep AR-7 2014	Feb-12	Jul-12	Mar-13	82015	5.0	28.5	6
Martande SS-1 2014	Jul-11	Aug-12	5/2013	Feb-16	13.2	33.5	12
Priyanka N-1 2015	Oct-11	Apr-12	-	Jul-15	6.1	-	6
Martande SS-2 2015	Jan-12	Jul-12	-	Jun-15	6.1	-	6
Sharma A-1 2012	Jul-10	Dec-10	Feb-11	Jan-12	5.1	10.7	6
Sharma A-2 2012 AG	Aug-10	Feb-11	Apr-11	Jan-12	6.1	9.16	6
Priyanka N-3 2017 AG	Apr-12	Oct-12	-	Mar-17	6.1	-	6
Pradeep AR-14 2013	Aug-11	May-12	6/2012	Jul-13	9.1	12.4	9
Martande S-1 2017	2/2013	Nov-13	May-15	Mar-17	9.1	22.3	6
Pradeep AR-9 2016	Jul-14	Mar-15	Aug-15	Aug-17	8.1	24.4	9
Pradeep AR-12 2017	Nov-13	Aug-14	2/2015	Oct-17	9.1	32.1	9
Agarwal E-1 2012	Sep-10	Jul-11	Oct-11	Sep-12	10.1	11.2	6
Pradeep AR-15 2015	Jan-14	Jun-14	Nov-14	Jun-15	5.0	7.06	6
Pradeep AR-11 2016	Aug-13	Jan-14	Mar-14	Aug-16	5.1	29.5	6
Kumari M-1 2016	Jan-12	Nov-12	Apr-13	Nov-16	10.2	43.6	9
Priyanka N-2 2015	Feb-12	Sep-12	-	Apr-15	7.1	-	6
Pradeep AR-13 2013	Jan-11	Sep-11	Dec-11	Jan-13	8.1	13.2	9
Pradeep AR-10 2013	Jan-11	Sep-11	Jan-12	Feb-13	8.1	13.2	6
Kathariya R-1 2014	Mar-11	Jun-11	Jul-12	Feb-14	3.1	19.3	3
Pradeep AR-2 2013	Dec-10	Nov-11	Mar-10	Mar-13	11.2	36.5	9
Pradeep AR-8 2012	Nov-10	Apr-11	May-11	Oct-12	5.0	17.3	6
Agarwal E-2 2012	Mar-11	Dec-11	Mar-12	Dec-17	9.2	70.0	9
Bajaj P-1 2012	Dec-10	Jul-11	Nov-11	Nov-12	7.1	12.2	6
Rao NS-1 2013	Nov-11	Apr-12	May-12	Aug-13	5.1	15.2	6
Sharma A-3 2017	Mar-10	Apr-11	May-16	May-17	13.2	12.2	6
Rao NS-1 2016	Jan-11	Nov-11	May-12	Jun-13	10.1	13.2	9
Kumari M-2 2016	Mar-12	Feb-13	Apr-17	May-17	11.2	1	9
Pradeep AR-3 2012	Nov-10	Jul-11	Sep-11	Sep-12	8.1	11.5	6
Pradeep AR-4 2011	Nov-09	Nov-10	-	Mar-11	12.2	-	6
Kanoriya R-2 2017	May-15	Oct-15	Oct-16	Mar-17	5.1	12.2	6

Table 2: item fulfilment per CONSORT guidelines checklist

Section/Topic	Item No	Checklist item	Fulfilment score	Fulfilment percentage
Title				
	1a	Identification as a randomised trial in the title	32	94.1
Introduction				
Background and objectives	2a	Scientific background and explanation of rationale	2	5.9
	2b	Specific objectives or hypotheses	16	47.1
Methods				
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	0	0
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	0	0
Participants	4a	Eligibility criteria for participants	0	0
	4b	Settings and locations where the data were collected	0	0
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	32	67.6
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	17	50
	6b	Any changes to trial outcomes after the trial commenced, with reasons	0	0
Sample size	7a	How sample size was determined	0	0
	7b	When applicable, explanation of any interim analyses and stopping guidelines	0	0
Randomisation:				
Sequence generation	8a	Method used to generate the random allocation sequence	14	41.2
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	0	0
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	4	11.8
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	3	8.8
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	5	14.7
	11b	If relevant, description of the similarity of interventions	0	0
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	33	97.1
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	8	23.5
Results				
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	10	29.4
	13b	For each group, losses and exclusions after randomisation, together with reasons	6	17.6
Recruitment	14a	Dates defining the periods of recruitment and follow-up	0	0
	14b	Why the trial ended or was stopped	0	0
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	3	8.8
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	0	0

Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	0	0
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	0	0
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	0	0
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	26	76.5
Discussion				
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	1	2.9
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	2	5.9
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	0	0
Other information				
Registration	23	Registration number and name of trial registry	7	20.6
Protocol	24	Where the full trial protocol can be accessed, if available	0	0
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	24	70.6

Table 3: Comparison between the information retrieved from the website registry and the published trial

Table 3 A: Information retrieved from the published trials

Title	Registration	Trial initiation	Trial termination	Enrollment sample	Age	Inclusion criteria (mm)			Blinding	Follow -up	Primary outcome	Sponsor
						PD	CAL	Bone				
Pradeep AR-16 2016	2600520	Sep-14	Jun-15	90	25 - 45	≥5	≥3	≥3	Triple masked	9	N/A	Pharmaceuticals, Institutional
Pradeep AR-1 2016	2386020	Jun-14	Dec-14	60	25 - 45	≥5	≥3	0	Triple masked	6	CAL	Pharmaceuticals, Institutional
Martande S-1 2017	2060032	Feb-13	Nov-13	96	30 - 50	≥5	≥4	≥3	Double ?	6	Radiographic defect fill	Pharmaceuticals, Institutional*
Pradeep AR-9 2016	2455869	Jul-14	Mar-15	99	30–50	≥5	≥4 - 6	≥3	Double	9	Radiographic defect fill	Pharmaceuticals, Institutional
Pradeep AR-12 2017	2274090	Nov-13	Aug-14	70	30 - 50	≥5	≥4	≥3	Double	9	PD	N/A
Pradeep AR-15 2015	2283515	Jan-14	Jun-14	70	25 - 55	5_6	4_6	≥3	Double ?	6	Complete bone defect fill	Pharmaceuticals, Institutional
Pradeep AR-11 2016	2048761	Aug-13	Jan-14	65	25–50	≥5	≥4	≥3	Double ?	6	Radiographic defect fill	Pharmaceuticals, Institutional

* Reported that study wasn't funded

Table 3 B: information retrieved from clinicltrials.gov

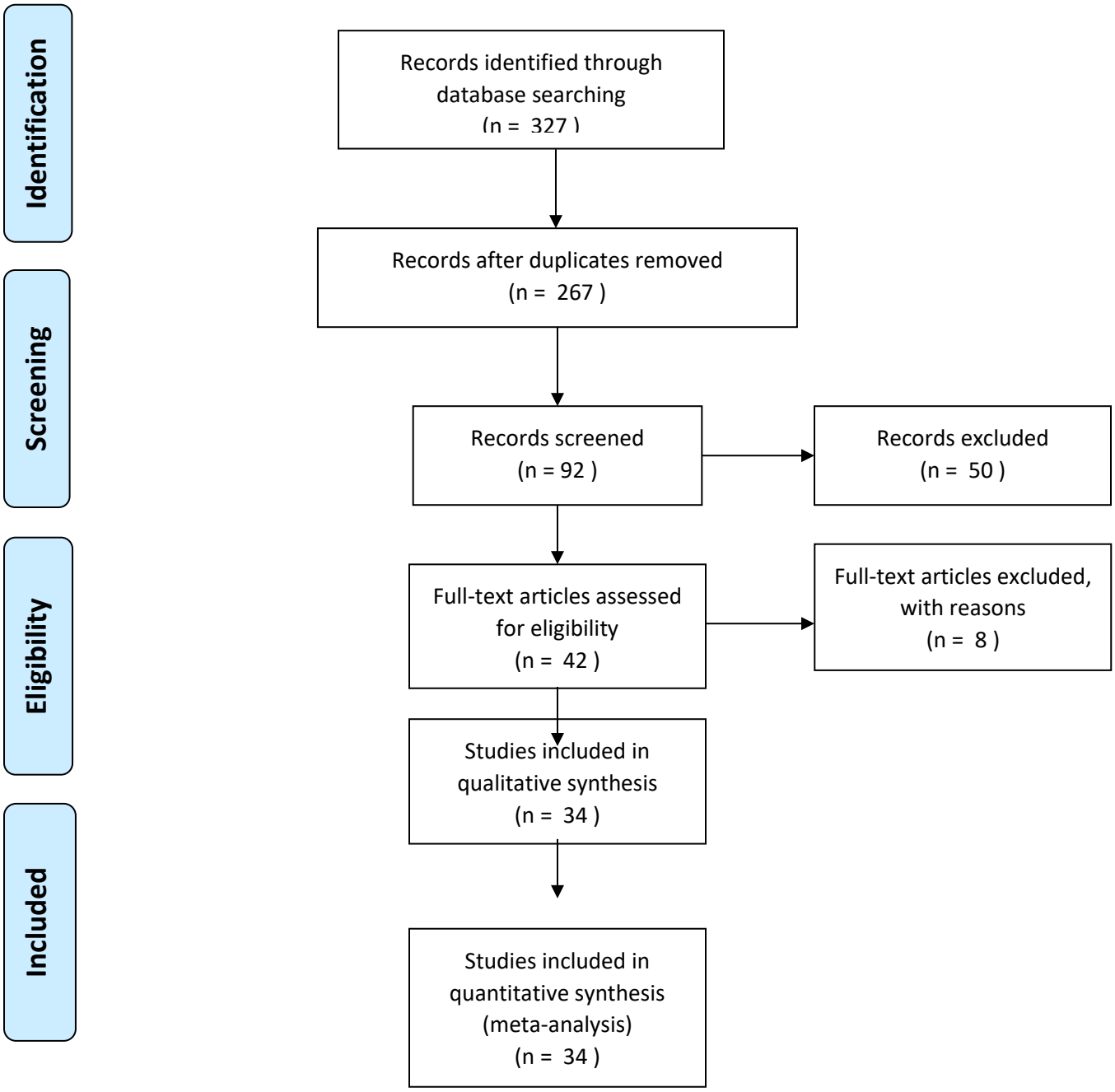
Clinicaltrials.gov

Title	First posted	Trial initiation	Trial termination	Enrollment sample	Age (yrs)	Inclusion criteria	Blinding	Follow -up	Primary outcome	Sponsor
Pradeep AR-16 2016	11/9/2015	Nov-14	May-15	45	30 -50	PD ≥5, CAL ≥4, bone loss ≥3	Quadruple	6	Radiographic defect depth reduction	Institutional
Pradeep AR-1 2016	3/11/2015	Jun-14	Dec-14	60	25 - 45	PD ≥5, CAL ≥3	Double	6	CAL	Institutional
Martande S-1 2017	2/11/2014	Feb-13	Nov-13	96	30 -50	PD ≥ 5 CAL≥ 4, bone loss ≥3	Quadruple	9	Change in Radiographic intra-bony defect depth	Institutional
Pradeep AR-9 2016	5/28/2015	Jul-14	Mar-15	104	30 - 50	Pds ≥5, cals ≥4 – 6, bone loss ≥3	Double	9	PD	Institutional
Pradeep AR-12 2017	10/24/2014	Nov-13	Aug-14	70	30 - 50	PD ≥ 5, CAL≥ 4, bone loss ≥ 3	Double	9	PD	Institutional
Pradeep AR-15 2015	11/5/2014	Jan-14	Jun-14	65	22 - 55	PD of 5- 6, CAL of 4 - 6 or PD ≥ 7, CAL of 6 - 9 and bone loss ≥ 3	Quadruple	24 weeks	Complete bone defect fill	Institutional
Pradeep AR-11 2016	1/29/2014	Aug-13	Feb-14	65	25 - 50	PD ≥ 5, CAL≥ 4, bone loss ≥ 3	Quadruple	6	PD	Institutional

Table 4: Discrepancies in the follow-up period of the RCTs.

Article	Variables (X, Y)	Decision
Pradeep AR-16 2016	X=Y	Non-realistic
Pradeep AR-5 2013	X<Y	Problematic/un-reliable
Pradeep AR-1 2016	X=Y	Non-realistic
Pradeep AR-6 2015	X>Y	Realistic
Pradeep AR-7 2014	X<Y	Problematic/un-reliable
Martande SS-1 2014	X>Y	Realistic
Priyanka N-1 2015	X=Y	Non-realistic
Martande SS-2 2015	X=Y	Non-realistic
Sharma A-1 2012	X<Y	Problematic/un-reliable
Sharma A-2 2012 AG	X=Y	Non-realistic
Priyanka N-3 2017 AG	X=Y	Non-realistic
Pradeep AR-14 2013	X=Y	Non-realistic
Martande S-1 2017	X>Y	Realistic
Pradeep AR-9 2016	X<Y	Problematic/un-reliable
Pradeep AR-12 2017	X=Y	Non-realistic
Agarwal E-1 2012	X>Y	Realistic
Pradeep AR-15 2015	X<Y	Problematic/un-reliable
Pradeep AR-11 2016	X<Y	Problematic/un-reliable
Kumari M-1 2016	X>Y	Realistic
Priyanka N-2 2015	X>Y	Realistic
Pradeep AR-13 2013	X<Y	Problematic/un-reliable
Pradeep AR-10 2013	X>Y	Realistic
Kathariya R-1 2014	X=Y	Non-realistic
Pradeep AR-2 2013	X>Y	Realistic
Pradeep AR-8 2012	X<Y	Problematic/un-reliable
Agarwal E-2 2012	X=Y	Non-realistic
Bajaj P-1 2012	X>Y	Realistic
Rao NS-1 2013	X<Y	Problematic/un-reliable
Sharma A-3 2017	X>Y	Realistic
Rao NS-1 2016	X>Y	Realistic
Kumari M-2 2016	X>Y	Realistic
Pradeep AR-3 2012	X>Y	Realistic
Pradeep AR-4 2011	X>Y	Realistic
Kanoriya R-2 2017	X<Y	Problematic/un-reliable

Figure 1: Flowchart of the search strategy



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