Reviewer's report

Title: Comparison of intervention effects in split-mouth and parallel-arm randomized controlled trials: a meta-epidemiological study

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Reviewer: Spyridon Papageorgiou

Reviewer's report:

Title: Comparison of intervention effects in split-mouth and parallel-arm randomized controlled trials: a meta-epidemiological study

Authors: Smail-Faugeron V, Fron-Chabouis H, Courson F, Duriex P and Trinquart L

Article Type: Bibliographic retrospective (meta-epidemiological) study; 22 pages; 3 tables; 3 figures; 1 supplemental table.

Summary: The authors have systematically selected and assessed systematic reviews with meta-analysis in the field of oral health. Their objective is to find possible systematic differences in treatment effects between parallel randomized controlled trials (RCTs) and split-mouth RCTs. They searched 4 electronic databases up to Feb 2013 and selected studies/extracted data from studies in duplicate. After assessing some descriptive characteristics for the included reviews and trials, they calculated within each meta-analysis Ratios of Odds Ratios (RORs) for binary meta-analyses and differences in standardized mean differences (#SMDs) for continuous meta-analyses according to the trials’ design. They then pooled across meta-analyses to get an estimate of systematic differences between RCT designs. According to their results, they could not find a systematic difference between the two designs for RCTs.

The paper addresses an interesting and useful question, which could provide an addition to the actual literature. Split-mouth RCTs are particularly helpful for some questions in oral research and it is important to research their reliability. The submission seems well-written and, the authors have done a good job summarizing in simple terms existing evidence. I have some suggestions for the authors (mainly in the analysis and presentation of the results), which they could consider and some minor typographical points. I would say a minor revision could be of use with some clarifications.

Discretionary Revisions (some minor essential revisions for the typographical points)

GENERAL COMMENTS:

Comment #1

About the nomenclature: I personally do not find very appropriate the terms “trialist”, “meta-analyst”, “reviewer”, etc. People who undertake meta-analyses are researchers, doctors, epidemiologists, etc. I wouldn’t say conducting a
systematic review or RCT defines the person. Secondly, a “reviewer” for example can be both a person undertaking a review and a person who conducts a peer-review of a study-i.e. it is confusing. You can maybe consider using different wording throughout the text, for example “systematic review author” or plain “author”. This is however just personal preference.

Comment #2
There are some systematic reviews that could be considered for inclusion and are missed. Listed Pubmed PMIDs: 20024665 / 23057701 / 19958442 / 12787212 / 18718396 and one from me (PMID 24062378), although the protocol for this was written a long time ago and the SEs have not been appropriately assessed. I did not check each of them if they provide actual raw data for each trial (so some of the listed reviews might be excluded) and these were searched rather hastily in Google Scholar (so there might be more missed reviews). You could consider searching manually for missed reviews.

SPECIFIC COMMENTS:
Abstract
Comment #3
Consider adding information about the analysis undertaken. You have until now described only the calculation of RORs and #SMDs for each meta-analysis, not the meta-epidemiological synthesis.

Keywords
Comment #4
You could maybe consider adding or replacing keywords like “parallel trial” or “meta-epidemiological”

Background
Comment #5
Overall the Background section is well-written. Some minor points:
-in the first sentence: maybe “in oral health” is better?
-first sentence of third paragraph: “handling and influence of data” is a little vague. You could consider rephrasing.

Materials and methods
Comment #6
I think the first paragraph of the methods could maybe omitted without information loss?

Comment #7
I see you used Scirus for this assessment-I too had found the platform to be useful in literature searches, but unfortunately it was discontinued. I also see you used no restriction for date or language, which is nice and as it should be. Did you by any chance take any measures to identify non-English systematic
reviews? Like searching for example in non-English databases, using non-English terms or contacting researchers? I personally find that checking in Google Scholar, even with just English terms, sometimes brings also some non-English papers, which is very useful.

Comment #8
Some minor points:
- Page 4, second paragraph, fifth line: “comand” can be “com and”.
- Page 5, second line: by “one binary and one continuous outcome” one might understand that you had to extract both a binary and a continuous outcome by each review. I am not sure, but I think this is not what you did. You could consider rephrasing.
- Same paragraph-“except non-randomized studies”: I would suggest you rephrase to clearly say that non-randomized studies were excluded/not extracted from each meta-analysis.

Statistical analysis
Comment #9
In this part of the study I have some comments. My first question is, why did you decide to analyze separately RORs and SMDs? Did you have a specific justification? You could consider for example converting the RORs to SMDs with the method of Hasselbad and Hedges (1995) (just one of the methods available) and pool all together, thereby increasing your sample size. This has been previously done in another meta-epidemiological assessment (Hartling et al., 2014).

Comment #10
You could consider adding in the text which exactly SMD you calculated-was it for example Cohen’s d?

Comment #11
You could consider adding in the results section how many authors were contacted and how many responded to the queries?

Comment #12
In paragraph 3 of page 6 I am a little confused. I take it you are talking about within-meta-analysis calculations, as the meta-epidemiological synthesis comes after. If this is the case, I would think it is a little difficult for all included meta-analyses to provide consistent results with both fixed-effect and random-effects models, especially given the extreme RORs or #SMDs, which are seen in some cases. If you have a priori decided to use a particular model with justification, it would be ok if you state so. Although, personally, I would be hesitant to consider a fixed-effect model.

Comment #13
Here my comment is on how exactly you calculated the RORs and #SMDs. You
cite of course the reference of Sterne et al. in Stat Med, but I would find it difficult to understand what you did, as this paper describes various methods. Maybe you could consider reporting exactly which method and/or the equations or macros you used? I think (just a hunch), that you pooled in each meta-analysis separately split-mouth and separately parallel RCTs and the manually calculated the effect measures and their SEs from the pooled ORs and SMDs. If this is the case, I think there are other method to use, which could be preferable. I think the authors could clarify this.

Comment #14
If I understand correctly, you used a random-effects meta-analysis to pool RORs and SMDs. Is it conventional method of moments procedure? Maybe you could consider using REML instead, as you report this previously in the paper? You could also consider Knapp-Hartung adjustments?

Comment #15
As you do use a random-effects model, you could consider (i) calculating the 95% uncertainty intervals around I2 (and I would suggest with the x2 approximation), (ii) reporting the tau2 and (iii) reporting also the 95% predictive intervals to properly accompany the random-effects results.

Comment #16
I would suggest you add some technical details including the statistical program you used and the # level you set.

Comment #17
You could maybe consider assessing some reporting biases for the meta-epidemiological synthesis. I know, there is no existing guideline about small-study effects in meta-epidemiological synthesis, but you could logically translate existing procedures in meta-meta-analyses.

Comment #18
What I would personally find interesting is to differentiate between the different types of split-mouth RCTs. For example, do the results differ between RCTs that assign treatment to mouth-sides / to quadrants / to jaws / to teeth / etc...I have however no clear idea of the whole sample of included meta-analyses and the included trials, and I do not know if this is applicable in your case.

Comment #19
I would suggest you include some sort of sensitivity analysis for the meta-epidemiological synthesis. You can consider for example comparing fixed-effect and random-effect models, includin one meta-analysis per review, omiting the most extreme outliers, etc

Results
Comment #20
The results are overall good written, except a minor point. I found 2 p values in
the first paragraph of page 9. However no mention is given about the test they come from and I prefer to have 3 decimal points. But then again, maybe you could omit them at all and just give the medians and the interquartile ranges.

Comment #21
You could consider including a forest plot with all included meta-analyses, showing 2 pooled estimates for each meta-analysis: for split-mouth and for parallel studies.

Discussion
Comment #22
The discussion is relatively well-written. You have included limitations of the present study. You could however also include a paragraph with the strength of the present study.

References
Comment #23
The reference format is overall correct. You might check once again for minor corrections. Check for instance Reference No. 11, 20, 25, 29.

Tables
Comment #24
In Table 1, you can consider capitalizing the first letter of the first word in each cell from the second column. You have it likewise in the other tables too. Also, the date from Needleman is missing (also in Table 3).

Table 2
Comment #25
I would suggest you modify a little the wording of the table. Firstly, consider minimizing the use of abbreviations where possible, as SRP or GTR might well be known to dentists but not to every reader of the Journal. I leave it to you, as this could make the table too large.

Comment #26
Again in this direction, you could consider modifying texts to make them more comprehensible. For example, “platform switch” could be “platform-switched implant restoration” or “Flapless procedure” could be “flapless implant insertion”.

Comment #27
For the tables abbreviations: when you have abbr.1+abbr.2 and the abbr.2 is not further mentioned in another cell of the table, I would consider listing them together. For example for “SRP+a-PDT”, a reader would have to search for SRP and then for a-PDT and then combine these two to make sense of the term. I would suggest either you list them together or do not abbreviate both.

Comment #28
Consider re-naming the first column “Meta-analysis”, as you here are listing multiple entries from each review (unlike Table 1 and Table 3).

Table 3
Comment #29
The columns “together” and “separately” are blank in the pdf I got. I suppose here you have inserted Yes/No or corresponding symbols. Please check if they have been omitted by the journal’s formatting procedure.

Figure 1
Comment #30
In the last two boxes on the left you can change “meta-analysis” to “meta-analyses”. Also, you could consider rephrasing “updates” to “outdated reviews” or “updated reviews”.

Figures 2 & 3
Comment #31
Consider aligning the Weight label to the column. In the first instance is too far left and in the second too far right. Consider adding somewhere in the figure the model used.

Supplementary appendix A1
Comment #32
Consider adding also here the date of the last search for consistency.

GUIDELINES FOR BMC MED RES METH
1. Is the question posed by the authors well defined?
   Yes
2. Are the methods appropriate and well described?
   Yes (description can be improved a little)
3. Are the data sound?
   Probably
4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
   Yes
5. Are the discussion and conclusions well balanced and adequately supported by the data?
   Yes
6. Are limitations of the work clearly stated?
   Yes
7. Do the authors clearly acknowledge any work upon which they are building,
both published and unpublished?
Yes
8. Do the title and abstract accurately convey what has been found?
Yes
9. Is the writing acceptable?
Yes

REFERENCES

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:
I declare that I have no competing interests.