Author's response to reviews

Title: The Methodology for Developing a Prospective Meta-Analysis in the Family Planning Community

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Author's response to reviews: see over
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Dear Editors:

Thank you for the extremely thorough and thoughtful review of our manuscript entitled “The Methodology for Developing a Prospective Meta-Analysis in the Family Planning Community”. What follows are responses directed to each of the reviewers’ comments. Attached are two copies of the manuscript, one with tracked changes and a clean copy. We look forward to your review of these revisions.

Thank you very much for the time and effort expended in improving this manuscript.

Sincerely,

David Turok

Reviewer #1 Comments:

1. Page 5: It may be helpful to draw a slightly clearer distinction between the usual multicenter study and PMA. In particular, you argue here that (in addition to the flexibility) it’s an advantage of PMA that individual sites can recruit a “feasible” number of subjects. That’s true relative to a typical meta-analysis, in which individual studies would presumably (although I admit, not necessarily) be powered adequately to address their respective questions, but it’s not an advantage relative to a multicenter study. Are you saying that it’s OK NOT to power the studies at the individual sites, and instead, power the overall PMA? I’m not arguing with the principle, just for a shade more clarity.

   Response to Reviewer #1 Comments:
   
   1. Thank you for pointing out this unclear wording. While it is true that only one site is powered by itself for the PMA primary outcome (Colorado), each site has a primary outcome such as pain with insertion or ease of insertion for a site-specific primary outcome. We have changed paragraph 2, page 5 to read as follows: “Additional advantages of the PMA methodology include the ability for individual sites to recruit only the required number of subjects for a site-specific primary outcome (in this case such as pain with insertion or ease of insertion) and to maintain autonomy over this smaller project. Combining results from each institution creates the power necessary to answer research questions requiring a larger number of subjects than many institutions could recruit individually. For example, only one site is powered for the primary PMA outcome in our study.”

2. Page 6: Some may want to interpret the word “pooled” as “combining into one big database and treating as one study.” This (as you know) ignores the retention of stratification by “study” in the analysis. Please add a reminder of the need to

   Response to Reviewer #1 Comments:

   2. We have added the following change to paragraph 1, page 6 to emphasize this important point: “Data are pooled with retention of stratification by study site and analyzed by the collaboration to determine the PMA primary outcome, while each site may analyze and publish its own data.”
retain such stratification throughout the study, including (especially) in the analysis.

3. Page 8: Just an opinion, but I don’t know if I’d go as far as saying, left to themselves, the sites “would LIKELY report incompatible data.” Doesn’t this depend on the field? I would suggest you soften this to say something like, “could potentially generate incompatible data.”

3. This has been changed. The sentence on page 8 now reads: “Without the collaborative decisions of the PMA, independent sites could potentially generate incompatible data, making meta-analysis difficult and decreasing the statistical power of the primary outcome.

4. Page 8: What do you mean by the analysis being more “accurate”? Less biased (in the statistical sense)? This is a vague term, as it’s not clear in which sense you mean it.

4. We have changed the wording of this sentence on page 8 to read: “In PMA, analysis of pooled results is more facile because of homogeneity of study outcome measures.”

5. Page 8-9: You don’t mention the need for a protocol for the combined analysis? I would definitely mention this point (and assume you already have, or are working on, such a protocol)?

5. The following sentence has been added to paragraph 2, page 8: “A detailed description of the PMA protocol and data analysis plan is available in the Cochrane protocol document.”

6. Page 9: I would suggest you add some caution around the concept of unique patient populations at each site. The worst case is complete overlap between site and subpopulation. If stratification by site = stratification by subpopulation, then you can’t separate out whether effect modification results from site or from population factors. This is just a caveat.

6. We have removed this sentence to avoid confusion about site-specific subpopulations.

7. Page 9: I very much (as a former academic) appreciate the point about authorship on individual site studies, but this raises the question above, about adequate statistical power at individual sites. If each site is underpowered, how do individual sites report results that have inadequate power or precision (and fail to reach statistical significance)? I know it’s easily possible to do proper reporting, but my point is that the site- 7. Please see the answer to number one above. Each site has a specific local primary outcome for which their study is powered. The combined results of the different sites are necessary to power the PMA primary outcome (except for one site).
specific results may best be interpreted in the context of the overall PMA.

8. Page 10: IUD’s may be ideal for SOME women, but certainly not all women. I don’t know that I’d make a sweeping generalization, as you do here, by referring to IUDs as “ideal.”

8. We have changed the sentence on page 10 to reflect that the IUD may not be the ideal contraceptive for all women: “IUDs are an ideal method of contraception for many women as they are effective, have few side effects or contraindications, require only a single act of motivation for many years of use and are highly rated among users [14].” In addition, references to the Society for Family Planning Guideline on IUD insertion in nulliparous women and the American Congress of Obstetricians and Gynecologists Practice Bulletin “Intrauterine Device and Adolescents” have been added in support of the statement.

9. Page 10: I would suggest that you need more (especially since you’re not in a family planning journal) on the motivation for evaluating misoprostol. What’s the basis for thinking it should work? Is there truly equipoise?

9. The following statements and references have been added to paragraph 2, page 10 to further explain this important point: “Several adjunct measures have been employed by healthcare providers to ease pain associated with IUD [21]. Although misoprostol is commonly used to dilate the cervix for procedures similar to IUD insertion such as in first trimester abortion [19, 20], hysteroscopy [21, 22] and endometrial biopsy [23], there is a paucity of data regarding misoprostol use by providers to ease IUD insertion in nulliparous women [24, 25].

10. Page 11: What was the predetermined sample size at each site? What was the justification for that sample size? What is (was?) the planned sample size overall? What power to detect what effect size does the overall PMA have? This may well be the topic of another paper, but it’s an important piece of this paper, as well.

10. Thank you for pointing out this oversight. The main goal of this paper was to describe implementation of a PMA in the family planning community for the first time. We do need to include the overall power calculation and sample size for the PMA and this has been added to paragraph 1, page 13. The predetermined sample size for each site and the site-specific primary outcomes are listed in Table 1.

11. Page 12: Who will do the final

11. The University of Utah is the
combined analysis? Is there a coordinating center? How was the decision made about who does the final analysis? Is this the role of the Cochrane review group (the Fertility Regulation Group)? Please clarify. This is a helpful point to make for those considering conducting a similar type of PMA.

12. Page 14: It’s not clear what you mean by “homogeneous data”. Presumably, you mean something like “using the same definitions of endpoints, the same data collection methods, etc.” The word “homogeneous” could be interpreted as a result (as in similar findings across sites).

12. We have removed the term homogeneous and replaced it with the following to prevent misinterpretation (paragraph 2, page 15): “By identifying the outcomes of interest prior to individual study design, the PMA allows generation of the same specific measured endpoints from the study sites.”

13. Discussion (or Methods): Are there plans for any subgroup analyses? Another advantage of PMA is that it allows subgroups to be defined in advance, and may even provide power for treatment comparisons within subgroups.

13. This is an excellent point and we have included plans for subgroup analysis in the Cochrane Protocol. In this paper, we wanted to focus more on establishment of the collaborative group and methodology used for the first PMA to be attempted in the field of family planning. We have included a sentence mentioning the planned subgroup analyses but without the details in paragraph 2, page 13: “In addition, specific subgroup analyses are delineated in the Cochrane Protocol document and include timing of insertion relative to menses, type of IUD inserted, and variations in misoprostol timing and administration [13].”

Note: Our currently anticipated sub-analyses include:

“1) Women who had their IUDs inserted during their menses vs. not inserted during menses
2) Type of IUD inserted (levonorgestrel IUD vs. copper T380)
3) Outcomes relative to the variation in route and timing of misoprostol/placebo administration.”
Reviewer #2 Comments:

1. I would like to see more within the article about how this review differs from many other PMA. In this example, the idea for the research seems to have come from one group (or person), rather than occurring to several different research groups at about the same time. For example, how many of the sites would have initiated such a randomized trial if they had not been approached to take part in the PMA? You write “After the principal investigator developed a preliminary PMA protocol, he identified potential collaborating investigators at other sites. Investigators at six sites joined the PMA collaborative.” Which seems to indicate that the research project began in one place and then others were asked to initiate studies. Your use of the term “site” rather than “trial” to mean the individual elements in the PMA also suggest that this is closer to a multi-centre trial than a PMA. How does it differ from multi-centre randomized trials of the past that were designed to be flexible enough to allow each centre to modify the overall trial design to meet local circumstances (for example, by using a radiotherapy regimen that was in use locally and comparing this with no radiotherapy). It would also be good to know what influence the other sites had on the design of the PMA. Did they influence the choice of the dose of misoprostol to test, the primary and secondary outcomes, or the eligibility criteria for the trial.

Response to Reviewer #2 Comments:

1. Interestingly, the PMA preliminary proposal had already been submitted to Cochrane when it was discovered there was already a trial ongoing at one of the potential PMA sites and another trial was planned at a different site. After the PMA was discussed among the participants, the importance of an adequately powered research effort to address this important area was agreed upon and the PMA collaboration instituted. The following sentence was added to the abstract: One site already had a trial underway and another site was in the planning stages of a trial meeting PMA requirements.

Each site in the collaboration had the flexibility to run their own trial, but the primary outcomes, secondary outcomes and eligibility criteria were negotiated by the group and agreed upon by the 6 sites. Other than these three items, each site was free to design a trial that was different in some way. An additional clarifying paragraph was added to page 9: The PMA also allows significant flexibility in trial design at individual sites. Other than the primary outcome, secondary outcomes and eligibility criteria agreed upon by the 6 sites, each site was free to design a trial that was different in some way. For example, although there is general agreement with the misoprostol dosing regimen of 400 mcg within the family planning community from pharmacokinetic data (Tang, Schweer et al. 2002; Meckstroth, Whitaker et al. 2006), decisions about route of administration and timing of dosing were left to the individual sites. As a result of this design freedom, one site is testing at home vaginal or buccal administration of misoprostol 3 to 4 hours prior to insertion while a different site is using administration 90 minutes prior to insertion. The group of collaborators had two in-person meetings and many email
communications before all members of the collaborative group agreed on the final PMA protocol.

2. Thank you for pointing out this oversight. The main goal of this paper was to describe implementation of a PMA in the family planning community for the first time; but we agree that we must show how this PMA is different from a multi-center trial. We have emphasized this important point by adding the following to the abstract: while each site maintains the freedom to design a specific trial.

3. Introduction: it would be worth discussing the difficulties faced by regular meta-analyses when they try to include all relevant data: selective reporting biases and unwillingness by researchers to share their data.

3. This is a great point. We have added the following to the introduction: Other pitfalls associated with meta-analyses when trying to include all relevant data include selective reporting biases and unwillingness by researchers to share their data.

4. When discussing why PMA might be more cost efficient than a multi-centre trial, it would be good to have more about the possible cost disadvantages of the PMA. For example, might there be economies of scale in a multi-centre trial, which are not available when separate trials are conducted at each site. This can be important if the placebo has to be made especially or if each site prints its own materials.

4. We have included the potential advantages of a multi-center trial as follows on page 9: While economies of scale in a multi-centre trial can be cost-effective in relation to placebo manufacture and printed materials, these savings may be quickly offset by the expense of site visits.

5. It would also be helpful to have more discussion of the problems that can arise in a PMA compared to a multi-centre trial. For example, will publication of the PMA need to wait for each site’s study to be completed, analysed and reported? If a site does not report their study, will it still be included in the PMA? If a study fails at one site (for example, because of local recruitment difficulties), what will happen to its data for the PMA? Will there be site specific Data Monitoring

5. Answers to these important questions follow: Publication of the PMA does not need to wait for reporting by all sites; PMA reporting can occur once all the data has been collected. Sites completing their study will be included in the PMA regardless of whether they publish results (but we anticipate all sites will publish their individual trial results). In the event an individual site fails to complete their trial, a decision will be made by the collaborative group about inclusion of that
Committees? Will they have access to data from the other sites?

site’s data. Even with failure at one site, there will likely be enough data to power the PMA. There is no central DSMB; however, each site was encouraged to have a data safety monitoring plan by the individual IRBs. The University of Utah trial protocol includes the following: “Data Safety and Monitoring: This study will be evaluated after each group of 50 patients is enrolled. The study will be stopped if there are >2 perforations in either group at any point. Data on perforations will be reviewed by Dr. Jennifer Van Horn in the Department of Ob/Gyn.”

6. Are you able to cite something to support the statement “IUDs are an ideal method of contraception as they are effective, have few side effects or contraindications, require only a single act of motivation for many years of use and are highly rated among users”? For example, is there a systematic review that shows this?

6. We have changed the sentence on page 11 to reflect that the IUD may not be the ideal contraceptive for all women: “IUDs are an ideal method of contraception for many women as they are effective, have few side effects or contraindications, require only a single act of motivation for many years of use and are highly rated among users (2010).” In addition, references to the Society for Family Planning Guideline on IUD insertion in nulliparous women and the American Congress of Obstetricians and Gynecologists Practice Bulletin “Intrauterine Device and Adolescents” have been added in support of the statement.

7. How will you ensure that future reviewers and others who use the results from the six sites and from the PMA do not re-use the data without realizing it?

7. This is an interesting point. All trials are encouraged to state they are contributing their data for a PMA. (Page 11; “Individual trial sites are encouraged to mention in publication of their individual results that their data are being contributed to this PMA.) The PMA will list the individual studies that are providing data for the meta-analysis. Potential future studies should document the sources of their data; however, we cannot ensure the data will not be misused by future reviewers.
8. I disagree that PMA is “new” as a research tool is “new”. It might be better to say “relatively new” since, as you show, there are examples from nearly 20 years ago.

8. We have changed the sentence to reflect the 20 years of PMA employment by changing “new” to “relatively new” as suggested.

9. Are you able to cite something (a personal communication, if not a published article) to support the statement that your review is the first PMA to be registered with The Cochrane Collaboration?

9. A personal communication with Lisa Askie, the Secretariat of the Cochrane PMA group has been cited with this statement.

10. Did you approach any sites that declined to join the PMA?

10. There were several sites that declined to participate in the PMA. The PMA was introduced at a meeting at the Reproductive Health 2008 conference attended by approximately 20 people. Four of the six collaborating trial sites were attendees at this meeting.

11. How will you decide if a site meets the requirement: “assuming subjects are properly randomized” for their data to be included?

11. The collaborative group makes the decision to include a site using criteria spelled out in the Cochrane PMA Protocol: “Trials that meet the inclusion criteria and have not published results involving this PMA’s outcomes of interest will be invited to join the Collaboration and share their data with the Collaborative Group. Trials that have not initiated or completed enrollment will be eligible to join the Collaboration.”

12. If you identify new trials in the future, will you invite them to join the PMA regardless of where they are being conducted? Do you have any concerns about adding further trials after the publication of the results from any of the existing six sites?

12. Other trials meeting inclusion criteria will be invited to join the PMA until it is published. We anticipate publishing the PMA as a Cochrane review that will be updated every few years. If the PMA results provide a conclusive answer, there may be very few future studies to analyze. If there are future studies to be added to the meta-analysis, this will be accomplished in the usual fashion for Cochrane reviews.