Author’s response to reviews

Title: Sublingual misoprostol versus standard surgical care for treatment of incomplete abortion in five sub-Saharan African countries

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Version: 2 Date: 5 November 2012

Author’s response to reviews: see over
The Editor, *BMC Pregnancy and Childbirth*

Via online submission

November 5, 2012

Dear Editor of *BMC Pregnancy and Childbirth*

We are writing in reference to our manuscript (#2034859616744562):


Thank you for the opportunity to address the referees’ comments. Below we provide a point-by-point response.

Referee #1

1. The main problem with the present publication is to see, what this study adds to what is already known? The authors explain that a lower dose of misoprostol (400mcg) should be evaluated, compared to the standard dose of 600mcg. Unfortunately the present study does not compare these two doses.

   The Background provides evidence that the efficacy of 400 mcg, as compared to 600 mcg, has already been established and that 400 mcg is a good alternative. Both are also included in the WHO essential medications list so there is no need for further study comparing these two regimens. As the text indicates, the smaller dose was selected in this study to provide cost savings.

2. Page 6, Background: The authors may explain in more detail what ‘additional evidence’ the present study provides compared to the already existing evidence. Especially compared to their reference 8 and other publications on this topic not listed among references.

   This study provides additional evidence of use of this regimen in lower level facilities and with lower level providers. We state that “We sought to gather additional evidence regarding 400 mcg of sublingual misoprostol vs. standard surgical care for treatment of incomplete abortion in the environments where need for economical non-surgical treatments may be most useful.” This study provides evidence from several other countries that confirms what was documented in Egypt (reference 8). To our knowledge, there are no other studies that compared 400 mcg to standard of care.

3. Page 7: “Women were randomly assigned to either one dose of 400 mcg of sublingual misoprostol (200 mcg tablet x 2) (Cytotec®, Pfizer, USA) or a surgical evacuation of the uterus following standard practice at each hospital (MVA or D&C).” – The authors may want to add whether information on the kind of anesthesia used for the surgical intervention, general, local or none.
No anesthesia was used for the surgical interventions; this has been added to the text.

4. Page 13: The authors mention in Discussion “This study confirms that ultrasound is not necessary for outcome assessment when treating incomplete abortion with misoprostol.” However no detailed results are given on this aspect in the result section. Furthermore this study has not been designed to evaluate the usefulness of ultrasound. The conclusion that “The majority of misoprostol cases were successfully evaluated without the use of ultrasound.” cannot replace a proper study and a clear and detailed result on this issue. Consequently this aspect should be deleted from the chapter Discussion. Furthermore any conclusion on this aspect would need to be limited to the setting of this study.

We have changed the discussion to say that our findings support previous research showing that the use of ultrasound is not needed for determining outcome assessment.

Referee #2

General comments
1. English languish needs extensive revision, some suggestion noted on the attached PDF file
   We have incorporated most of the suggested edits. In some cases, the suggested language changes were either not grammatically correct or were not proper English and so the original wording was kept as is.

2. Registration number better to be at the end of methodology section of the abstract
   This has been done.

Methods
3. Level of randomization is not clear it central or stratified by site, I understand from the written language that it is just pulling of RCTs from multiple centers in a none systematic way
   The multicenter sites were randomized together and the two country-level sites were randomized separately. This has been clarified in the text.

4. The way of randomization again is not clear
   See # 3 above.

5. The way of allocation concealment again is not clear
   Allocation was not concealed as the two arms were markedly different. However, allocation was unknown to the woman and the provider until she consented and an envelope was opened.

6. The inclusion criteria is a bit heterogeneous as the method used in the diagnosis is not the same in all study sites
   The inclusion criteria were the same at all study sites.

7. Last sentences in the second paragraph of the methods section how randomization between two arms (all patients in the same arm should be treated on the same way,) while the management in the surgical arm done according to each hospital norms, this should be done exactly in the same way using the same anesthesia and the same adjuvant drugs in order to be eligible for comparison
The comparison is with standard of care as has been done in the past in many other studies. None of the sites used anesthesia (this has been added to the text) and sites provided analgesics and antibiotics per their clinical norms.

8. Nothing written in the methodology about a consent form and about approved from any ethical board or at least health authority approval
   The first paragraph of the Methods section states that study protocols were approved by the national ethical review boards in each country and that all participants gave written, informed consent.

Results
9. All tables are difficult to interpret as percentages are stratified according to the item in the raw not in the columns, all percentages in the same column should be to the same base.
   Percentages for each question/cell in the tables are calculated based on the number of participants for whom data are available. We believe this is the clearest way to present the findings.

10. Intention to treat analysis requires that all percentages in the columns to be calculated relative to the number recruited at the top of the column
    We respectfully disagree that analysis of outcomes, side effects, and satisfaction should be based on intent to treat and have only included women who completed the study and for whom data are available.

11. In table 2 the title should be written eg the success rate of the study interventions
    We prefer to keep the title as is since Table 2 includes more than just success rates.

12. In table 3: how did you define normal or heavy bleeding or spotting , should be standardized rehabilitation, again intention to treat
    Level of bleeding was defined by each woman. This is the standard approach for both abortion and incomplete abortion studies where the side effects are monitored and recorded by the participants at home.

13. Figure 1: should be named study flowchart . You should write how many patients approached who many excluded according to the eligibility criteria then the number left for randomization
    We have changed the Figure name as requested. We do not have documentation of how many women were approached in total.

Discussion
14. In the first paragraph of page 13, The authors concluded that “study confirms that ultrasound is not necessary for outcome assessment when treating incomplete abortion' with misopristol "based on what, nothing in the given results says that.
    We have changed the text in the Discussion to say that our findings support previous research showing that ultrasound is not necessary for outcome assessment.
Conclusion
15. It is difficult to conclude at the end of a study that it is established
We do not understand this comment.

16. Better to restrict to what is written in the abstract’s conclusion.
We have removed the Conclusion section and moved its former content in the Discussion.

17. No reference in the discussion section
We think that this comment refers to the Conclusion; we have removed this section.

Minor Essential Revisions
18. Minor changes were marked on the attached PDF
We have incorporated most of these changes. (See response to #1 above.)

19. Please write the software used to calculate the sample size
The program used to calculate the sample size was created in-house based on guidelines from the seminal publication: Cohen J. Statistical power analysis for the social sciences. 1977. Academic Press, New York.

20. Not that sometimes written g, ug or mcg, it should be unified as mcg
We have changed the text to be consistently mcg.

Referee #3

Minor essential revisions
1. Key words, line one: Use sentence case - Incomplete abortion, Post Abortion Care (PAC). Key word should go to the end of abstract
This has been changed and moved as suggested.

2. Abstract, line one: 400 g misoprostol – should read 400 g of sublingual misoprostol
The word sublingual has been added.

3. Background, third paragraph, line one: cite reference
We have edited the first two sentences to clarify that references are indeed provided for this first line.

4. Method, 1st paragraph, 17th line - sounds contradictory to randomization
This line has been removed to avoid confusion as this was a separate part of the research.

5. Method, 1st paragraph, 19th line: elaborate which of these numbers stands for a randomized trial
Both of these numbers are for randomized trials. Randomization process is clarified in proceeding paragraph.
6. Method, 2st paragraph, 3rd sentence: indicate what were guiding principles for provider to discharge patients in all study sites/countries (to ensure discretion within tight study protocol)
Discharge following misoprostol administration was based on the provider’s and woman’s comfort.

7. Results, 1ST paragraph, 2nd line: delete sentence in bracket – sounds contradictory to randomization or elaborate on how they avoided allocation bias on the selection of subjects (patients)
We have added to the text that in Burkina Faso, the randomization was a 2:1 allocation.

8. Results, 4th paragraph, 5st sentence: correct p-value shown on table 3 is p=0.02 (not p=0.25)
This has been changed.

9. Discussion, 1st paragraph, last sentence: ‘learning curve’ with misoprostol – from whom?
Citation required.
The text has been edited for better clarity.

10. Discussion. 3rd paragraph, 3rd line: delete repeated coma
The extra comma has been deleted.

Discretionary revision

11. Method, 1st paragraph, last three sentences: can safely be deleted without distorting the methodology
We have deleted the two sentences regarding additional sites.

12. Method, 2st paragraph, 1st sentence: different surgical procedures and equipment’s were used. More elaboration needed on how standards and consistence were ensured in the study
Per the study design, the aim was to compare misoprostol to the surgical standard of care for treatment of incomplete abortion which could have been either MVA or D&C. There was no difference in outcome between the different surgical methods (they were all successes).

13. Results, 3rd paragraph, 1st sentence: as well, the outcome might be affected by IRB conditionality on Senegal to use ultrasound?
We do not believe that ultrasound use impacted outcome as ultrasound was more likely to be used with women in the misoprostol arm than with women in the surgical arm regardless of IRB requirements.

14. Discussion, 2nd paragraph, 1st two sentences: revisit to get the leader get the link
We do not understand this comment, but we have reworded the text a bit to improve clarity.

15. Results, 1ST paragraph, 3nd line: 29 women lost for follow-up – some literature (Stewart A, 2002 p.110) do advise lost to follow-up be analyzed as part of the group (known as being analyzed on an ‘intention-to-treat’ basis)
We very much appreciate this comment but we do not believe that the women who were lost to follow-up should be included in our analysis. Many women undergoing both abortion and incomplete abortion treatment do not return for follow-up because they are confident that their
evacuations are complete so it would not make sense to include them as failures. On the other hand, including them all as successes might inappropriately inflate the efficacy rates so it seems most prudent to keep them out of outcome analysis.

Major compulsory revision
16. Method, 2nd paragraph, 2nd sentence: pills under the tongue and swallow remaining tablet fragments sounds method mix (sub-lingual and oral misoprostol). Elaborate reasons for remnants of tablets were not spit out to make it pure sublingual misoprostol. This is the standard protocol for administering sublingual misoprostol.

17. Limitations of the work (if any) need to be stated
A paragraph on limitations has been added to the Discussion.