Reviewer's report

Title: How to assess success of treatment when using multiple doses: the case of misoprostol for medical abortion

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Reviewer: Gilda Piaggio

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'How to assess success of treatment when using multiple doses: the case of misoprostol for medical abortion'

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Trials

Methodology

This is a methodological paper. It compares methods of analysis for two or more consecutive doses of misoprostol after mifepristone for medical abortion trials. The authors present arguments in favor of using survival rates instead of binomial proportions to analyze the outcome success of medical abortion.

The analytical part (section 3, called Results), which is the central part of the paper, is clear and very well written. It is important to publish this methodological paper for researchers to understand what is being done in the analysis of these abortion trials data. However, the illustration of the methods, the discussion and the conclusions should be improved (see my comments in Major Compulsory Revisions).

The structure of the paper needs to be changed, because the present structure is relevant for a research study (Background, Methods, Results, Discussion, Conclusion). Section 2, Methods, has a single paragraph summarizing what will be done. Section 3, Results, does not contain results, but a description of existing methods of analysis. This section should have another name. I leave it up to the Editor to suggest a proper structure.

- Major Compulsory Revisions: The author must respond to these before a decision on publication can be reached. For example, additional necessary experiments or controls, statistical mistakes, errors in interpretation.

1) Background, 2nd paragraph: the definition of the main outcome to assess the efficacy of multiple doses used in many papers is ‘complete abortions (without surgical intervention)’. The authors are also taking this event as the main outcome in their development, but this should be made clear. This is relevant because when a woman has surgical intervention, this is because medical abortion failed, therefore the outcome for this woman should be failure, and surgical intervention is not a competing risk, as stated in section 3.2.1, 1st
paragraph, but an intervention resulting from failure.

2) Methods, 1st paragraph: the first sentence conveniently describes the analytical comparison of methods. However, the description of the illustration using simulated data should be improved and extended. Nine simulated scenarios were generated, so please describe which are these scenarios and justify the choice of the rates used. How were the values for columns (1) to (8) determined? How were the point estimates calculated? See also my comment 6) below for Table 1.

3) Section 3.2.1, 1st paragraph: see comment 1) above. In my comment 1) I argue that surgical intervention is not a competing risk but an intervention resulting from failure of medical abortion. If surgical intervention took place after the first dose of misoprostol and before the second dose, one has to consider, before dealing with surgical abortion as a competing risk, why would doctors perform surgical intervention without waiting until the second dose of misoprostol.

4) Discussion, the two paragraphs: the two paragraphs under the Discussion section propose new methods that are not related to content of the article. The discussion should be mainly about the main point of the article, namely problems with using binomial and the advantages of the two alternative methods considered in the paper, survival analysis and competing risks, and in what circumstances one or the others can be used. Perhaps some bits could be taken from the Results section because they belong to the Discussion section, but see also next comment 5).

5) Discussion, issues that are absent: continuing from previous comment 4), I suggest issues for discussion that should be included. Why most authors have used binomial proportions? Is the follow-up period long enough and time measured reliably in the abortion wards of the centres, to use survival analysis? Usually women stay in the hospital until abortion status is assessed, so censored data is not an issue in this type of trials. Is surgical abortion a competing risk or an intervention resulting from failure of medical abortion?

6) Table 1: it took me a long time to understand Table 1. It shows an illustration of the estimation using the different methods, assuming different scenarios. I would like to suggest modifications of Table 1 in order to improve clarity:

a. The nine scenarios are insufficiently described in the first two columns. I would use as heading of the first column the following: “Rate of medical abortion after the first dose= Rate of medical abortion after the second dose”. The present heading makes one think that the column refers to the overall rate.

b. Explain how the columns (1) to (8) are derived from these assumptions: for example, for the first line, after the first dose success is 700/1000=0.70 and after the second dose it is also 0.70 (190/271) . For column (5), n2 are the failures minus the competing events minus the censored subjects (n2=n1-r1-d1-c1).

c. One has the impression that the estimates in columns (9) to (13) are estimating the values in the first column (70%, 80%, 90%), but this is not the case. This should be made clear.

d. Is it reasonable to assume that the rate of medical abortion after the first dose
is the same as the rate of medical abortion after the second dose?

- Minor Essential Revisions: The author can be trusted to make these. For example, missing labels on figures, the wrong use of a term, spelling mistakes.

7) There is previous WHO work doing the comparison of survival analysis methods and competing risks for IUD studies. Even though the comparison refers to the analysis of a contraceptive method, not to abortion, this work should be acknowledged. The references are the following:


8) Results, 3.1, 1st paragraph, last 5 lines: the follow-up period during which occurrence of abortion is assessed is quite compact, at least compared with follow-up periods in IUD studies for example. Also, Peto et al (ref 14) refer to prolonged observation of each patient (which is usually months or years). Is the probability of success in medical abortion varying through the short observation period in the hospital?

9) Results, 3.1, 2nd paragraph starting with ‘Under certain circumstances’: I don’t see the relevance of this paragraph.

10) Results, 3.1, 6th paragraph, starting with ‘Therefore’: perhaps using the binomial proportion has no problems for medical abortion (see my comments 5) and 8)).

11) Results, 3.1, 7th paragraph, starting with ‘Additionally’: shouldn’t it be ‘the problem with (1) and (3)’?

12) Results, 3.1, 8th paragraph, starting with ‘The most common reasons’: see my comment 1) about surgical abortion. Also, last sentence is not clear.

13) Results, 3.2, 1st paragraph: You could add for clarity, after Gallo et al: ‘in their systematic review of more than one dose of misoprostol after mifepristone’. Also, where should the additional information be ‘incorporated’?

14) Results, 3.2, 2nd paragraph: this paragraph advocates the use of time from treatment initiation to the observation of the event, and of timing of dose administration. From my experience in analyzing abortion studies, the time from treatment initiation to observing the event is not accurately collected. I have encountered many problems with this variable and with other time variables, across all centers.

- Discretionary Revisions: These are recommendations for improvement which the author can choose to ignore. For example clarifications, data that would be useful but not essential.
None.

Points in the Guidelines:
1. Is the question posed by the authors new and well defined?
   Answer: Yes
2. Are the methods appropriate and well described, and are sufficient details provided to replicate the work?
   Answer: They should be improved. See Major Compulsory Revisions
3. Are the data sound and well controlled?
   Answer: not applicable.
4. Do the figures appear to be genuine, i.e. without evidence of manipulation?
   Answer: not applicable.
5. Does the manuscript adhere to the relevant standards for reporting and data deposition?
   Answer: this is a methodological paper.
6. Are the discussion and conclusions well balanced and adequately supported by the data?
   Answer: Discussion and Conclusions should be improved. See my comments.
7. Do the title and abstract accurately convey what has been found?
   Answer: Results and Conclusions in the Abstract should be modified according to changes in the manuscript resulting from Major Compulsory Revisions.
8. Is the writing acceptable?
   Answer: Yes.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**
I have no competing interests