Author's response to reviews

Title: Immediate vs. Delayed Insertion of Intrauterine Contraception after Second Trimester Abortion: Protocol and Rationale for a Randomized Controlled Trial

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Author's response to reviews: see over
Editors-in-Chief,
BMC Trials,

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Dear Sirs;

Thank you for reviewing this randomized controlled trial protocol manuscript “Immediate vs. Delayed Insertion of Intrauterine Contraception after Second Trimester Abortion: Protocol and Rationale for a Randomized Controlled Trial “, as submitted for consideration of publication in Biomed Central’s journal “Trials”.

We have reviewed the thoughtful suggestions of the statistical peer reviewer as forwarded and have these specific responses:

1. The sample size calculations are correct (my program gives 348 and 372) assuming that 2-sided alpha of 0.05 had been used, though it could be argued that a continuity correction should have been used which would increase each by about 50. The 366 is, of course, too precise since a number of assumptions and estimates have gone into the calculation, so “about 370” would be better.

We agree in spirit with not overstating the precision of sample size calculations, but have found in the past that some reviewers prefer to see unrounded results and have taken the path of least resistance in this regard.

2. The treatment effects anticipated are very large and, even if theoretically justified, may not be found in practice leading to smaller, but still clinically worthwhile, effects being missed.

This is an appropriate observation. However, the efficacy of the devices is well established and we have sufficient prior evidence on low return rates following the current practice (i.e. delayed insertion) that we believe the ethical course is to take a fast track approach.

3. If there is no rationale for believing that the two devices will differ in the likelihood of early insertion being beneficial (I didn’t see one), the trial could have been designed on the basis of the overall population, with a subgroup analysis to test for any interaction between device type and early/late insertion. This would have lead to a (much?) smaller sample size or the possibility of detecting smaller effect sizes (see point 2) with the same sample size.

The rationale for two different groups is that the expulsion rates of the two devices are expected to be differ. As we are not in a position to randomize devices we have decided to keep the trials separate to avoid "muddying the waters”.

4. The exclusion criteria (page 7) list some post randomisation exclusions, yet the analysis section (page 11) says that ITT analysis will be used. The latter is correct and no patient should be excluded from the trial post randomisation (unless they withdraw their consent) - see also next point.

Our thinking on this issue has evolved since submission of the proposal and we are now in complete agreement with this recommendation. We have amended the protocol accordingly. As such we now have removed all post randomization exclusions

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excepting those that in real life would preclude a woman from choosing this contraceptive method, consistent with keeping the study conditions as close as possible to the real life, intention to treat perspective.

The paragraph in question on page 7 now reads (revision in red):

“Exclusion Criteria

Women are not eligible if they intend to move from BC within the next year or if they intend to conceive within one year. In addition, if they have a contraindication to the use of the IUC they have chosen (see Table 2) or are currently enrolled in another clinical trial they will be excluded. Post randomization exclusion factors include perforation or excessive bleeding at the time of their abortion or uterine anomaly. These exclusions are designed to be only those which, in real life, would preclude a woman from being able to choose this method of contraception. This study has no minimum age criteria for enrollment.”

5. If a chi-square test is to be used for analysis, how will patients who are lost to follow-up prior to one year be treated - e.g. will they be assumed not to have had a pregnancy if they hadn’t had one prior to loss? Wouldn’t a time-to-event analysis be better, thereby allowing patients who are lost to follow-up to be censored at the time of loss (while still checking for any differential loss between the arms)?

We have chosen a simple comparison of proportions as our main analysis for the sake of transparency of interpretation, since the availability of administrative data should result in minimal loss to follow-up. Nonetheless, your point is well taken and it is our intention, to take this into account in accordance with our submitted analysis plan (see page 14) given below.

As a check, we will also conduct analysis to account for partial follow-up. Since our outcome definition is essentially composite and the relevant risk periods differ by components, Kaplan-Meier estimates for each component event will be determined and composite estimates will be obtained by summing the estimated cumulative event rates (calculated as 1 - the survival function) at the time-points indicated in our operational definitions. Confidence intervals around the difference in these estimates will be calculated using the bootstrap.

We thank you for these thoughtful reflections and for any other suggestions you may have.

With kind regards,

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