Author's response to reviews

Title: A three arm randomised controlled trial comparing Gonadotrophin Releasing Hormone (GnRH) agonist long regimen versus GnRH agonist short regimen versus GnRH antagonist regimen in women with a history of poor ovarian response undergoing in vitro fertilisation (IVF) treatment: Poor responders intervention trial (PRINT).

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Author's response to reviews: see over
5th October 2007

Dear Editors,

Re: MS 1346048711155159

Title: A three arm randomised controlled trial comparing Gonadotrophin Releasing Hormone (GnRH) agonist long regimen versus GnRH agonist short regimen versus GnRH antagonist regimen in women with a history of poor ovarian response undergoing in vitro fertilisation (IVF) treatment: Poor responders’ intervention trial (PRINT).

We have addressed the comments from the reviewers point by point, and we believe the changes we have made have improved our manuscript. We thank the reviewers for their comments.

The changes have been underlined for easy identification.

All authors agree with the amended manuscript, and give their permission for final submission to Reproductive Health. We look forward to hearing from you.

Yours sincerely
Dr Sesh Kamal Sunkara MRCOG.
Comments to the Author

Reviewer 1:

“Excellent”.
We thank the reviewer for his comment.

Minor Essential Revisions
Missing reference.
We have added the missing reference in the revised manuscript. The missing reference was number 3. Lashen H, Ledger W, Lopez-Bernal A, Barlow D: Poor responders to ovulation induction: is proceeding to in-vitro fertilization worthwhile? Human Reproduction 1999, 14: 964-969.

Reviewer 2:

“This is a well-thought and prepared protocol for a three-arm randomised trial comparing……………………………………”
We thank the reviewer for his comment.

Discretionary Revisions (which the author can choose to ignore)
There is one point that I would like the authors to consider. It was noted that patients will be randomized early in the process. It is important to note that since an intention-to-treat analysis should include all patients that were randomized regardless of whether or not they received the allocated treatment; the early administration of randomization may affect the final results.

The comment by the reviewer regarding an intention-to-treat analysis is valid. When designing the trial we made every effort to reduce the time interval from the point of randomisation to the time when the woman started her treatment cycle. We therefore decided against randomising women at the time of the outcome (ie when a cycle fails) even if she wished to pursue further treatment. At our Unit women with poor outcome are seen routinely at a clinic appointment approximately after 4-6 weeks later. After discussion if a woman shows a clear interest in having further IVF treatment and meets the eligibility criteria, the trial is discussed at the clinic and the woman is randomised at that point. We found that this is the most feasible point of randomisation. With the GnRH agonist short regimen and the GnRH antagonist regimen the treatment (start of medications) starts with the start of a period. The woman is advised to contact the Unit a few weeks before her expected period so that arrangements can be made for the medications to be available on time. For this reason it would not be feasible to randomise at the point of actually starting the treatment. Most women start their treatment cycle 1-2 months following their clinic appointment. In general we have found that there is minimal attrition in numbers of couples who accept to have treatment at the follow up clinic and commence the treatment.
Comment by Prof FM Helmerhorst:

“Any trial on this subject that does not have a living child as a clinically relevant endpoint is useless. I know that people are already happy when the end point is ongoing pregnancy”.

We agree that live birth rate is the most clinically relevant outcome. This issue was discussed extensively in our pre-trial meetings. However, given the low numbers of live births in poor responders, a final pragmatic decision was made based on consensus that number of eggs would be the primary outcome. However, we will report on clinical pregnancy, on-going pregnancy and live birth rates, although we appreciate that the study will be underpowered for these outcomes. We believe although the study would be underpowered for these clinically relevant outcomes, the outcome data can be pooled in systematic reviews, thus contributing to the totality of the existing evidence. We acknowledge the choice of our primary endpoint is a pragmatic one, although it doesn’t represent the ideal outcome.

A three arm RCT is very complicated. My suggestion is a two arm RCT: short agonist vs short antagonist.

We acknowledge that a three arm trial is complicated compared to a two arm trial. The main issue is to do with the risk of Type I error which arises from multiple pair-wise comparisons (A vs B, B vs C, and A vs C). We have taken this into account in the analysis plan. Our statistical plan was developed by an epidemiologist with expertise in trials, and reviewed by Prof Javier Zamora, Medical Statistician and Associate Professor of Biostatistics, University of Madrid. It underwent further statistical review by Mr Jamie Griffin (Statistician) as part of the Research Ethics Committee. We believe we can robustly address the complexities a three arm trial presents.