Reviewer’s report

Title: Prospective, randomized, double-blind, placebo-controlled phase IIa clinical trial on the effects of an estrogen-progestin combination as add-on to inpatient psychotherapy in adult female patients suffering from anorexia nervosa

Version: 1 Date: 29 Aug 2017

Reviewer: John Reece

Reviewer’s report:

This trial protocol describes a clinically important, scientifically interesting, and well-design randomised controlled trial to assess the effect of hormonal treatment on a range of psychological, physiological, and neuropsychological outcomes in women with a diagnosis of anorexia nervosa. This is an important trial that has the potential to inform a new branch of clinical intervention for sufferers of this disorder. I applaud the researchers on their efforts. This is a very challenging trial, and the authors have shown great care in presenting such a rigorous trial protocol. I look forward to the publication of the results of this trial. I am happy to recommend that this protocol be accepted for publication with the following minor required amendments:

Line 44-45. I don't know the literature personally, but I was very surprised to read that there are no evidence-based psychopharmacological interventions for the treatment of AN. I'm not questioning the authors assertion; nor am I requiring an amendment. But I am very surprised to read this. Given the prevalence of AN, it surprises me that drug treatment as not been investigated.

Lines 61 - 63: I accept the outcomes and summary of the Watson review, but surely there have been other relevant meta-analyses that can be briefly reported here. These should be briefly summarised in this section. If no such publications exist, then this should be noted.

Line 246-267: The exclusion criteria, while well-justified, are very restrictive! How can the sample size be guaranteed with such extensive exclusion criteria?

Section 285: Who will govern the randomisation and how will it be done? Computer-based random numbers? Coin toss? And who will control this?

Line 241: I have a number of suggested minor amendments in the statistics section.

- No mention is made of the calculation and reporting of effect size measures and measures of clinical significance. Both are relevant to a trial of this type and should be included.

- Why has an a priori decision been made not to consider any form of data imputation as part of the intention to treat approach? If the amount of missing data is low and meets the necessary conditions, why would some form of imputation not be considered? Please explain this approach.
- Why has the decision been made to use non-parametrics to compare baseline values? If the data meet the assumptions, I would have thought that parametric procedures would be more appropriate. Please explain this approach.

- The power analysis is unconvincing. The use of a trait anxiety measure as the basis for the sample size estimation seems inappropriate given the primary outcomes of the study. A further attempt should be made to drive the power analysis from the perspective of the primary outcomes, even if it means extrapolating from another clinical sample. One needs to be creative when conducting a power analysis in an area where there is little research in the specific area. Another approach is to drive the power analysis from the perspective of the available sample size. If the maximum possible sample is fixed and known, which is often the case, conduct the power analysis with the sample size as a fixed parameter and provide the power of reliably identifying effects of varying magnitude; for example, "with a sample of this size, small effects will be observed with a power of X, moderate effects with a power of Y, and large effects with a power of Z". Then make every reasonable and justifiable attempt to argue for why you will observe effects that have a reasonable power of being identified. In addition, provide more detail around the power analysis: the type of test being used, is it one- or two-tailed, at what time point in the trial are these power calculations related to? I accept the challenge of this exercise, and I understand the Phase IIa limitations in conducting sample size estimation, but I would contend that a little more can be done in this part of the protocol.

With these suggested amendments addressed appropriately, I am happy to recommend acceptance of this protocol for publication.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

Yes

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

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Needs some language corrections before being published

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