Reviewer's report

Title: A randomized trial to investigate the effects of pre-natal and infancy nutritional supplementation on infant immune development in rural Gambia: The ENID Trial: Early Nutrition and Immune Development

Version: 1 Date: 27 May 2012

Reviewer: David Osrin

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Major compulsory revisions

The trial is already registered and has ethical approval, so a review at this point is not looking for comments on the design or procedures but on the presentation of the protocol for publication. The ISRCTN entry suggests that the trial is already well under way. I note that ethical approval was received on 20th August 2008 and the entry was amended on 4th October 2010. Was the start date 1st October 2009? How far have you got? Is the completion date still 30th September 2013? Could the authors insert some dates into the protocol?

Thinking about how protocols are presented as benchmarks against which trials will be reviewed by data monitoring committees, and against which the findings will be presented according to CONSORT guidelines...

1. My main suggestion is to clarify the presentation of outcomes and analysis. I suggest that you create a subheaded section, ‘Outcomes’, and clearly specify the primary and secondary outcomes. Also specify which of several measurements – or what treatment of serial measurements – the primary outcome is to be assessed on. Thymus size is measured at 1, 8, 24 and 52 weeks. What will you compare? For response to immunizations – humoral and cellular - it sounds like you will compare findings at 3 timepoints. All of them? A composite index? The latest one?

2. Er… how many participants are there in the trial? Are the 1000 enrolments in the trial profile there because you think you'll lose 200, some before and some after birth? You don’t say so.

3. The ISRCTN entry has exclusion criteria. They should be added to the protocol.

4. I suggest a little more on the consent process. Is consent verbal or signed? Are the participants given information sheets or an oral explanation of what will be required of them? It’s usual to say a little about these issues.

5. It’s usual to mention whether or not there are planned interim analyses and stopping rules.

6. Is there a data monitoring committee (DMC)? It sounds like Drs Bojang and Edmond are doing this. The current recommendations (I'm thinking of DAMOCLES) are only recommendations, but presumably there's a reason why
you have chosen not to have a DMC?

7. p6. The section on randomization and allocation is part of the section on the intervention. I’d suggest giving it its own section and adding half a sentence on the sequence generation (what application was it done with?). Who did the allocation and who gives the field assistants the allocated supplements to give to the participants?

8. While not crucial in detail at this stage, I’m afraid I’m hazy on the analytical plan. It’s perhaps too concise. What will be compared with what? I’d suggest you spell out which allocation groups will be compared in (i), (ii) and (iii).

Minor essential revisions

1. Background>General evidence…: “… consequences for…”

2. The background section mentions that there might be effects of seasonality and lipid-based supplements on immunocompetence. Could the authors say a little about micronutrients, since they are part of the trial.

3. Likewise, since the primary outcome is thymus size, it would be good to have a couple of evidenced sentences explaining how robust this is as an index of immunocompetence. And perhaps the same for responses to immunizations.

4. Study design> “… women will be randomized … and their infants will be randomized further…”

5. Setting and participants> p6> “… principal investigator…”

6. Intervention – pregnancy> “… compliance with the supplement is assessed…”

7. Scheduled pregnancy and delivery measurements… > expand VCT.

8. Intervention – infancy> “… to promote exclusive breastfeeding for all participating women.”

9. Decide if you are writing 6 or six and stick with it.

10. I think it might be good to signpost the primary and secondary outcomes with subheadings. It seems that the single primary outcome is thymus size, but you use the words “A primary outcome measure for the study” to describe it. Is it ‘a’ primary outcome or ‘the’ primary outcome?

11. Analytical plan> This isn’t clear enough for readers. I’ve read it many times and I’m still confused. There must be a better way of saying it:

12. “In each case we consider analysis of both (a) the full data set…” Do you mean here that you will do a standard factorial analysis in which you split the dataset in half using different cuts to look at different exposures?

13. “… and (b) also in the subset of data for which the control is given for the treatment not involved in the analysis…” I think you mean that you will compare exposure X (with and without concomitant exposure Y? You don’t say) with the single control group in which there is neither exposure?

14. “We also assume that… Collinson et al’s data…” This sentence is missing a verb.
15. Table 5. Although the headings such as (i) refer to the text, it would be better if they were stated in the table, as it should stand alone. The table should tell us which is the outcome in question. Presumably, log thymus size. It isn’t clear what you mean by main effects in contradistinction to pairs of main effects. A standard factorial analysis would compare pairs of allocations, wouldn’t it? What exactly is meant here? Is the first column a non-factorial analysis comparing one allocation group with two control arms, or two allocation groups combined with two control arms combined?

16. I think we need more explanation of the analysis plan. Looking at the trial profile, in the first randomization, 500 infants will receive MMN and 500 PE. In the second randomization the total allocation is to 800 infants. The analytical plan text says that the trial aims to enroll 800 mother-infant pairs, but the diagram shows 1000. Presumably you have factored in loss to follow-up, perinatal and infant deaths. Could you make this clear in the text.

Discretionary revisions

1. Title: the English feels a bit wrong, doesn’t it? “… to investigate the effects of pre-natal and infancy nutritional supplementation…” How about “… prenatal and infant…” or “… prenatally and in infancy…”?

2. The trial is looking at something specific: thymus size and immunological outcomes. The supplements will make babies, and infants, bigger. Clearly, the causal pathway from food to immunocompetence is not the question, but I suspect that readers will wonder about it. For example, if immunocompetence and infant size are collinear, adjusting for weight might vitiate the observed effect of the supplement on, say, thymus size. A brief discussion of some of the issues might be useful.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests.