Author's response to reviews

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

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Author's response to reviews: see over
The Editor  
BMC Pregnancy and Childbirth  

August 6th 2012  

Dear Sir,  

**Re: Moore, SE et al. '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'**  

Thank you for considering our trial protocol for publication in *BMC Pregnancy and Childbirth*. We have carefully considered each of the points made by the reviewer, Dr David Osrin, and would now like to resubmit a revised version of the paper.  

We include herewith a point-by-point response to each comment made by Dr Osrin, and a revised version of the protocol. We hope that these adequately address the majority of the reviewer’s concerns.  

We thank you in advance for reconsideration of this manuscript.  

Yours faithfully,  

Dr Sophie Moore, PhD  
Head of Station, MRC Keneba
Response to Reviewer’s comments:

We thank Dr Osrin for his careful review of our protocol paper, and for the comments made. We include herewith a point-by-point response.

Major compulsory revisions:

We note the reviewer’s request for the inclusion of dates into the protocol (Page 5, Study Design). Whilst ethic’s approval was indeed obtained in 2008, the start of the trial was delayed until April 2010 owing to a problem with the supply of the LNS supplements to The Gambia. The trial started in April 2010, and antenatal recruitment is planned to end in December 2012 (with the last infant reaching 12 months of age in approximately August 2014).

1. We have now included a separate section ‘outcomes’, as suggested (Page 11, Study outcomes), and clearly defined the primary and secondary outcomes. We acknowledge that this was not very well described either within the manuscript or within the ISRCTN entry, so we will also amend the latter accordingly.

2. The number of trial participants has been clarified (Page 6, Setting and participants).

3. Specific information on exclusion criteria, has now been added (Page 5, Setting and participants).

4. Further, more detailed, information has been provided on the process of consent (Page 5, Setting and participants).

5. We have added further details on the planned interim analyses and stopping rules (Page 6, Setting and participants).

6. On advice from the MRC’s Clinical Trial’s Manager in The Gambia (Dr Jenny Mueller), we were advised that a full data monitoring committee would not be required, rather Drs Edmond and Bojang, in their respective capacities of Independent Trial Monitor and Data Safety Monitor, would assume responsibility for the role of data safety monitoring. The main basis of Dr Mueller’s advice is that nutritional supplements of this nature are not considered as medicinal intervention products, and hence there is no requirement to conduct the trial according to full GCP. No further comment has been added to the manuscript in relation to this point.

7. We have now made a separate section on randomization and allocation and included more specific detail, as requested (Pages 7 & 8).

8. We have included additional detail in the analysis plan, hopefully improving clarity and responding to the specific point raised here and below (Pages 11-13).

Minor essential revisions:

1. Background>General evidence … ‘Consequences on’ replaced with ‘consequences for’.

2. We have decided not to add further detail on micronutrients, since the background section is not meant to be a review of the literature on nutrition and immune function. We have not, as the reviewer indicates, discussed any potential evidence.
for the impact of lipid-based supplements on immunocompetence, rather we only mention that they may be a better vehicle for delivery of micronutrients. We felt that, to include an adequate summary of what is known about the relationship between macro- and micro-nutrients in immunocompetence would take the background section away from what the journal requests, e.g. ‘a summary of the background to the research, and its aims’.

3. The reviewer asks for further evidenced sentences explaining how robust thymus size is as an index of immunocompetence. To date, little direct evidence exists to support a direct link between postnatal thymic size and immunocompetence, although the observational data summarised within our manuscript (e.g. the evidence that the thymus is highly sensitive to the early environment and predicts infectious disease mortality in infancy) justifies its potential importance. Further, inclusion of cellular measures of immunity within the current study will hopefully further validate TI as a marker for the future. We have however added some further information (Page 11) to describe the role of the human thymus to help enhance this part of the manuscript.

4. Study design> ‘...women will be randomized’ now changed to ‘...and their infants will be randomized further’.

5. Setting and participants ‘principle investigator’ has been deleted, as this section has been updated.

6. Intervention – pregnancy> p6 ‘compliance to the supplement is assessed’ has been changed to ‘compliance with the supplement is assessed’.

7. Scheduled pregnancy and delivery measurements > VCT has now been spelt in full.

8. Intervention – infancy > ‘.. to promote exclusive breastfeeding to all participating women’ has been changed to ‘.. to promote exclusive breastfeeding for all participating women’.

9. Where appropriate, all numbers < 10 have now been spelt out in full.

10. See response to Point 1 in Major revisions section. We have now clarified ‘the’ primary outcome, and amended text accordingly.

Points 11 to 16 are all in relation to expanding the analytical plan. This we have done (see response to Point 8 under major revisions), and we hope these changes satisfy all of the reviewers concerns.

Discretionary revisions:

1. We agree the title could be improved, so have amended to your first suggestion, ‘prenatal and infant’.

2. Whilst we appreciate the comments regarding the mechanisms of effect, we believe inclusion of any significant comment within this protocol paper is not relevant, and should be saved for the manuscripts resulting from the trial. We do however, take on board these thoughts.