Author's response to reviews

Title: A Cluster-Randomized, Placebo-controlled, Maternal Vitamin A or Beta-Carotene Supplementation Trial in Bangladesh: Design and Methods

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Author's response to reviews: see over
Dear Editors:

We are pleased to enclose the revised manuscript entitled “A Cluster-Randomized, Placebo-controlled, Maternal Vitamin A or Beta-Carotene Supplementation Trial in Bangladesh: Design and Methods”, assigned MS# 1959845324473273. We thank the editors and reviewers for their careful feedback, which we have incorporated into this revision, evident in the “tracked-changed”, and “clean” copies of the manuscript, as attached. The following specific concerns were addressed as follows:

Associate Editor:
1. We have cited the Vitamin A maternal survival trial paper by Kirkwood et al. from the May 2010 Lancet, and the accompanying Letter to the Editor, as requested.

Reviewer 1:
1a, b: We have included a new table, which describes in detail the timepoints where initial consent and reconsent with participants occurs, as well as the specific data collection timepoints, and the level of staff conducting these activities.

1c: The rationale for the 5-weekly cycle has been added into the manuscript, reflecting a standard length of time (with biological variability) between pregnancy surveillance visits to allow normal menarcheal cycles to occur (28±4 days, as per Chiazze Jr, L; Brayer, FT; MacIsco Jr, JJ; Parker, MP; Duffy, BJ (1968). "The length and variability of the human menstrual cycle". JAMA : the journal of the American Medical Association 203 (6): 377–80. PMID 5694118). This also lowered the frequency of unnecessary HcG testing.

1d. The details of blocking used for randomization have been added, as requested.

2. The conclusions have been restructured to highlight several specific ‘lessons learned’ specific to this trial that we believe have general application. Throughout the text, however, we highlight specific strategies that can be adapted more widely in community trial implementation. We have removed the term ‘innovation’ from the title.

Reviewer 2:
1. The primary a priori comparisons of interest were groups A vs. C and B vs. C, or the active treatment arms vs. placebo (C). We considered A and B to be two comparable treatment groups, so
their comparison was not of interest from a design point of view. We handled the comparison as two independent two-group comparisons.

2. The formula used was, as the reviewer points out, the standard 2-group formula. We were aware of the desirability to increase the number of control clusters (i.e., by the square root of the 3, the number of treatment groups) but this would have been impractical due to our already huge sample size, and cost-prohibitive. Also, due to the masked nature of the trial, we could not inflate the placebo group without unmasking the trial arms to some extent.

3. The final design effect, 1.21, was set \textit{a priori}, based on measured outcomes from our earlier NNIPS-2 trial, carried out \~250 miles to the west of our current study area, in the rural plains of the east-central Nepal. It was not adjusted as data was collected. The sample size of the trial was increased mid-trial, based on a lower-than-expected, observed pregnancy-related mortality rate that was noted during a data safety and monitoring board meeting. The increased sample size was obtained using the same design effect.

4. The planned and conducted analyses will be described in detail in the papers that focus on reporting primary and secondary outcomes of the trial. However, while we believe the range of analyses planned for addressing the many outcomes of the trial goes beyond the scope of this manuscript, we have reported and emphasized two key features of design, site selection and randomization, evident in presented tables: the degree to which the study site "resonates" with national, rural development, health and infrastructural qualities, as a basis for generalizing trial findings, and the comparability of sector characteristics achieved with randomization.

5. In addition to responding to the helpful reviewer comments, however, we have in the interim given the paper's introduction greater thought, leading us to offer a rewritten version of it, along with further edits to lead paragraphs in the Methods. We realize this is unusual, and will fully understand if this is seen as requiring further review, but our intent has been to help inform and bring the reader more quickly to purpose and detailed content of the paper. It became evident to us the paper needs an introduction that highlights major themes surrounding the conduct of large community nutrition trials in the developing world, rather than a too-brief, and (now, to us) less useful review of maternal vitamin A deficiency and supplementation trial outcomes. We think the revision will vastly improve the paper's ability to catch the attention of readers, and induce them to read the entire manuscript. We very much hope the editors and reviewers agree.

All contributing authors have reviewed and approved the content of this revised manuscript. We thank you in advance for your positive consideration of this manuscript and will be glad to respond to any further queries or suggestions you may have regarding this submission.

Sincerely,

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Assistant Professor