Author’s response to reviews

Title: An effectiveness study of an integrated, community-based package for maternal, newborn, child and HIV care in South Africa

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Author’s response to reviews: see over
Dear Editor,

Here is how we responded to the comments from reviewer 1:

The authors present a very well written protocol addressing an important issue. The cluster design appears robust and well specified, with appropriate statistical analyses specified.

Thank you

There follow some minor points which might enhance the clarity of the paper if addressed:

1. Page 2: It would be useful to give more detail on how the authors ‘identified three key implementation gaps affecting progress’ – the three identified look plausible and important, but where there are a fourth, fifth and sixth implementation gaps sitting perhaps just behind these that might also have been of importance?

We have added a more specific (and referenced) response to this comment – see page 4.

2. The primary outcome – ‘HIV free survival at 12 weeks’ – given the breadth and complexity of the package of interventions, is 12 weeks long enough for all the benefit to have a chance to accrue? Did the authors think of including a longer term follow up e.g. at 6 or 12 months to see if any benefit observed at 12 weeks was sustained over a longer period?

The primary purpose of the 12 week assessment point is to measure the effectiveness of the antenatal and intrapartum regimen in reducing peripartum mother to child transmission. While there will still be a risk of further transmission postnatally through breastfeeding that would require much longer follow up, preferably to nine or twelve months and the study funding would not allow for this. Furthermore the main focus of the study is on improving neonatal caring practices and health care seeking and not longer term outcomes. We have added a sentence to the discussion outlining this limitation of the study. (see my addition on pg. 17)

3. Page 3 – ‘adapting and testing Asian community based studies in various African contexts’- useful if the authors could be more expansive and insightful in why the findings in Asia can’t reliably map straight on to the African contexts?

Thanks for this comment. We have added a sentence and a reference on page 8 clarifying this issue.

4. Page 5 ‘MTCT may occur during breastfeeding but the greatest risk is with mixed feeding’ – this needs some more explaining / evidencing, since naively you might have thought that exclusive breastfeeding with an HIV mother would confer the highest risk, and exclusive bottle feeding the lowest, and mixed feeding somewhere between these two?

Several research studies in Africa have found that exclusive breastfeeding carries a lower risk of HIV transmission compared with mixed feeding (breast plus solids or formula milk) such as: Coovadia et al Lancet 2007; Coutsoudis et al Lancet 1999; Illiff et al AIDS 2005; Kuhn et
al Plos One 2007; Becquet et al Preventive Medicine 2008. We have added these references to support this sentence in the paper.

5. Page 8 ‘The question is not merely to develop an efficacious package but also to identify and test delivery strategies that enable scaling up’ – the scaling up part is the most difficult to get to grips with in this Protocol, and probably understandably the least well articulated (given the complexity). It would be good to expand on this aspect. For example, in the Economic Evaluation (page 15) the authors state that ‘costing is a critical component of an effectiveness trial to inform scale up’ – but aren’t many costs of a scale up one-off costs pertaining to infrastructure and capacity building?

Thank you for this very useful comment. In our understanding, the reviewer is raising two issues. First, that the intervention design has taken into account factors inform scaling up. Secondly, that scale-up costs are largely one off costs. The distinction between one-off and repeatable costs is to highlight activities that will occur at a national level once. For example, the content of the intervention will not be developed in every district, thus activities such as manual development and intervention design are examples of one off costs. In contrast; recruitment of community health workers, training of community health workers and supervisors, will have to be replicated each time the intervention is rolled out to a new district. Another factor that affects scale-up is human resource requirements. In this trial the time use of community health workers has been captured in detail. This information will be useful establishing whether community health workers can take on additional activities or not.

We have added a full paragraph on page 15 of the manuscript in response to this comment.

6. Page 9 –‘levels of exclusive and appropriate infant feeding at 12 weeks’ – what is ‘appropriate’ defined as here?

Appropriate in the context of HIV transmission would mean either exclusive breastfeeding or where appropriate (i.e. WHO conditions are met) exclusive formula feeding. We have changed this sentence to read “levels of exclusive breast or formula feeding at 12 weeks”

7. Page 9 ‘to assess post intervention levels of maternal depression’ – at what time point – 12 weeks?

Yes, at 12 weeks. We have changed the text

8. Page 10 ‘... a baseline survey of all clusters was conducted in order to check on the homogeneity of clusters ... neither stratification nor matching was performed’ – what measures were involved in establishing this homogeneity?

We used baseline data on HIV testing amongst pregnant women to determine the intracluster correlation coefficient. This indicator was used since it is a measure of access to PMTCT services which is one of the study outcomes. Based on the consistent testing rates across the clusters it was deemed that stratification of clusters would not be required. Matching was not considered since the number of clusters to be randomised was large (30) and unlikely to result in failed randomisation.

9. Page 10 – given the nature of the intervention and the short follow up time (12 weeks) is an attrition rate of 20% really acceptable – couldn’t this be reduced a fair bit?
This was an estimate of the worst case scenario for sample size calculations. Early indications are that the attrition rate will be closer to 9% - considerably better than 20%

10. Page 11 – the authors discuss the key issue of contamination, but the explanation ‘all effort have been made to avoid contamination ...’ could be more comprehensive and hence hopefully convincing? Specifically there is only 1 CBHW per cluster, and most of the deliveries (98%) are in 1 hospital – naively that would seem to make it quite easy for contamination to seep in?

Over 90% of women giving birth in Prince Mshyeni Hospital remain in hospital for less than six hours. It is unlikely for contamination to seep in in that context. At cluster level care was taken to ensure significant barriers or distances between intervention and control clusters. The focussed, one on one, and individualised nature of the intervention will in itself, significantly limit the possibility of contamination.

11. Page 12 ‘In each intervention cluster there is one CBHW who covers all households in the cluster’ – how many separate contributions might be made from a single household e.g. sisters, daughters, multiple families within household, and then twin or multiple births? As well as adjusting for cluster are the authors adjusting for clustering within a household?

In this study there will be no clustering at household level since only a maximum of one mother and one child per household will be recruited. Hence clustering within clusters will only be adjusted for.

12. Panel 2 – not really clear what the process measures are as distinct from the outcome measures?

We agree with the reviewer on this issue. We have changed this in the text.

Thank you