Author’s response to reviews

Title: A mixed methods feasibility study of the Kusamala Program at a nutritional rehabilitation unit in Malawi

Authors:

Allison Daniel (allison.daniel@sickkids.ca)
Meta van den Heuvel (mathilda.vandenheuvel@sickkids.ca)
Melissa Gladstone (m.j.gladstone@liverpool.ac.uk)
Mike Bwanali (mikebwanali7@gmail.com)
Wieger Voskuijl (wieger.voskuijl@gmail.com)
Celine Bourdon (celine.bourdon@sickkids.ca)
Isabel Potani (isabelpotani@gmail.com)
Sara Fernandes (31638@lstmmed.ac.uk)
Jenala Njirammadzi (jnjjirammadzi@medcol.mw)
Robert Bandsma (robert.bandsma@sickkids.ca)

Version: 1 Date: 29 Aug 2018

Author’s response to reviews:

We would first like to thank the two reviewers for their time and for helping to improve the quality of our manuscript with their insightful comments.

Reviewer #1:

This paper is a report of an internal pilot study using mixed methods to explore the implementation of the Kusamala Program in an NRU setting and developmental outcomes in children with SAM six months after inpatient treatment. There is a strong rationale for the study with the intervention being evaluated being potentially effective and able to be delivered at an opportune time for developmental outcomes to be
improved. I have the following comments on the paper, particularly on the quantitative elements which is my expertise.

1. Line 281 - 'Child, primary caregiver, and household characteristics did not differ between intervention and comparison arms in the internal pilot trial.' Were actual statistical tests conducted (results not shown) or is this statement made on the basis of looking at the descriptive data? Either way it is not generally considered good practice to compare baseline characteristics between intervention and control, just to present the descriptive data as Tables 1-3. By definition, as the participants have been randomly allocated to intervention or control they are random samples and therefore comparable.

Response: Statistical tests had been conducted, yet we agree that it is not appropriate to compare these baseline characteristics due to the randomization of participants. We have removed the sentence about the comparison of participants between the two study groups:

2. Line 306 - 'Although not the primary aim of the....' This hypothesis testing should not be reported. In the reporting of pilot trials it is better practice to report difference in means and 95% confidence intervals. As was stated this was not one of the aims of the study so difference in means and confidence intervals are not necessary either.

Response: The hypothesis testing as well as means and confidence intervals have now been removed from the results section, as we agree it is not necessary to include this information in the reporting of this pilot trial.

3. Line 320 - this sample size calculation may be correct but further information is required.
   a) Was the ICC calculated from your data?

   b) What is the average cluster size?
c) Why an effect size of 0.5?

d) Does it include any adjustment for loss to follow-up?

The average and median cluster sizes for the internal pilot study were 2.6 and 2.0 primary caregivers and their children, respectively (see histogram below).

An intracluster correlation coefficient was not calculated from our data because of small cluster sizes which would inflate the size of the coefficient, and therefore we used an arbitrary value of 0.05 which has now been explained in the section about the sample size calculation:

“An effect size of 0.5 was used to represent a potentially clinically significant change in MDAT z-scores to justify the implementation of the Kusamala Program. Cluster sizes from this internal pilot trial were small for the calculation of an intracluster correlation coefficient, and therefore a value of 0.05 was selected based on the postulation that developmental outcomes will not vary greatly by cluster. Based on $\alpha$ of 0.05 and 80% power, an estimated minimum of 158 children per arm (N=316) should be included in the analysis of the full trial.”

We have also now added a description in the limitations:

“One limitation of the internal pilot trial is that enrollment was lower than anticipated. This could be attributed to the scale-up of community-based efforts to manage malnutrition. Therefore, the average and median cluster sizes of 2.6 and 2.0 participants, respectively, were smaller than expected. This meant that an intracluster correlation coefficient was not calculated from the internal pilot study data for the recalculation of the sample size.”

We have also now specified that the sample size should be increased to account for contingencies:
“To account for contingencies, an increase in the sample size by 25% would be necessary meaning that 200 children per arm (N=400) should be included in the full trial.”

4. Figure 1 - this makes it looks like all potential participants were assigned to clusters and then the clusters randomised to intervention or control. Once in a cluster participants were enrolled into the study and data collected. Is this correct? If so, this is not clear in the Methods section. If not the figure needs the enrolment/eligibility boxes at the top of it.

Response: This is correct, and we have now further explained this in the methods section with the following text:

“Children with SAM and their primary caregivers at the NRU were screened for eligibility to participate by two staff members who were blinded to the allocation before and after enrollment. Between one and six primary caregivers and their children were assigned to a cluster of participants. These clusters were subsequently randomized to either receive the intervention or the standard of care according to a computer-generated random allocation sequence generated a-priori by a biostatistician.”

5. Figure 2 has no title, can not tell if it is data from discharge or follow-up. I would suggest presenting both on the same figure and not including additional file 2.

Response: We have modified the figure to include data from discharge and follow-up. We have also made sure to include a title for Figure 2, “Boxplot of MDAT z-scores for gross motor, fine motor, language, and social domains in children with SAM at discharge and follow-up” on line 313. Additional file 2, which included a table of MDAT z-scores at discharge and follow-up, has now been omitted from this submission.
Minor comments

The Abstract on the title page differs from the Abstract on the manuscript, the latter being the better version.

Line 225 - 'difficult' should be 'difficulty'

Tables 1 to 3 - columns are not aligned

Line 337 - 'willing participate' should be 'willing to participate'.

Response: Thank you for your attention to these details. Each of these errors, including the grammar/spelling, table formatting, and abstract discrepancies, have been revised.

Reviewer #2:

This study is reporting the results from the internal pilot of a cluster randomised controlled trial. To understand this paper better, I had to read the published protocol for the full trial. In order for this to be a standalone paper, this paper would benefit from including more information on the full trial rather than just making reference to the published paper.

The study has three objectives:

1. Determine engagement and adherence rates of participants to the Kusamala Program
2. Obtain data on outcomes to re-estimate the sample size
3. Gain insight into barriers and enables to the implementation of the Kusamala program.
Participants - The authors list some criteria for participants not being enrolled, but I cannot see mention of these in the protocol paper.

Response: These were not specific exclusion criteria but were rather logistical reasons for the possibility of potentially eligible children not being enrolled to this study. As these are not scientific reasons for excluding participants, we have now removed the sentence:

“Participants were not enrolled if they were: active in another study at the time of screening; eligible for studies taking place at the NRU; or admitted to hospital more than three days prior to the intervention start day.”

This is a cluster trial in that the participants make up clusters within the same hospital, so selection bias could be a real problem, since staff will know what the last cluster were randomised too, so may select participants based on guessing what the next cluster may be allocated too. Since this is cluster trial, need to ensure no selection bias, it is not entirely clear how the participants were selected and allocated to the treatment groups, was this sequential?

Response: Participants were first enrolled to groups which were subsequently designated as intervention or comparison groups based on a randomization sequence generated by a biostatistician. We aimed to minimize selection bias by ensuring that those recruiting participants to groups were blinded before enrolling participants as well as afterwards, with just nurses delivering the intervention being aware of the allocation. We have now specified this in the description of enrollment of participants in the following text:

“Children with SAM and their primary caregivers at the NRU were screened for eligibility to participate by two staff members who were blinded to the allocation before and after enrollment. Between one and six primary caregivers and their children were assigned to a cluster of participants. These clusters were subsequently randomized to either receive the intervention or the standard of care according to a computer-generated random allocation sequence generated a-priori by a biostatistician.”
Results - Order of results should follow the objectives.

Response: The results section has been re-ordered to follow the objectives; more specifically, the section of participant engagement and adherence was moved before the section of child developmental outcomes.

The authors present outcome data with p-values for the MDAT z-scores, and discuss the results in terms of there being no significant differences. I am not sure is appropriate to present outcome data for an internal pilot beyond that needed for the sample size re-estimation, but that may be a personal preference.

Response: This point was also raised by the other reviewer, and we agree that for this pilot trial it is not necessary to present a comparison of data of the two study groups. We have now omitted the analysis of outcome data.

If presenting outcome data, then this should be at the end of the results, or just in a table, with the summary data presented with no p-values. Any text on the results should just describe the data and no statistical analysis should be undertaken. Statistical analysis is not appropriate.

Response: This was also brought up by the other reviewer, and we agree that the analysis was not appropriate, and it has now been excepted from the manuscript. We have included just a short paragraph in the results about developmental outcomes because it is relevant for the recalculation of the sample size, which is one of the three objectives.

The sample size re-estimation section should provide information on the calculations for the full trial, so the reader knows how the parameters have changed. From the results, I don't know if the re-estimation means the sample size needs increasing or not. This is later in the discussion, but since this is one of the objectives, this section needs expanding.

Response: Additional information has now been added in the results section to indicate that the original sample size calculation was higher than the one done in this pilot trial, and that this sample size should be increased to account for contingencies:
“This number is lower than the original sample size calculation of 160 children per arm (N=320) in the original study protocol, which will be followed since it is higher than the recalculated sample size. To account for contingencies, an increase in the sample size by 25% would be necessary meaning that 200 children per arm (N=400) should be included in the full trial.”

The discussion is very long. It could be stream-lined to focus on how the internal pilot has informed the continuation of the full trial, and any changes made. Some of the content of the discussion would be better placed in the results.

Response: The discussion was shortened to only include information that informed changes to the full trial, with any repeating information deleted and descriptions made more concise.