Author's response to reviews

**Title:** Acceptability and impact on anthropometry of commercial available versus locally developed Ready-to-Use Therapeutic Food in pre-school children in Vietnam.

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**Author's response to reviews:** see over
Reply to reviewers.

First of all, we would like to thank the reviewers for the thoughtful comments which has enabled us to improve on the manuscript substantially.

Reviewer 1: Daniel Schwekendiek
Reviewer's report:
Major concerns:
- As the title indicates, the authors focus on both the “acceptability and impact on anthropometry” of RUTF. In order to assess the “impact”, the authors merely use anthropometric measurements before and after the experiment. The main observation that anthropometric measurements have significantly improved invite various interpretations and explanations – some of which might have been outside the control of the researchers (spurious correlation such as history effects not to mention experimenter expectancy effects). I would have at least expected to see an anthropometric comparison with a non-exposed control group - or even better, of a placebo-controlled group, to rule out spurious correlation issues and experimenter biases. The results of the study are promising though.

Reply authors.
We absolutely agree with the reviewer that a control group would have been ideal. However, as we have tried to make clear in the manuscript, the primary outcome of the study was to test the acceptability of the product, not the impact on anthropometry, as a follow-up study on the impact of the product was planned if the acceptability was proven to be OK. This follow-up study has been finalized recently, and a manuscript is being prepared. But to make this more distinct, we have rephrased the last sentence of the introduction.

- Minor comments.
INTRODUCTION:
- “Severe acute malnutrition (SAM)” is not defined, i.e. based on WHZ? BMI? MUAC? Which cut-Offs?

Reply authors.
Has been added to the introduction

- “main underlying causes of malnutrition”: change into “main underlying causes of CHILD malnutrition”

Reply authors.
Has been added

- “mixture of milk powder” & “many studies, most in Africa, have demonstrated”: it makes me wonder if lactose intolerance, highly prevalent in Asia (including the two surveyed nations Cambodia and Vietnam), matters.

Reply authors.
Probably it does matter. In Cambodia, soya milk is much more popular than cow milk. But in our study, we didn't find any significant increase in diarrhea. Indeed, incidence of diarrhea was very low during the 1 month intervention, so we have no data to discuss this point.

- “Acute malnutrition among children … is 17%”: The paper starts with “severe acute malnutrition” but now you refer to acute malnutrition. Please be more consistent.

Reply authors.
Sentence has been changed for consistency

- “About 7.1% of the children under 5 years of age are wasted in Vietnam, i.e. with a W/H <-2 Z-score.”: What is the reference population? There are two reference groups (NCHS/WHO and WHO standard).

Reply authors.
This is using the WHO standards for breastfed infants. Although the 2 standards give slightly different results with respect to prevalence of wasting and stunting, the authors believe it is outside the context of the present manuscript to discuss this.

ACCEPTABILITY TRIAL
- “Children were recruited from 2 kindergartens”: Please give some background information of the two sites.

Reply authors.
Has been added

ANTHROPOMETRY AND MORBIDITY DATA
- More information about the anthropometric measurement procedures need to be provided: MUAC was measured where (left arm vs. right arm, mid-point of upper arm vs. mid-point of biceps)? How was height measured (standing, lying down)?

Reply authors.
Has been added

RESULTS
- “22.7% (n=15) were classified as Moderate Acute Malnutrition (MAM)”: This is inconsistent to the introduction where you discuss SAM and severe SAM.

Reply authors.
We do not really see the inconsistency. RUTF are used for the treatment of severe acute malnutrition (SAM), and the product developed in Vietnam is for the treatment of SAM. However, as the effectiveness of the product had not been verified at the time of the acceptability trial, we found it unethical to test the acceptability of the new product in children with SAM, a serious and life-threatening health condition.
Therefore, we selected children with a WHZ>-3. However, at the same time, we didn't want to give children who might be overweight an energy-dense product for 1 month. Hence the requirement of a WHZ between -3 and -1 z-score. Unfortunately, this inclusion criteria was left out of the final draft of the manuscript, but we have put it back again.

Because of the selection criteria, about 25% of the study population had moderate acute malnutrition (MAM), being a WHZ-score between -3 and -2. Although RUTF is used for the treatment of SAM, supplementary foods (RUSF) are being advocated for the prevention of SAM, and often given to children with MAM. Hence, we think it is important to report in the manuscript the percentage of children with MAM.

DISCUSSION
- “The study was indeed conducted in July, the warmest month of the year”: I wonder if the previous study in Cambodia was also conducted during the monsoon season.

Reply authors.
The study in Cambodia had a much longer duration, as the report investigated more the reasons for failure of the introduction of PlumpyNut in Cambodia, which included but was not limited to issues with the acceptability.

- “This increase in HAZ-score most likely represents catch-up growth in these chronically undernourished children. There has been some debate on whether catch-up growth is possible after 2 years of life”: Please delete this whole paragraph. The debate on catch-up growth is related to stature in adulthood, i.e. whether or not children can reach their TERMINAL genotype-stature later. The authors’ study just covers 4 weeks, and height recovery of preschool children in the short or mid-run is well known.

Reply authors.
The reason why we had included this sentence is because in SE Asia there is a strong tendency to focus on only the first 2 years as period for stunting reduction. Indeed, the current advocacy of ‘first 1000 days' by many UN organizations reinforces the idea by many policymakers in Vietnam that after 2 yrs of age, nothing can be done on improvements in height. We have removed the phrase on catch-up growth, but maintained the paragraph on height increases.

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:
I declare that I have no competing interests
Reviewer 2: Max Oscar Bachmann

Reviewer’s report:
This study investigates a potentially important subject. The has serious limitations which cannot be corrected by revision of the manuscript:
1. A cross-over design is inappropriate when the effect of treatment is likely to persist after the first treatment period.
2. The sample size is small
3. The one week follow-up in each treatment condition is short for anthropometric changes
4. It is therefore likely that the finding of no difference in anthropometric outcomes is a result of small size and short follow-up, rather than equivalent effectiveness for the two treatments.

Reply authors.
We assume the reviewer refers to a persist effect on anthropometric indices, and that the sample size is small to detect changes in Z-scores. We agree with the reviewer, but as also explained above to Reviewer 1, the primary goal of the study was to test the acceptability of the new product, not the impact on anthropometric indices. A follow-up study, with a larger number of subjects, on the impact of the product was planned if the acceptability of the product was proven to be OK. This follow-up study has been finalized recently, and a manuscript is being prepared, showing equivalence between PlumpyNut and the Vietnamese product (the composition being slightly adapted after the acceptability trial.
Concerning point 3, each treatment condition was 2 weeks, not 1 week. The reason we did a 2 week acceptability trial is that we had concerns with other acceptability trials which offer the product only 1 time to a subject. RUTF are normally given for 8 weeks, so duration is an important aspect of the acceptability in this case. The sample size of ~60 children is relatively large for an acceptability trial.

However it is worth reporting even underpowered randomised trials, and the differences in acceptability of the two foods are relevant to their future uptake. There are several problems with the manuscript which could be corrected with revision:
1. There should be a sample size calculation to show whether the sample size and duration of follow-up would provide sufficient power to detect a clinically significant difference in effects.

Reply authors.
This has been added to the methods section. Again, please note that acceptability was the main outcome, not anthropometrical indices.

2. The mean values or percentages of each outcome at baseline, after the first treatment period, and after the second treatment period, in each group, should be reported.
3. The estimated differences in effects of the two treatments should be reported. That is, the differences between arms in mean or percentage changes in outcomes during each treatment period, with 95% confidence intervals, should be reported. P>0.05 if uninformative, especially given the small sample and short follow-up.

**Reply authors.**

We assume the reviewer requests this data (point 2 and point 3) to be included in the manuscript to test the equivalence between the 2 products in terms of effect on weight and height gains. However, we have not provided this data intentionally as the study was not meant to be an equivalence study, but an acceptability study. The sole reason for reporting on the effect on anthropometrical indices, for both products combined, is to indicate that the approach in general is promising to improve weight and height in these children. This is an important point to make in our view, as stunting reduction is high on the agenda of many national and international organizations, and there is a lot discussion on these kind of tools. However, as correctly remarked by the reviewer himself, the sample size is too small to make meaningful conclusions on the equivalence (or difference) between the 2 products in terms of impact on weight or height gains, perhaps leading to erroneous conclusions. A study specifically designed to test the equivalence of the 2 products has recently been completed,

**Quality of written English:** Acceptable  
**Statistical review:** Yes, and I have assessed the statistics in my report.  
**Declaration of competing interests:**  
'I declare that I have no competing interests'
Reviewer 3: Saskia de Pee

Reviewer's report:
Major Compulsory Revisions
1. Most children who suffer from SAM are below two years of age. Why has the acceptability of the RUTFs been tested among children aged 3-5 years?

Reply authors.
The reason for selecting children with an age between 3 and 5 years, and a WHZ between -3 and -1 score was that the main outcome of the study was the acceptability of the product, and not impact on anthropometric indices. Assessing acceptability in children <3 yrs of age is difficult, as reliable answers to questions on whether a product is liked or not are hard to obtain. In younger children, acceptability is mainly accessed through the amount eaten, but as we were trying to optimize the product, we were more interested in what could be changed to improve acceptability. As explained to the other reviewers also, a follow-up study, with a larger number of subjects, on the impact of the product was conducted last year, in children with SAM and a mean age <2 yrs. This study showed that intake of the (slightly modified) Vietnamese product was higher than of PlumpyNut (manuscript in preparation).
We have added a paragraph in the methods section to clarify this.

Especially the hard, dry consistency of the local product is of concern when it is to be consumed by children, from the age of 6 months onwards.

Reply authors.
Recently we have also developed a spread-like RUTF, besides the bar-like product, which will be used infants and young children.

2. Please provide more detail about the nutrient content of HEBI in comparison to Plumpy'Nut, including the content of n-3 and n-6 fatty acids, and state whether the nutrient content has been estimated using food composition data for the raw ingredients, or has been based on actual analyses. Especially whether HEBI has a composition in-line with the specification for RUTF for SAM treatment should be clear from the information provided. Also, please give a range for the content of the different ingredients. And, whey is shown as an ingredient in figure 1, but not mentioned in the text, please adjust where necessary.

Reply authors.
The composition is based on food composition tables. In addition, micronutrient content has been verified by the laboratory of UNICEF in Copenhagen. The Vietnamese product fulfilled all UNICEF requirements for a RUTF, including those for n-3 and n-6 fatty acids. We have changed Table 1 to provide more information on the content of the product, with the table now giving macro and micronutrient content of the local product. The product contains whey, to fulfill the UNICEF requirement of 50% of proteins to be from milk protein.

3. What is the water content of HEBI, and what is its shelf-life?

Reply authors.
The HEBI contained less than 2.5% of water, thereby fulfilling UNICEF guidelines for RUTF. Shelf-life is currently being tested by stability study, but at the moment it is >1yr.

4. What are the costs of HEBI compared to imported Plumpy’Nut?

Reply authors.
At the moment, the price of the HEBI is comparable to that of PlumpyNut, although it is not easy to give a price of a product during the experimental phase, as several batches were discarded before the product was finalized.

5. What was the caloric content of the snacks that were normally given to the children at school, i.e. how much more energy did the children receive compared to what they normally received at school?

Reply authors.
There are no “normal” snack meals; since it varies between children and depends on what the parents put in their child bag.

6. If inclusion criteria included WHZ >-3 and <-1 (text), why were there two children in the study with a WHZ<-3, and why does figure 2 show inclusion as WHZ-score<-1.1 (instead of <-1.0) and not show a lower limit?

Reply authors.
The 2 children with a WHZ<-3 were just above the cut-off during the selection measurement (1 month before the start of the study), but were below -3 on the actual start of the study. It was decided to keep the 2 children in the study, as alternative (exclusion, and referral to the health centre, where the parents would receive nutrition information only) was found unethical.

7. The text of the last two paragraphs of the discussion is too speculative, in particular:

a. The increase of HAZ-score that was observed occurred with consumption of a very nutrient-dense product (RUTF) that also includes milk powder. Saying that a lower cost, more sustainable food intervention would probably also achieve this, without specifying its characteristics (energy and nutrient density, nutrient content, type of foods) cannot be done. Please remove.

Reply authors.
We understand the point the reviewer is trying to make, but we do not state that a lower cost, sustainable food intervention will achieve the same, but that it might improve nutritional status too. We have reworded the paragraph to make this more clear.

b. Also, whereas catch-up growth in length may be possible to some extent, other damage of co-occurring nutrient deficiencies, such as impaired cognitive development due to iron deficiency may not be repairable, and it would be important to remind the reader about that – prevention is better than treatment.

Reply authors.
We completely agree with the reviewer that prevention is better than treatment. However, the reason to include this paragraph in the discussion is to make policymakers aware that interventions are also needed after the first 1000 days, in addition to earlier interventions. We do not argue for a switch in focus from infancy and early childhood to later in childhood.

c. The extent to which stunting can be reduced by supplementary feeding for the treatment of moderate malnutrition is limited, because the duration of such treatment is short, and could only occur among children that are identified and eligible for treatment.

Reply authors.
At the moment, there is no clear solution, no golden bullet, for the prevention of stunting. We agree with the reviewer that blanket supplementary feeding for populations is no solution. But we think it is outside the scope of this manuscript to go into the discussion on tools to prevent stunting.

Minor Essential Revisions
1. Introduction, 2nd paragraph, please note that the note by WHO, WFP, UNICEF, SCN on RUTF for SAM treatment specifies a very specific composition in terms of nutrient content.

Reply authors.
Done

2. Please clarify whether IMAM in Vietnam treats children with SAM and MAM the same way, and whether both would be eligible to receive RUTF (refer to last paragraph of introduction).

Reply authors.
Done

3. Plumpy’Nut could in principle also be produced locally, unless its main raw ingredients are not available. Please clarify why different ingredients were used for HEBI. Was it related to familiarity with the type of product? And if so, is the existing green bean cake also consumed by children aged 6-11 months?

Reply authors.
Peanuts were identified as being 'unusual' as food product for children. Therefore, we switched to mung beans, which are indeed consumed by infants in SE Asia often as part of the porridge they receive. Also, existing green bean cakes melt in the mouth very quickly so they may be consumed by children less than 12 months, however we do not know if parents give them or not to their child.

4. What indicator was used for ‘reluctance’ of children towards RUTF?

Reply authors.
Reluctance meant refusing to eat the product the first time the teacher presented it, but after encouragement by the teacher the child try the offered food. Reluctance was differenced from “Refusal”, which meant that the child completely refused the offered product even after being encouraged twice by the teacher. This has been added to the methods section.
5. Discussion, 6th line, should this be ‘accepted BY…’ instead of ‘accepted FOR children in Vietnam.’?

**Reply authors.**

Done

6. How was the difference between the terms taste and palatability explained to the 3-5 y old children in such a way that they could understand and give their score?

**Reply authors.**

The questions were translated into Vietnamese, where those two words are easier to understand and easier to be differenced than in English. The questions were asked by the field assistant with the help of the teachers, and we used a facial 3 points hedonic scale, where “Smiley” faces were added next to the number to help the children to understand the question. The 3 facial expressions used were designed to correspond a child’s feeling concerning the food. Children could point to the smiley to be scored by the field assistant.

7. Table 3, please state that a higher score for hardness indicates increased hardness rather than better acceptability.

**Reply authors.**

Done