Author’s response to reviews

Title: Efficacy of different strategies to treat anemia in children: A randomized clinical trial.

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Author’s response to reviews: see over
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Editorial Office
Nutrition Journal

Attached please find the revised version of the manuscript entitled “Effectiveness of different strategies to treat anemia in children: A randomized clinical trial” as a potential original contribution for publication in the Nutrition Journal.

Below you will find the responses to each reviewer comments and suggestions. We believe that with the recommended changes the paper has improved considerably for publication in the Nutrition Journal.

Sincerely yours,

Jorge L Rosado, PhD.
Reviewer 1

Grammar and punctuation throughout are still not at an acceptable level for publication. In general, the manuscript still requires major work. Items that authors stated were addressed or corrected within the first revision were not all completed or were not completed throughout the manuscript.

Additional issues to address:
1. Objective of the study should be specific. Suggest begin sentences with: the objective of the study was...
   We started the sentence as suggested at the end of background section (Page 5 Line 11).

2. Did not make correction of not using first person tense.
   First person tense is no longer used throughout the paper as suggested.

3. In abstract need to be specific when the dosing was given. ie daily.
   The dose frequency was now included in the abstract (Page 2 line 11).

4. Need to include the cut-off values used for total iron and ferritin in the abstract.
   The cutoff value for hemoglobin was included (Page 2 line 7); however the cutoff values for total iron and ferritin were not included, since we do not mention results that involve these variables.

5. Should address the percentage within the population that are non-breastfed vs breastfed children since this is an issue with generalizability. Also need to let the reader know that if the child was formula fed, the percentage that were on iron fortified vs iron-free formula. Using only Non-BF infants should also be addressed in the limitations section.
   In the limitation section the issue of generalizability and the percentage within the population that are non-breastfed is now addressed. None of children in the study were formula fed. This is now mentioned in the subjects section of the paper.

6. Have not made corrections throughout manuscript of not beginning sentences with acronyms.
   Beginning with acronyms is now avoided in the manuscript.

7. Need to make it very clear that the water is considered a fortified food in abstract as noted in the paper.
We mention the treatment group or groups instead of “fortified food” to avoid confusion in the abstract.

8. Within the conclusion: 1. Need to clarify what you mean by had higher increments in Hb. 2. As results are stated: ‘In general, the supplements were less acceptable than the food fortification strategies’. Need to clarify if the less acceptable by participants or by treatment outcome. The way it is written is not clear.
   1. The sentence was rephrased to make it clear (Page 16 lines 11-12).
   2. It was clarified that some treatments were less accepted by participants (Page 16 line 16).

9. Still need to define 10 blocks of children.
The explanation of and justification of the randomization method is now more extensively explained in the paper (Page 6 lines 12-15).

10. Was enough of the water provided for food preparation of the whole family, only children, or only study participants and how did you confirm that it was used only for those intended?
   Enough water was provided and was assured by periodic visits to the home by delivering new bottles of water before the previous bottles were empty. Water for cooking was used for the family that was the only way to assure intake of fortified water of participants in the study. This is now better explained in the methods section (Page 9 line 25).

11. You note that the presence of adverse events was recorded every week. Why was this not done at each visit to minimize recall error.
   Adverse events were recorded each visit. Values were reported per week instead of per visit for clarity. An explanation is included in the text (Page 7 line 20).

12. Did not note in manuscript as stated in your comments that you included: WHO child growth standards were adapted appropriately using SPSS syntax based on whether or not the child length or height was used.
   We used the SPSS macro provided by the WHO to calculate z scores which is mentioned in the text (Page 10 line 19). Length or height is one of many variables considered by the program to calculate z scores.
13. In the biochemical measurements section- Need to move the information on the cut-off values for total iron and ferritin to the area where they are being defined rather than after the CRP data.
   **Text was moved as suggested (Page 9 line 3).**

14. Your definition of compliance is not clearly stated as written: ‘compliance was achieved when a child accomplished 4 months consuming treatment’.
   Compliance is not the correct word to use when referencing completing treatment. Also used in the Table 5.
   **The word was replaced to “completing the treatment”**

15. Knee height is added to Table 4 but there is no mention of it in the methods or results section.
   **Knee height methods were included in the anthropometry evaluation section (Page 8 lines 6-7).**

16. Figure 2. need to be specific in defining the a & b. Different from what?
   **Figure 2 legend now explains the differences that represent different letters.**

17. Your numbers in figure 1 are not the same as those discussed in the paper.
   ie screened 577 vs 574?
   **Values were corrected accordingly (Page 5 line 18).**

18. Figure 2. If you have the bar for anemia you do not need the bar for non anemic.
   **The non-anemic part of the bar was removed, although we prefer to leave the 0-100% scale to make it easier to visualize the proportion of children that were no longer anemic.**

19. Footnotes for figures do not include the abbreviations used so they need to be included since all tables and figures should be able to stand alone.
   **Treatment abbreviations were included in every table**

20. In your acknowledgements you use CRF’s and I did not identify where that was defined previously.
   **CRF’s was replaced for “case report forms” (Page 18 line 15).**

21. Still spelling out hemoglobin within sentence even after inserting abbreviation. Noted that this was fixed but it has not been completed.
Hemoglobin is abbreviated throughout the paper.

21. In one section you use fortified foods and another you use fortified complementary foods does the later also include the water. Need to be consistent. 
Fortified complementary food is referred to FCF treatment and fortified food is referred to FW treatment, such differences are now clear throughout the paper.

22. Still does not have a well stated strong conclusion. Conclusion should also include information about the generalizability of the results. I could not identify the sentence added that addresses what this research has contributed to science. 
The population to which this study is generalizable to is mentioned in conclusions. Instead that one strong conclusion, the whole paragraph describes several conclusions of the study. A sentence was added to make clear the contribution of concentrating on other micronutrients and the higher efficacy of supplements.

Reviewer 2

Compulsory revisions: There needs to be some interpretation of the ferritin results in the discussion--some speculation as to why it increased so dramatically in the IS group and, surprisingly, decreased in the IFS and, to a lesser extent, FW, groups. If these supplement strategies are not maintained, it seems like the IFS children are likely to become anemic again more rapidly than the other groups. 
The IFS group decreased ferritin but the final values were still within an acceptable range and similar to the other groups. Analysis adjusting for the initial concentration of ferritin (that was higher in IFS group) did not show significant differences.

Minor essential revisions:
p 8, line 19: "3,5mL 5 mL" doesn’t make sense
The sentence was corrected (Page 8 line 22).

p11, line 7: "found not to be significant"
Sentence was corrected (Page 11 line 14)

p11, line 13: "characteristics were not significantly different" or "characteristics did not differ"

Sentence was corrected as suggested (Page 11 line 21).

p11, line 21: sentence "Subgroup analyses in hemoglobin response showed same effects than analyses in overall children" is very unclear

Sentence was corrected (Page 12 lines 5-6)

Table 2-4: MMS here is defined as Multiple micronutrient "syrup" rather than "supplement"; similarly IFS has a more extensive definition than that used throughout the paper. Be consistent. In the table of abbreviations those descriptions could be defined. For example, MMS multiple micronutrient supplement (prepared as syrup), etc.

Treatments definitions are now consistent and defined

Table 4: the last column was cut off on my copy