Author’s response to reviews

Title: The Low Indexes of Metabolism Intervention Trial (LIMIT): Design and baseline data of a randomized controlled clinical trial to evaluate how alerting primary care teams to low metabolic values, could affect the health of patients aged 75 or older

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Author’s response to reviews:

Wednesday, June 08, 2017

To Hilary Logan,

BMC Health Services Research

Subject: Manuscript BHSR-D-16-00466

Dear Editor,

We are grateful for the valuable and constructive comments.

Please find enclosed our revised manuscript, "The Low Indexes of Metabolism Intervention Trial (LIMIT): Design and baseline data of a randomized controlled clinical trial to evaluate how alerting primary care teams to low metabolic values, could affect the health of patients aged 75 or older".

Our response to the comments are provided here, as requested, point by point:
Editor Comments:

1) Please include all author email addresses on the front title page.
   Done.

2) Please include the date of registration of your clinical trial in the abstract. Please ensure this is also included in the abstract in the submission system.
   Done.

3) Please change the title of the Introduction, Background and Rationale section to Background
   Done.

4) Please move all Tables to the end of the manuscript or upload as separate Table files
   Done: Tables were moved to the end of the manuscript.

5) Please ensure that all figures/tables and supplementary files are cited within the text. Any items which are not cited may be deleted by our production department upon publication. Please ensure that all supplementary files are named with an informative title. Please also provide all titles/captions for any images/tables after the references as plain text.
   Done.

Please also add a section “Supplementary files” where you list the following information about your supplementary material:

- File name

- Title of data

- Description of data

Done.
Please note you may remove the SPIRIT checklist at this stage.

Removed.

Please note that at this stage it is not necessary to upload a cover letter as supplementary file

Removed.

Please note that we added an ad-hoc supplementary file: "A manuscript that contains tracked changes" in case it is needed for the reviewers.

Reviewer reports:

Maya Vadiveloo (Reviewer 1): Overall, the manuscript is improved, but there remain a few additional issues that require clarification.

1. Introduction: The flow in the introduction remains awkward and the rationale for study difficult to follow. Some specific comments:

   - Line 27-28 is awkwardly phrased and lacks a necessary justification regarding the both the biologic plausibility of why low BMI, HbA1c, and serum cholesterol require more attention and some evidence of the numbers of elderly adults currently who are not flagged by low values and who may experience higher morbidity and mortality as a result.

   We rephrased the background (introduction) section (from line 20 of page 5 to line 58 of page 6) to make it more fluent and in line with the specific remarks.

2. Line 39- when the authors refer to nutritional intervention trials, it is not clear what the outcomes are in those trials, making the interpretation of the sentence difficult.

   This issue is now referred to. (Background section, lines 51-55, page 5)

3. Transitions are needed between lines 45 and 46. Something like, "Similar to BMI, the correlation between xxx and xxx is U-shaped for both HbA1c and total cholesterol..."

   We now refer to this common U-shape in the 2nd paragraph of the background section (lines 29-35, page 5).
4. A bit more discussion on HbA1c targets in the elderly would help the reader understand if the issue that needs to be addressed in the elderly is over-treatment or A1c targets that are too aggressive—especially because the authors specifically focus on patients taking 2 antidiabetic medications—do the criteria change for 1 medication or for individuals who are pre-diabetic? Intriguingly, (and similar to BMI and cholesterol targets,) current practical target definition for HbA1c has no "lower limit". Hence, we prefer the term 'over-treatment'. We found a reference only regarding patients taking 2 antidiabetic medications. We have no reason to suggest a different HbA1c target for patients taking 1 antidiabetic medication. We rephrased the 4th paragraph to make it clearer. (Background section, lines 4-15, page 6)

5. Line 18 (2nd page of introduction)- can the authors please define low-risk Low risk was defined in the reference. We added this information as requested. Framingham Heart Study equation is used only for ages 30-74. The reference is only given as an example to a known burden of overtreatment. (Background section, lines 24-29, page 6)

6. A transition is needed between the discussion of cholesterol and screening malnourished patients— the authors move from talking primarily about population statistics and then move to clinical populations (e.g. hospitalized), and it is not clear how the 2 are connected. We now refer to the common issue of seldom flagged low metabolic values in the 2nd paragraph of the background section. (Background section, lines 27-30, page 5.) The issue of lack of data on community based clinical intervention, and the context of the given reference are rephrased in the background section's 6th paragraph. (Background section, lines 31-59, page 6)

7. Line 22-24 ("made significant effect" is awkwardly phrased— additionally, using numbers to show the effect would be more convincing. We rephrased this sentence too, to put the reference in the right context. Numbers in this reference are less important here. (Background section, lines 41-49, page 6)

8. Can the authors add two additional sentences/ideas somewhere in the introduction: 1) It is not clear to a non-expert in this area that healthcare practitioners are "missing" these individuals—adding some numbers to let the reader know that x% of hospitalized patients meet these risk
criteria yet only x% are referred for additional counseling. The "so what" of the problem still seems missing from the introduction. Additionally, could the authors please try to add a bit more detail about the intervention in the Introduction- e.g. After the authors mention the previous success of the previous family medicine intervention, they could indicate something about the current intervention (i.e. is it a single email that the nurse or MD receives? Is it upon enrollment?).

We hope our revised background section makes the rational clearer now. The (renamed) baseline data section (lines 10-51, page 10) shows the most relevant numbers while the "so what" of the problem is summarized (unchanged) in the Discussion section (lines 14-18, page 12).

Objectives:

- It may be valuable to indicate that the primary objective is to see if the intervention improves patient survival across 7 groups of high risk patients.

True, thus we qualified the description as per your suggestion. (Objectives section, lines 13-17, page 7)

- Line 50-51- what are the authors referring to when they say "the number needed to treat" (the number of patients?)

The sentence was revised to: "The number needed to treat (i.e. number of e-mails sent) to prevent any death in one year will be assessed as a measure of clinical significance". (Objectives section, lines 25-28, page 7)

Table 1:

- The authors state that the effect on mortality will be analyzed for each LIMIT subgroup, but subgroup G only has 8 participants. Based on the power calculations, it does not seem that the authors are powered to detect subgroup differences without combining some subgroups.

Added: "The effect on mortality will also be analyzed for each LIMIT subgroup that has a sufficient number of participants (groups: A,B,C,F)"
Methods:

- The authors discuss controlling for confounding, but it would be useful to know what confounding variables are being considered and how they are being measured.

Added: "The proportion of deaths between two groups will be also compared by using a logistic regression model in order to control for confounders: age, gender, BMI, Cholesterol level, HbA1c%, previous MI, IHD, CVA, TIA."

- As with the introduction, a bit more description of when and how frequently a reminder email was sent would be helpful to better understand the intervention.

Revised to "The one-time intervention letter provided relevant patient data and an alert to the primary care providers (physician and nurse) about low values of BMI, HbA1c% or cholesterol with an advice to consider appropriate dietary and medical revision." (line 32-33, page 8)

- How are the authors handling the automatic emails that were sent but not opened by the physician or healthcare practitioner?

Added: "Emails were resent, during the first 3 months, only if a "recipient's mailbox is full" message was received." (lines 44-47, page 8)

General

Could the authors consider some kind of flow diagram to show how the >40,000 in the Southern and Northern districts moved to 8,584 study participants and 7 subgroups (e.g. just the first row of numbers for each of the 7 subgroups in Table 5)?

Added as a supplementary file: "LIMIT's - Flow Diagram"

Table 3:

- For criteria "c" the word "all" should be changed to "both".

Done, thanks.

Language corrections were made, too.
We would like to thank the reviewers again for their thorough and thoughtful remarks.

Sincerely, on behalf of all authors,

Nir Tsabar