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

Authors:

Nir Tsabar (Tsabar.Nir@Gmail.Com; nir.tsabar@clalit.org.il)
Yan Press (yanpr@clalit.org.il)
Johanna Rotman (hannekero@clalit.org.il)
Bracha Klein (kleinbr@clalit.org.il)
Yonatan Grossman (yonatangr@clalit.org.il)
Maya Vainshtein-Tal (may@clalit.org.il)
Sophia Eilat-Tsanani (eilat@clalit.org.il)

Version: 2 Date: 14 Apr 2017

Author’s response to reviews:

Saturday, March 25, 2017
To Hilary Logan,
BMC Health Services Research
Subject: Manuscript BHSR-D-16-00466
Dear Editor,

We are grateful to the reviewers for their time and valuable comments.

Please find enclosed our revised manuscript, "The Low Indexes of Metabolism Intervention Trial (LIMIT): Design and initial results baseline data of a randomized controlled clinical trial to evaluate how alerting primary care teams to low metabolic values, would could affect the health of patients aged 75 or older".
Our response to the comments are provided here, as requested, point by point:

Reviewer #1:

1. The discussion on BMI and unintentional weight loss could be more thorough. For example, some research in large populations questions the "BMI paradox" and this could be better flushed out in the introduction. Similarly, the question about whether older adults should receive nutritional counseling to increase their body weight should be supported by evidence, as it is not clear that weight gain is recommended, and if it is recommended, what the target should be.

We acknowledge the uncertainty regarding optimal BMI and regarding weight gain counseling for the elderly. To better highlight this in the "Introduction, Background and Rationale" chapter:

(1) We added the sentence "However, an optimal individual BMI in the elderly population is a debated issue (e.g. ref. [10-13])" (Introduction, page 5, line 13) and added two references.

(2) We changed the sentences "These trials were few and small-sized (26-210 patients each). More research is needed to study which older adults in the community will benefit from nutritional counseling to increase their body weight." to "These trials were too few and too small in size (26-210 patients each) to draw conclusions whether older adults should receive nutritional counseling to avoid weight loss. Hence, more research is needed." (Introduction, page 5, line 16)

2. The link between the background and the gap that the LIMIT study is trying to fill could be made more clearly. For example, is the purpose of the trial to more consistently intervene in these identified "high risk" groups- this is not clear from lines 111-114 and the subsequent objectives.

We agree. Thus the sentence is changed from "This ongoing trial (LIMIT) is thus aimed at adding empirical knowledge in the fields of malnutrition, chronic disease treatment, medical management and informational intervention." to "This trial (LIMIT) is thus aimed at intervening in these identified high risk groups by way of sending an e-mail reminder about their low metabolic values" (Introduction, page 6, line 10)
3. I think it would be more valid to use a time-to-event survival analysis than a t-test for the primary outcome.

In this trial, we predicted death to occur only in a small proportion of the subjects during the one year period of the trial (less than 20% in any risk group). Being a discrete event, a t-test would be valid to use for analysis. Moreover, while survival analysis may be valid too, we should minimize post hoc changes to the trial protocol. As survival analysis may be interesting, its results will be published, but not as a primary outcome.

4. Additionally, do the researchers plan to examine whether the intervention effectiveness is mediated by changes in the secondary outcomes?

Yes, we do. We thus added the sentence: "The mediation of survival differences by the secondary outcomes will be assessed by examining correlation of primary outcome versus secondary outcomes at the subject level, e.g. by performing a logistic regression." (Statistical analysis section, page 12, line 18)

5. I had difficulty following the randomization process. Are there 7 subgroups where within each subgroup some participants are randomized to receive the intervention and others are randomized to receive usual care? If so, is the study powered based on these 7 groups? Similarly, now that emails are no longer being sent to the Southern district nurses, how does that affect the randomization scheme and study power?

(1) Details and examples of the Microsoft Excel technique used for the automated randomization process will be elaborated by the first author upon request. As described, each of the 7 subgroups was automatically randomized to intervention and usual care (1:1). The assignment of participants in each arm is shown for each group in table 5.

(2) The sample size needed in order to achieve the required study power was estimated based on previous email-intervention results [1] assuming similar effect in all seven groups put together. This previous email-intervention did not include emails to nurses. Hence, we believed our estimation was still valid.
(3) The decision not to send emails to the Southern district nurses was made after the randomization and after sending the emails to the primary physicians. Thus, it did not affect the randomization scheme.

6. BMI, HbA1c, and cholesterol have different effects on overall mortality- how will the authors address this in their analysis?

> The specific intervention effect on each subgroup's overall mortality will be analyzed and reported too. To clarify this, we added the sentence "* The effect on mortality will also be analyzed for each LIMIT subgroup (see table 4)." under table 1. (objectives section, page 8, line 1)

7. It would be useful if the authors could touch on the clinical significance in addition to the statistical significance of the intervention.

> We agree and thus added the sentence: "The number needed to treat to prevent any death in one year will be assessed as a measure of clinical significance". (objectives section, page 6, line 19) A reference is added too.

Rahim Moineddin (Reviewer 2): Comments on 'The Low Indexes of Metabolism Intervention Trial (LIMIT): Design and initial results of a randomized controlled clinical trial to evaluate how alerting primary care teams to low metabolic values, would affect the health of patients aged 75 or older'

The authors in this paper simply described their participants and reported the baseline measures. How useful they are I am not sure.

Their primary outcome was death from any cause within one year; however, there is no comparison or report of the outcome.

> This manuscript is indeed aimed at describing the design and baseline data of the participants. Hence, we hereby modify the title to: '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'. (Title, page 1, line 2)

In table 1, they suggested using chi-squared test for comparing deaths between intervention and controls. In table 1 (we suppose table 5 is referred to, NT), there are some baseline differences between two groups, therefore authors should adjust for those differences and then compare the proportion of deaths between two groups using an appropriate statistical method such as logistic regression.

> We agree and are grateful for this comment and thus added the sentence "The proportion of deaths between two groups will be also compared by using a logistic regression model in order to control for confounders." (Statistical analysis section, page 12, line 5)

Several outcomes in table 1 are not continuous, for example dispensed anti-diabetic drugs in criterion b patients, emergency room visits etc. Using nonparametric test or regression methods for count data are more appropriate for comparing this type of data than a t-test. The underlying assumption in t-test is that the data is normally distributed and this condition must be examined before t-test is applied.

> To clarify, we changed the sentence "Differences between the arms of the study will be examined using Chi-square test (or Fishers' exact test) for categorical variables and T-test (or Wilcoxon two sample test) for continuous variables." to "Differences between the arms of the study will be examined using Chi-square test (or Fishers' exact test) for categorical variables, T-test for continuous variables with normal distribution and nonparametric Wilcoxon two sample test for continuous variables without normal distribution." (Statistical analysis section, page 12, line 14)

Analysis Methods column in Table 1 (Objectives section, page 7) was corrected accordingly.

Language corrections were made, too.

We would like to add our clinical research coordinator Rinat Lasker in the acknowledgments section. (page 17, line 4)
The references were updated using Endnote.

We would like to thank the reviewers for their thorough and thoughtful remarks.

Sincerely,

Nir Tsabar

(Signature of corresponding author on behalf of all authors)