OPEN PEER REVIEW

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Peer Review Report for "Common Limitations and Challenges of Dietary Clinical Trials for Translation into Clinical Practices"

Author(s): Parvin Mirmiran, Zahra Bahadoran, Zahra Gaeini

Review Timeline:

Submit Date:	4 Sep 2020
Revised Date:	1 Mar 2021
Accepted Date:	29 Mar 2021

Revision (0)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Reviewer | **Revision** (0)

13 Nov 2020

Dear AE,
Thank you for providing me the opportunity to review this interesting manuscript. Although the main objective of the manuscript is not clearly stated; the authors have expressed that despite the importance of nutrition clinical trials (NCT), translation of their findings into public health strategies and evidence-based practice(s) is challenging and problematic due to limitations in the study design, implementation and finding' interpretation. Therefore, the main focus of the paper is on common challenges of NCTs and some possible solutions. The manuscript is basically making this argument by addressing the complexities of the NCTs as opposed to the pharmaceutical clinical trials.
- Although there are important points being addressed in the paper, I do not find any point of novelty in the content. It is too broad and lacks proper organization in writing. It lacks a clear and directive introduction and conclusion. While the manuscript is more close to a commentary, using subtitles such as “results” or declaring ethical approval of “the study protocol” is somehow unexpected.
- The manuscript can make a good commentary if being rewritten and shorten. Otherwise, I would not recommend publishing it in the present form.
Thanks.

REFEREE: Reviewer | **Revision** (0) 22 Nov 2020

Dear AE,
It is a well written paper and the scientific writing of the paper is suitable. Just I think it should be checked for some terminology. For example instead of nutrition clinical trial it is recommended to write dietary clinical trial. Because nutrition clinical trial might be involved either supplementation and supplementation is not the target of paper . If the author state that why she/he named it "Nutrition Clinical trial", I would be thankful. However, I found that this paper is just focused on dietary interventions. The limitations regarding blindness and methodological limitation is discussed very well. In the field of nutrition we do not have such good debates regarding the methodological concerns and I think the authors can focus on this point in their strengths of the study. The paper discussed well regarding different limitations in the field of dietary clinical trials.
Thanks.

REFEREE: Reviewer | **Revision** (0) 24 Nov 2020

Dear AE,
The objective of the manuscript is not fully explained. The background focused on nutrition clinical trials; however, the aim stressed the comparison of the nutrition trials and pharmacological trials.
- Not enough evidence was provided in the results. Trials of single nutrients or bioactive food compounds were mentioned to be similar to pharmacological trials. But no evidence was mentioned here. This point was seen throughout the manuscript.
- The small magnitude treatment effect of NCTS should be discussed. The small effect of foods or nutrients is not comparable with drugs. Each type of trial should have its own effect size explanation. As we consume the foods for the long term, they have more effects with chromic intakes. They are not comparable with pharmacologic agents. Authors should explain and interpret deeply.
- The claims of authors need more explanation and examples. For instance, how the inadequacy of authors' measures and insufficient intervention duration to high dropout rate, low adherence limit the translatability of the findings at NCTS.
Thanks.

REFEREE: Associate Editor | **Revision** (0) 25 Nov 2020

Dear EIC,
Based on the reviewers' comments the manuscript requires extensive revision.
REGARDS

REFEREE: EIC | **Revision** (0) 25 Nov 2020

Dear Author,
You should prepare a major revision.
Thanks.

OPEN PEER REVIEW

Revision (1)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Reviewer 1:

It is a well written paper and the scientific writing of the paper is suitable. Just I think it should be checked for some terminology. For example instead of nutrition clinical trial it is recommended to write dietary clinical trial. Because nutrition clinical trial might be involved either supplementation and supplementation is not the target of paper. If the author state that why she/he named it "Nutrition Clinical trial", I would be thankful. However, I found that this paper is just focused on dietary interventions. The limitations regarding blindness and methodological limitation is discussed very well. In the field of nutrition we do not have such good debates regarding the methodological concerns and I think the authors can focus on this point in their strengths of the study. The paper discussed well regarding different limitations in the field of dietary clinical trials. *R: Agreed. "Nutrition clinical trial" terminology has been changed to "dietary clinical trial" in the revised manuscript.*

Reviewer 2:

Thank you for providing me the opportunity to review this interesting manuscript.

Although the main objective of the manuscript is not clearly stated; the authors have expressed that despite the importance of nutrition clinical trials (NCT), translation of their findings into public health strategies and evidence-based practice(s) is challenging and problematic due to limitations in the study design, implementation and finding' interpretation. Therefore, the main focus of the paper is on common challenges of NCTs and some possible solutions. The manuscript is basically making this argument by addressing the complexities of the NCTs as opposed to the pharmaceutical clinical trials. Although there are important points being addressed in the paper, I do not find any point of novelty in the content. It is too broad and lacks proper organization in writing. It lacks a clear and directive introduction and conclusion. While the manuscript is more close to a commentary, using subtitles such as "results" or declaring ethical approval of "the study protocol" is somehow unexpected. The manuscript can make a good commentary if being rewritten and shorten. Otherwise, I would not recommend publishing it in the present form.

R: The main objective of the review was to focus on the limitations of different types of study designs for nutrition clinical trials, and we have tried to provide some practical solutions to reduce those limitations. Furthermore, we aimed to discuss how different natures of nutrition vs. pharmaceutical interventions make dietary clinical trials difficult to translate into public health and evidence based practices. The review could be a practical guide for researchers in the field of health cares, and gives new hints in dietary clinical trials. The objectives of the manuscript and novelty points of our review have been added to revised manuscript (page 5, lines 1-5).

The structure of the manuscript was based on the journals guidelines, although it has been restructured accordingly.

Reviewer 3:

The objective of the manuscript is not fully explained. The background focused on nutrition clinical trials; however, the aim stressed on the comparison of the nutrition trials and pharmacological trials. Not enough evidence was provided ion results. Trials of single nutrients or bioactive food compounds were mentioned to be similar to pharmacological trials. But no evidence was mentioned here. This point was seen throughout the manuscript.

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The claims of authors need more explanation and examples. For instance, how the in adequacy of authors measures and insufficient intervention duration to high dropout rate, low adherence limit the translability of the findings at NCTS.

The main objective of the review was to focus on the limitations of different types of study designs for nutrition clinical trials, and we have tried to provide some practical solutions to reduce those limitations. Furthermore, we aimed to discuss how different natures of nutrition vs. pharmaceutical interventions make dietary clinical trials difficult to translate into public health and evidence based practices. The objectives of the manuscript have been revised accordingly (page 5, lines 1-5).

Some examples of nutrition clinical trials and their effect sizes compared to pharmaceutical trials effect sizes (page 6, lines 9-19), examples of low adherence rate and high attrition rate of nutrition clinical trials (page 15, lines 4-9), and examples of duration of interventions in dietary clinical trials (page 16, lines 8-10) have been added to the revised manuscript.

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Revision (1)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Associate Editor | **Revision** (1) 29 Mar 2021

Dear EIC,
The authors' responses to the comments are satisfactory. The manuscript is suitable for publication in the IJEM.
Thanks.

REFEREE: EIC | **Revision** (1) 29 Mar 2021

Dear Author,
The document is reviewed carefully by the reviewers. According to their comments and your revisions as requested, this manuscript is accepted.
Thanks.