Author’s response to reviews

Title: A new phototherapy regimen during winter as an add-on therapy, coupled with oral vitamin D supplementation, for the long-term control of atopic dermatitis: study protocol for a multicentre, randomized, crossover, pragmatic trial. The PRADA trial

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Dear Editor,

We are very pleased to be given the opportunity to submit a revised version of our manuscript TRLS-D-18-00412R1 entitled “A new phototherapy regimen during winter as an add-on therapy, coupled with oral vitamin D supplementation, for the long-term control of atopic dermatitis: study protocol for a multicentre, randomized, crossover, pragmatic trial. The PRADA trial.” by Catherine Droitcourt et al. We thank the reviewers for their careful reading, and their insightful comments. We are pleased to address their comments in a point-by-point response below. We did our best to take into account all the points and we believe we are now able to submit a substantially improved revised version of our manuscript.

In the manuscript, changes are in colored text. As requested, we provide both marked and unmarked versions of the manuscript.
We hope that the changes we made have improved our manuscript and made it acceptable for publication in Trials.

On behalf of the authors,

Yours sincerely,

Catherine Droitcourt

Reviewer #1: The manuscript is much improved. Please see some additional comments below.

Thank you for your comments.

1. In "Additional file 1", please correct the value of base correlation from 0.06 to 0.6.
   
   Reply: this point has corrected in the "Additional file 1".

2. P.4, line 78: please remove ".
   
   Reply: The " has been removed.

3. In 'Sample size' section, p.12, line 247, please remove text "...and any correlation between them for each level of repeated measures”. This is not true - since, as you noted next, GLIMPPSE assumes standard deviation to be the same across the repeated measures, the correlation is actually 1.
   
   Reply: The text "...and any correlation between them for each level of repeated measures" has been removed.

4. I am not sure what the relevance is of the sentence "Of note, the minimum clinically significant difference for the PO-SCORAD score is around 9 points." You assumptions for evolution over time imply that the average difference between the groups (which changes over time) is smaller than 9. Perhaps you could add a clarification to the above sentence explaining that you actually chose to size your study based on a smaller difference.

   Reply: The minimum clinically significant difference for the PO-SCORAD is indeed around 9, but we adopted a stance enabling the detection of a smaller difference, which means we are in an
even better position to detect a clinically relevant difference. This point has been clarified as follows: "It can be noted that the minimum clinically significant difference for the PO-SCORAD score is indeed around 9, but we adopted a stance enabling the detection of a smaller difference, which means we are in an even better position to detect a clinically relevant difference." (page 13, lines 254-257)

5. P.16, line 344 and line 349: I would suggest removing "Patient" from the list of factors since it is a bit confusing. Factors usually mean "covariates" and "Patient" is not a covariate; when you said that you will analyze a repeated measures model, this already implies that you will be accounting for correlated repeated measurements from the same patient over time.

Reply: We agree with the reviewer and have removed the word "Patient" from the list of factors. The revised version of the manuscript has been modified as follows: "This means that we need to consider the following factors: Period: first winter / second winter, Order: Phototherapy - No phototherapy / No Phototherapy – Phototherapy, and Carry-over." (page 16, lines 346 and 348).

6. P.17, line 353, paragraph starting "For descriptive purposes...": do you intend to calculate average and standard deviation of the scores by visit? If yes, please say so. An average and standard deviation over the entire trajectory would not be very meaningful. You also say that "normal distribution... will be checked at this stage"; normal distribution should really be checked when doing the modeling, it does not really affect the descriptive statistics. Perhaps you could simply modify this sentence by saying "normal distribution assumed in the modeling analysis... will be checked at this stage".

Reply: Yes, we intend to calculate descriptive statistics of the PO-SCORAD per visit. The revised version of the manuscript has been modified accordingly. We also modified the following sentence: "Normal distribution assumed... in the modeling analysis will be checked at this stage." The revised version of the manuscript is modified as follows: "For descriptive purposes, it is instructive to carry out an analysis based on a summary of the statistics (a quantity calculated from each curve), which can reflect important aspects of the problem at hand: we have chosen the area under the curve (AUC), and the mean amplitude of PO-SCORAD score ranges. Descriptive statistics (mean and standard deviation) of the PO-SCORAD for each visit will also be provided. Normal distribution is assumed in the modeling analysis for the primary outcomes (PO-SCORAD severity score over two one-year periods; cumulate consumption of TAT during winter) and will be checked at this stage." (page 17, lines 362-368).
7. P.17, line 362: "Mixed model techniques (PROC MIXED) will be applied with a restricted maximum likelihood (REML) estimation method, because it enables the use of different covariance structures for the covariance matrix, in order to find the most suitable covariance structure for the data." This is simply not true. Maximum likelihood (ML) method can accommodate different covariance structures just as well. I don't think you really have to justify use of REML in this paper - I believe you don't even need to state that you will use REML, such details are usually left to the statistical analysis plan - but in general REML is used because it produces unbiased estimated of variance and covariance parameters.

Reply: The revised version of the manuscript has been modified as follows: "Mixed model techniques (PROC MIXED) will be applied." (page 17, lines 371-372)

8. It seems that in the 'Sample size' section you say "However, an interaction of the time and treatment should be taken into account as we anticipate this could happen.", but in the 'Statistical methods', time by treatment interaction is not mentioned in the list of factors you intend to include in the model (pp.16-17). Please clarify whether this interaction will or will not be included in the model.

Reply: We clarify the description of statistical modeling as follows: "We will use a single model with the following main effects Treatment-1 (Phototherapy / No phototherapy), and Treatment-2 (vitamin D / placebo), Period, Order and Carry-over term as well as an interaction term between Treatment-2 and Treatment-1. As an interaction of time and treatment could occur we plan to add an interaction term to the model." (pages 16-17, lines 349 to 353)

9. The paper now goes into a very detailed description of the analysis of PO-SCORAD, but the analysis of cumulative consumption of TAT is still left completely unspecified, apart from mentioning it in the hierarchical procedure. This needs to be corrected. Please provide some description of the planned analysis of TAT.

Reply: We describe the planned analysis of TAT as follows in the revised version of the manuscript: "The other primary outcome, the cumulate consumption of TAT (number of tubes) during the winter, is a quantitative variable. It will be analysed using a mixed model with the following main effects: Treatment-1 (Phototherapy / No phototherapy), and Treatment-2 (vitamin D / placebo), Period, Order and Carry-over term as well as an interaction term between Treatment-2 and Treatment-1. As this outcome is a summary of winter consumption, no interaction of time and treatment will be added to this model." (page 17, lines 353 to 359).
10. I am still bothered by a seeming disconnect between the stated goals of the study regarding vitamin D and the analysis methods. On p.9, line 171, you state: "In the same population, we will be testing the long-term control provided by oral supplementation of vitamin D vs. placebo in a randomized, superiority, double-blind, parallel-group trial." Are you not interested in a possible stand-alone effect of vitamin D? If you are, you could actually test it by testing the main effect for vitamin D in the models. If you are not, then I think you should modify the sentence above by saying that you are actually interested in studying whether vitamin D may modify or enhance the effect of phototherapy.

Reply: We have indeed included a main effect for vitamin D in the model, please see description of the statistical modeling: "We will use a single model with the following main effects Treatment-1 (Phototherapy / No phototherapy), and Treatment-2 (vitamin D / placebo), Period, Order and Carry-over term as well as an interaction term between Treatment-2 and Treatment-1." (pages 16 and 17, lines 349 to 352)

11. Please check the manuscript for typos. I would also suggest that the manuscript, especially the new parts added in the revision, should be reviewed by a fluent English speaker.

Reply: The revised version has been reviewed by a native English speaker, and should now be improved. For reasons of clarity, these language-related changes have not been made apparent in the revised version.