Reviewer’s report

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

Version: 1 Date: 03 Jan 2019

Reviewer: Yuliya Lokhnygina

Reviewer's report:

The manuscript is much improved. Please see some additional comments below.

1. In "Additional file 1", please correct the value of base correlation from 0.06 to 0.6.

2. P.4, line 78: please remove ".

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.

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.

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.

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".

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.

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.

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.

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.

11. Please check the manuscript for typos.
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Please indicate how interesting you found the manuscript:

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