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: 0 Date: 18 Nov 2018

Reviewer: Yuliya Lokhnygina

Reviewer's report:

In general, this paper is quite well written and the protocol mostly follows SPIRIT 2013 guidelines for a clinical trial protocol. However, several issues need to be addressed.

1. There is a reference to "Figure 1" in the paper, however, no figure has been included with the manuscript. Please correct this.

2. Table 1 mentions 18 post-screening visits - how often will visits occur? Every 6 weeks? Please clarify in the text.

3. The Outcomes section needs to be clarified. Will all outcomes be used to evaluate the effects of both phototherapy and vitamin D interventions? The "Primary outcome" subsection needs to be renamed "Primary outcomes" and re-worded. Only at the end of the Statistical methods section, it became clear that there is not one primary outcome constructed using a hierarchical procedure, but actually two primary outcomes that will be evaluated with a multiplicity adjustment.

4. Please explain why EASI scores will be analyzed only over 1 year, while patients are going to be followed up for 2 years and the secondary outcomes will also be analyzed over 2 years. I suppose this makes sense for the evaluation of phototherapy, since only winter data will be used (I assume) - but what about the evaluation of the effect of vitamin D?

5. Recruitment: it is fairly concerning that patients could be screened in January yet would have to wait until September to be randomized. Some patients may drop out of the study before they are even randomized because of the long wait. What if in September it turns out that the number of patients that can be randomized is less than planned - will additional patients have to be identified and then randomized next September, delaying the trial completion? Perhaps the authors could address this concern in the Discussion. The alternative, of course, would be to allow patients to be randomized throughout the year and then address seasonal effects in the analysis.

6. The Statistical methods section needs to be considerably clarified. Importantly, specific hypotheses need to be specified - without them, it is impossible for the reader to evaluate whether the chosen models are even appropriate. When repeated measures are analyzed, there are many possible hypotheses that could be of interest. For example, investigators may expect
that in both placebo and vitamin D groups, measurements follow average linear trajectories over time and one hypothesis of interest may be that the trajectory in vitamin D group has negative slope, indicating that EASI scores decrease over time (I assume that smaller scores are better - this needs to be clarified in the paper), while the trajectory in the placebo group may be expected to be flat. In this situation, the appropriate hypothesis would concern difference in the trajectory slopes. Or - investigators may not be willing to assume a specific form of the trajectories (i.e. linear) and instead they may be interested in the estimated average difference at a single timepoint (often, last visit). Or - the investigators may be interested in comparing average differences across all timepoints, etc. In this study, I cannot tell from the paper which hypothesis (or hypotheses) the authors intend to evaluate.

The first sentence in the Statistical methods section says that 4 repeated measures will be analyzed for the primary outcome - please clarify what you mean by "4 measures", do you refer to the number of the outcomes or the number of repeated measures? In general, description of the model(s) needs to be much clearer, and I would urge the authors to consider how models of this type are usually described in the literature. Specifically, please clarify:

1) whether a single model or separate models will be used to evaluate the effects of the two interventions, phototherapy vs no phototherapy and vitamin D vs placebo.

2) The distribution that will be assumed for the outcomes (normal? Poisson? etc.)

3) The number of repeated measures that will be analyzed for each outcome. Currently, it appears that for the analysis of the effect of phototherapy 8 repetitions of each outcome (4 measured in the first and 4 in the second winter) will be analyzed, is this correct? If a separate model were to be used for the analysis of the effect of vitamin D vs placebo, the authors need to clarify whether they will include in the model a) outcomes collected at all visits, or b) outcomes collected at all post-screening visits, or c) outcomes collected at visits 2-18, or d) some other combination.

4) The terms that will be included in the model(s). Currently, it appears that for the analysis of the effect of phototherapy, the model will include terms for treatment (phototherapy vs no phototherapy), time period (first/second winter), treatment order sequence (Phototherapy - No phototherapy / No Phototherapy - Phototherapy) and carry-over term, which is appropriate. Of note, if this model will only be used to analyze outcomes from the first and second winter, then a carry-over term should not be necessary - in fact, the authors made this point on p.20. Additionally, the authors note that they would consider including interaction between vitamin D/placebo and Phototherapy/No phototherapy terms to allow for possible effect modification. In that case, it would also be advisable to include a main effect for vitamin D/placebo in the model.

5) It appears that the modeling analysis of the effect for vitamin D/placebo have not been addressed at all, apart from possible phototherapy effect modification. Please either confirm that this was indeed the intention or include the detailed description for such model.
Please note that the items "Methods for any additional analyses (eg, subgroup and adjusted analyses)" and "Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)" from the SPIRIT checklist have not been satisfactorily addressed in the paper. Please include these items in the paper or alternatively, include a reference to a document where these details can be found.

7. Sample size: please include a reference for GLIMMPSE, as well as the version of this software. It appears that sample size calculations were only done for the evaluation of one intervention (I assume it's phototherapy) - were sample size calculations performed for the evaluation of vitamin D vs placebo? Sample size evaluation needs to match the analysis methods specified in the Statistical methods section, and I am not sure whether this is the case. A mixed model fitted using PROC MIXED with REML does not provide Hotelling-Lawley trace test, why was this particular test used for sample size evaluation? Please provide some brief justification.

Provided "Additional file 1" with sample size and power calculations is certainly helpful, yet it is still confusing to me how the investigators ultimately chose their sample size. The first figure provides a scenario apparently used to evaluate a main effect hypothesis - although there is clearly time by treatment interaction present, according to the data entered, since the differences between groups at different timepoints are not the same. Using the provided numbers, my GLIMMPSE calculations resulted in a total of 168 subjects needed for the evaluation of the main effect hypothesis using Hotelling-Lawley trace test with 80% power. The second figure provides a different scenario, with no specified hypothesis. Assuming that the main effect hypothesis is still of interest, GLIMMPSE yielded that a total of 298 subjects are needed to achieve 80% power - note that this is more than 240 subjects selected by the authors. Finally, a table provided in the document considers different assumptions for the means and SD (quantified by scaling factors) - this table does not seem to be related to the previous two scenarios as it now states a clinically meaningful difference of 7 - so, either the outcome trajectories are not considered to be parallel in time between the two groups, or perhaps the hypothesis was switched from main effect to grand means. To summarize, the authors are to be commended for including an additional file with the details of the sample size and power calculations, but this file needs to be clarified considerably to clearly state the assumptions and the hypotheses tested. I believe it may be the easiest (and clearest) to simply include all the options used in GLIMMPSE for these calculations.

On p. 13, the authors state that "This calculation is performed considering a parallel-arm design; hence, using a cross-over design, only 120 patients are required." I believe this to be an incorrect statement. Sample size needed for a parallel arm trial cannot simply be halved in order to infer sample size needed for a cross-over trial since calculations for a parallel arm trial do not include assumptions about the effect of time period, treatment order sequence and carry-over effect.

8. Please clarify whether or not the data monitoring technician will be independent from the sponsor and from the rest of the study investigators.
9. Please address the SPIRIT guideline item regarding interim analyses and stopping guidelines: "Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial".

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