Author's response to reviews

Title: Efficacy of Vision Restoration Therapy after Optic Neuritis (VISION-Study): Study Protocol for a Randomized Controlled Trial

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Author's response to reviews: see over
Dear Editor,

Thank you very much for giving us the opportunity to revise our manuscript entitled

"Efficacy of Vision Restoration Therapy after Optic Neuritis (VISION-Study): Study Protocol for a Randomized Controlled Trial "

which we have thoroughly revised following the reviewer comments. We have addressed all the issues raised in the attached point by point response.

The final manuscript was approved by all authors.

We believe that our manuscript has substantially improved and hope that you will now find it suitable for publication in TRIALS.

Yours sincerely,

Jan Dörr, MD
Point by Point Response to Reviewer

Manuscript: 1052243302674026

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Major concerns

1) Authors should provide enough details to allow replication of the analysis and to guarantee that analyses will be performed in accordance to protocol. For example, would they analyze the improvement from baseline? Would they adjust for prognostic variables? Which ones? With what method? Without scale transformation? As their variables are numerical, they can read, for example the chapter about “the analysis of change” in “Statistical Issues in Drug Development” from Stephen Senn, Wiley.

We clarified some important aspects of data analysis in the manuscript. For example, we now clearly state, that endpoints will be analyzed as changes from baseline. The respective paragraph now reads: “The primary outcome parameter is the change (improvement) of the extent of the visual field after three and six months of training in comparison to baseline as determined by […] The secondary outcome parameters are outlined below and are also evaluated as changes from baseline.” As described in the manuscript the VISION study is a pilot study, meaning that all endpoints will be analyzed in an exploratory and descriptive manner and that the eventually reported findings will not allow confirmative generalization. As such, adjustments e.g. for possible confounders or multiple testings are not a priori specified. We have clarified this issue in the ‘statistical analysis’ section. As a matter of course, a detailed description of the analyses eventually performed will be provided with the publication of the study results.

2) As the control intervention is not included in the standard of care, please be aware that any positive conclusion will rely on the assumption that this intervention has no negative effects. If feasible, please provide references to justify this.
The reviewer here addresses the very important issue of adequate control intervention which is one of the most challenging issues in this study. The saccadic training software used here as control intervention is part of an established large software suite for cognitive rehabilitation (RehaCom, Hasomed, Germany). Efficacy of this software has been demonstrated in numerous trials (e.g. Friedl-Francesconi Z Exp Psychol. 1996). There is no evidence for any negative effects. We clarified and referenced this in the manuscript.

3) More randomization and concealment details should be provided. Who uses the ‘freeware’ program? Which one? How was the list stored? Does the researcher who recruits patients have access to this list before enrollment? How would authors guarantee (to a quality assurance professional) that the allocation arm was unknown before enrollment? How does the ‘independent’ person tell the patients what treatment to follow? How ‘independent’ is the outcome evaluator from researchers who train patients with allocated treatment? How would authors avoid patients asking questions to the follow-up and evaluator researchers about the intervention?

We completely re-wrote the respective paragraph in order to provide the requested details on randomization and concealment.

4) As dropouts and protocol violations would compromise results and interpretation, please, consider methods to boost adherence to the protocol.

Adherence to the protocol is indeed a crucial issue. Patients are comprehensively informed on the background, subjects and expectations of the study. The treatment procedures, in particular the use of the software and the treatment procedures are carefully explained. An unblinded member of the study team is available for all treatment-related problems or questions and – if necessary also for home visits. Execution of treatment (frequency and duration) is documented by the software and upon transmission via internet can be evaluated on a regular basis.

5) Please consider if, in your population, having access to a PC at home should be specified as eligibility criteria.
We have indeed extensively discussed this issue. Since in our patient population virtually all do have access to a PC at home we decided to provide those rare patients who do not have access to a PC with a standard PC for the time of study participation. So, there is no need for specification of PC as inclusion criterion.

Optional choices

1) Please, consider providing the effect size (difference between groups) with the 95% CI for the results reported on page 5, line 1.

Data provided are the mean changes over baseline at final evaluation in both groups as reported in the paper by Kasten et al (Nat. Med. 1998). We now added the standard error of the mean provided in the paper. The effect sizes can be calculated from these data, however the 95% CIs were not provided.

2) Please, consider switching your trial from ‘pilot’ to ‘pivotal’. Although I see your arguments in the discussion, this change would allow proving the effect if its size is moderate. [For a numerical outcome, 80 patients permit testing an effect size close to the SD. See, for example, the Nomogram on “Practical statistics for medical research” from Douglas G. Altman.] Since the intervention has been tested under other conditions (ref 40), you may derive reasonable values to justify the sample size rationale. If the statistical analysis and the required power result in a reasonable effect size, you will have some reasonable chances (estimated by the power) of demonstrating efficacy. [I’m not completely sure if this change can be made after the trial has started –but, if so, it should be masked to the results. I would appreciate the editor’s point of view. Should you agree on it with your ethical committee?] Please note that this change will imply guaranteeing that the analysis is protected against multiplicity; for example, clearly stating main outcome, analysis, and ITT population

We appreciate this reasonable suggestion and in fact, extensively discussed this issue in the forefront of the trial. However, since this intervention has never been tested in the context of optic neuritis and has moreover been met with substantial criticism we decided for a two-step approach with an initial pilot study for generation of concrete hypotheses and as a basis for a sound sample size calculation for a second, confirmative trial, if reasonable. We therefore would prefer to stick to this concept.