Author's response to reviews

Title: New therapeutic approach to Tourette Syndrome in children based on a randomized placebo-controlled double-blind phase IV study of the effectiveness and safety of magnesium and vitamin B6

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Author's response to reviews:

Dear Prathap Tharyan,

Please find attached the manuscript revised in accordance with your recommendations.

I. Clonidine (often with methylphenidate) is commonly used to treat Tourette’s syndrome- this could be mentioned in the background section.

The following text has been included in the background section: [Clonidine (often with methylphenidate) is commonly used to treat Tourette’s syndrome [1,2]].

II. The hypothesis mentions a placebo control arm but there is no other mention of a placebo in the methods of the manuscript or the registration document under interventions (except in the flow diagram) or how this will be masked to prevent un-blinding of participants and investigators. More details of this are required to be mentioned explicitly.

The following text has been included in “Preparation and labelling of treatment procedures” [The active principles of the treatment group were obtained via commercially available drugs. The placebo used was created in the hospital’s pharmacy department, emulating the excipients and volume of the experimental medication.].

III. Will the allocation envelopes be serially numbered? This section needs re-wording to ensure that allocation concealment would indeed be maintained.

The following text has been included in “Randomization, blinding and assignment to treatment group” [The allocation envelopes will be serially numbered to ensure that allocation concealment is maintained within the pharmacy department at
each hospital.]

IV. Information on who will recruit subjects (keeping allocation and recruitment separate) and who will assess clinical outcomes is lacking as is who exactly will be blinded. Will adequacy of blinding be assessed?

The following texts have been included in “Recruitment of patients”:
- The primary healthcare paediatricians in the whole region were informed about the EECC, so that patients could be referred to the clinics where the study was being carried out.
- The doctors responsible for making the scale evaluation when a patient was included in the study referred him/her to the pharmacy department to be included in one of the two study groups, using the randomization table.

V. Will multiple raters be used to evaluate clinical outcomes using the specified rating scales? If so, what about inter-rater reliability?
This is explained on page 13, under specific methods of evaluation, corresponding to reference 31.

VI. No details of how the PET data will be interpreted and what parameters will be assessed.

The following text has been included in “Measurement instruments”: [Qualitative changes in the metabolism pattern within the prefrontal cortex and in the basal nuclei will be evaluated. This will be complemented with a quantitative study of the normalized rates of metabolism in such zones.]

VII. Would not Repeat measures ANOVA with adjustments for baseline imbalances and scores be more appropriate than multiple t test.

[We believe that a Repeat measures ANOVA would be appropriate if the sample size so demanded. However, for the very small sample size required in our case, what is more suitable is a non parametric test for repeat measures, rather than ANOVA and the t test. The following text has been included in the statistical analysis section: “non-parametric Repeat measures with adjustments for baseline imbalances and scores”]

VIII. Since randomization was not stratified by concurrent treatments, it is possible this will need to be adjusted statistically.

The following text has been included in “Data Analysis”: [Statistical adjustment was performed by means of a multivariate model including the variable group (experimental and control) and concomitant treatment (Yes/No).

IX. The word clinical “assay” seems to refer to clinical trial and could be substituted throughout. Tight editing for grammar and content could reduce the length of the manuscript and improve readability.
[ The expression “clinical assay” has been replaced with “clinical trials”, throughout; and “fase IV assay” changed to “phase IV study”]

* The protocol has been revised and translated by an native English expert
translator; see Acknowledgements section.