Author’s response to reviews

Title: Protocol for the STAR (Sheffield Treatments for ADHD) project: a pilot study assessing the feasibility of the Trials within Cohorts (TwiCs) design to test the effectiveness of interventions for children with ADHD

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Author’s response to reviews:

Reviewer #1: This manuscript is a protocol for a proposed pilot study assessing the feasibility of a trial design to test the effectiveness of treatment for children and adolescents with ADHD. Generally this is a well written protocol on an important research question concerning real pragmatic considerations for the treatment of ADHD. I do have some issues that I feel could be addressed to improve the overall clarity of the paper.

1. This study describes how trials can sit within a longer term cohort design (TwiCs), with justification of the heterogeneity within current differing trials taken from differing populations. However the use of a "cohort" design can be selective and restrictive in its own way and this should have some acknowledgement. Please see addition to feasibility outcomes (lines 12-14, p 15).

2. The STAR project aims to test two treatment interventions in comparison to TAU. The authors chose two "novel" treatments to test the feasibility to recruit. This seems a little counterintuitive, in the sense that perhaps many parents may expect a standardised offer of treatment (e.g. more conventional) and as the objective is to test feasibility of recruitment overall it is surprising that novel treatments are to be offered, and may influence who might wish to take part, is there a danger of selection bias?
• Regarding recruitment to the cohort: participants recruiting to the cohort do not know about the interventions, so at this stage it is immaterial whether they are novel or not.

• Since recruitment is of already diagnosed children (not those newly diagnosed), conventional treatments are likely to already have being accessed by families, and we ask about this. We want to test the adjunctive effectiveness of other approaches to see if they might address gaps in provision.

• Thank you for your comment regarding the novelty of the treatments: on reflection we realised that in fact nutrition is not strictly a ‘novel’ intervention, although considered CAM in most surveys: the NICE guidelines advise physicians to ask and recommend a healthy diet (before suggesting pharmaceutical interventions) (NICE, 2009). Therefore we have reworded our description.

3. In relation to the point in number 2, as this study will test 2 novel treatments, it makes it all the more difficult to assess the efficacy of the treatment due to a restrictive background literature (i.e. no findings for nutritionist interventions), though the authors have outlined the expected level of effect to reach full trial status. MRC (2008) advice for complex interventions (as both are) is to first establish their effectiveness before exploring the efficacy of components.

4. Whilst I see that the authors will control for the effects of age, practitioner, medication, and condition severity, I wonder about duration of condition (i.e. time since diagnosis) and previous treatment and treatment range etc. Thank you. We agree, these are interesting factors. Participants are asked in the questionnaire about all treatments they are accessing, and about the date of diagnosis (page 9, line 9), so we can potentially explore their effect. It is not planned to control for these at this pilot stage.

5. How will teachers be blinded, this is not clearly explained in the protocol? Please see page 10, line 10.
6. Usually (within UK) there is a consent and assent process for children who take part in research and the normal cut off is the age of 16 (self-consent), this is not explained. Especially as the authors describe a postal recruitment but also a telephone recruitment strategy where consent will be taken over the phone, will this be with the child and parent/carer, what if one says yes and the other no? If either one does not consent, this is taken as lack of consent. P8, lines 12-18 have been edited to make this clearer.

7. Whilst the authors give estimations of expected participation and attrition rate, they do not give estimations of the participation rate for the recruitment of teachers, is there any previous trials that can offer data for this? We have not identified any.

8. Will practitioners have a CBR check and will information on their previous experience in the treatment of children with ADHD be taken? Yes.

9. I wondered if there was any PPIE engagement in the design of this pilot, if not why not (e.g. acceptability of recruitment materials, procedures etc)? Do you mean Public Patient Involvement? And if so, yes, patients were on the steering committee, piloted the outcome measure and contributed to recruitment suggestions. Please see additional sentence on page 8, lines 2-3.

10. It is always good practice to attempt to collect reasons for why participants do not wish to take part within a feasibility study, it might be good to assess this? This information is being collected.

Reviewer #2: This is a well-written comprehensive protocol. However, the structure of the protocol could be enhanced by introducing subheadings within each section. Sub heading have now been included where appropriate
The last section of the Background should be re-written to provide the Aims and Objectives, which should link directly to the Outcomes. This has now been revised.

The Methods section should include the following headings: Inclusion/exclusion criteria, Randomisation, Outcomes, Statistical analysis, Sample size. These sub-headings have now been included.

In the Outcomes section (which currently is placed under the "Results" section), please could you differentiate between "feasibility outcomes" and "patient-centred outcomes". You have listed primary and secondary outcomes (in the Results section) - these are the patient-centred (or efficacy) outcomes. You have described feasibility criteria in Table 2 - these relate to the feasibility outcomes. It would be useful to combine these together in a new "Outcomes" section in the Methods. This section should explain how you plan to measure the feasibility outcomes (ie it should include the information and footnotes given in Table 2.)

Regarding randomisation, please can you explain how allocation concealment is achieved, and how the randomising clinician will be informed of the next allocation? (For example, does the clinician phone the statistician who has the list locked in their desk drawer to find out the next allocation)? Now added. Please see p8, lines 10-13

Stratification information (found on p8 line10 and p10 line 40) should not include the block size - please remove this information. Done on p8, and duplicated information removed from p 10.

Statistical Analysis (currently found in the Results section):

p13 line 3: "Baseline data will be adjusted for potential co-variates such as..." I think you mean that the outcome will potentially be adjusted for these additional covariates in the ANCOVA model? Please reword this sentence to clarify your meaning. Done. After advice, Regression analysis was suggested to be most appropriate to explore the influence of covariates, therefore the text has been adjusted accordingly.

p13 line 57: Please emphasize that this study is not powered to detect significant differences; hence analysis will focus on confidence interval estimation, rather than hypothesis testing, and that any statistical testing will be considered as exploratory. Done.
p13 line 27: As the study is not powered to detect significant differences in the characteristics of patients who do/not accept treatment, I would suggest that you instead assess these differences clinically (rather than statistically). Thank you. SMD comparisons added.

p14 line 22: Similarly, I would suggest that you add "clinically significant" before "differences" in this sentence. Done.

p13 line 57: Can you give a bit more information about how you plan to carry out the CACE analysis, as I don't think this is possible in SPSS? Thank you. We have decided that CACE analysis is not applicable at this pilot stage (as well as not being manageable using SPSS), and we have therefore removed mention of it in the document.

I have a few additional minor comments:


p4 line 37: add a semi-colon after reference [28]

p5 line 29: add a semi-colon (instead of a comma) after "pocket"

p8 line 27: add an "s" to ask (ie asks)

p9 line 11: remove comma after 55

p13 line 5: capitalise "l" in "last" (ie Last)

p 15 line 13: remove bracket and space after "consultation" ie ") "

Table 1: add horizontal line between rows showing T scores of 70+/66-70

Thank you so much for pointing these out. And for really useful and helpful comments.