PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Simvastatin as a neuroprotective treatment for Parkinson's disease (PD STAT): Protocol for a double-blind, randomised, placebo-controlled futility study
AUTHORS	Carroll, Camille; Webb, Douglas; Stevens, Kara; Vickery, Jane; Eyre, Vicky; Ball, Susan; Wyse, Richard; Webber, Mike; Foggo, Andy; Zajicek, John; Whone, Alan; Creanor, Siobhan

VERSION 1 – REVIEW

REVIEWER	Kate Maclagan University College London, UK Co-applicant on NIHR EME grant (grant no. 16/167/19) with Camille Carroll
REVIEW RETURNED	26-Mar-2019

GENERAL COMMENTS	- Is it accurate to describe the population recruited as having moderate severity Parkinson's disease? Is mild-moderate, or just Parkinon's disease, more appropriate given the eligibility criteria? - The abstract was clear and easy to understand. - Table 2: Study schedule was easy to follow. The header for V1 didn't display properly on the pdf I viewed. - It may be helpful to add the visit numbers e.g. T1, V1 etc. to figure 1. - The protocol allows prescription of supportive medications to allow patients to attend in the OFF medication state. Is a secondary analysis to look at the effect of this planned? - No imputation of missing data is planned: this may be helpful in cases where rescue medication is administered and it is not possible for participants to attend in the OFF medication state at a subsequent timepoint which could potentially bias results. - p. 13 - line 43 - 'Sudden' should be changed to 'suspected' - p. 14 - line 28 remove 'the' before study documentation - p. 14 - line 50 change 'on all documents' to 'for all documents' - p. 14 - line 59 change 'discrepant data will be' to 'discrepant data are' - Have you considered following the CONSORT guidelines for noninferiority trials when reporting the results of the trial? This may be more appropriate for this trial design than the original CONSORT guidelines. Piaggio G, Elbourne DR,Altman DG, Pocock SJ, Evans SJ; CONSORT Group. Reporting of noninferiority and equivalence randomized trials: an extension of the CONSORT statement. JAMA. 2006;295(10):1152-1160. Piaggio G, Elbourne DR, Pocock SJ, Evans SJW, Altman DG, CONSORT Group FT. Reporting of Noninferiority and Equivalence

	Randomized Trials: Extension of the CONSORT 2010 Statement. JAMA. 2012;308(24):2594–2604. doi:10.1001/jama.2012.87802 - The statistical analysis states the primary analysis will be on an intention to treat basis. Given participants must comment the higher dose to be included, it may be better to describe this as a modified intention to treat. - Is it worth considering a planned secondary analysis of the primary outcome with adjustment for change in LED?

REVIEWER	Sarah Pirio Richardson University of New Mexico Health Sciences Center Department of Neurology USA
REVIEW RETURNED	03-Apr-2019

GENERAL COMMENTS	This study protocol describes an ongoing study assessing simvastatin as a neuroprotective agent in Parkinson disease. The manuscript is written clearly with fully delineated rationale, methods and statistical approach. There are no results presented consisted with the aim of publishing a study protocol.

REVIEWER	Jordan Elm Medical University of South Carolina, USA
REVIEW RETURNED	14-Jun-2019

GENERAL COMMENTS	The protocol is thorough and well written. This is a phase II trial, but it is being rigorously conducted with double-blinding, randomization, and a control group.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Kate Maclagan
Institution and Country: University College London, UK
Please state any competing interests or state 'None declared': Co-applicant on NIHR EME grant (grant no. 16/167/19) with Camille Carroll.

Please leave your comments for the authors below
- Is it accurate to describe the population recruited as having moderate severity Parkinson's disease? Is mild-moderate, or just Parkinson's disease, more appropriate given the eligibility criteria?
One of the inclusion criteria for the trial is wearing off (see Table 1) and so the term "moderate" is appropriate. However, we did not have a lower H&Y cut off and therefore agree that mild-moderate is appropriate. We have therefore removed the term "moderate" from the title of the paper.

- The abstract was clear and easy to understand.
- Table 2: Study schedule was easy to follow. The header for V1 didn't display properly on the pdf I viewed.
Thank you for this feedback. In our pdf the header is displayed and we hope the editorial team will ensure this, if the paper is accepted for publication.

- It may be helpful to add the visit numbers e.g. T1, V1 etc. to figure 1.
We have added these as requested.

- The protocol allows prescription of supportive medications to allow patients to attend in the OFF medication state. Is a secondary analysis to look at the effect of this planned?
- No imputation of missing data is planned: this may be helpful in cases where rescue medication is administered and it is not possible for participants to attend in the OFF medication state at a subsequent timepoint which could potentially bias results.
We thank the reviewer for these suggestions. The full statistical analysis plan is currently being drafted and will be reviewed by the trial data monitoring committee and trial steering committees, including two independent statisticians. We will discuss these suggestions with the oversight committees. The statistical analysis plan will be finalised and signed off prior to the trial statisticians receiving outcome data.
At a minimum, we will be reporting the number and proportion of participants who received supportive medications in order to attend in the OFF state (by allocated group), and if sufficient numbers of participants are categorised as such, we plan an exploratory analysis of the primary outcome exploring the effect of supportive medication, acknowledging the study is not powered for this analysis. With regards to multiple imputation, given this study is not a definitive superiority trial, there is a need to minimise the number of sensitivity analyses. We anticipate that the number of participants who do not attend in the OFF state due to the requirement for rescue medication will be low; however, we will take advice from our oversight committees.

- p. 13 - line 43 - 'Sudden' should be changed to 'suspected'
- p. 14 - line 28 remove 'the' before study documentation
- p. 14 - line 50 change 'on all documents' to 'for all documents'
- p. 14 - line 59 change 'discrepant data will be' to 'discrepant data are'
We thank the reviewer for highlighting these errors and have corrected the manuscript with these suggestions.
- Have you considered following the CONSORT guidelines for noninferiority trials when reporting the results of the trial? This may be more appropriate for this trial design than the original CONSORT guidelines.
Piaggio G, Elbourne DR,Altman DG, Pocock SJ, Evans SJ; CONSORT Group. Reporting of noninferiority and equivalence randomized trials: an extension of the CONSORT statement. JAMA. 2006;295(10):1152-1160.

Piaggio G, Elbourne DR, Pocock SJ, Evans SJW, Altman DG, CONSORT Group FT. Reporting of Noninferiority and Equivalence Randomized Trials: Extension of the CONSORT 2010 Statement. JAMA. 2012;308(24):2594–2604. doi:10.1001/jama.2012.87802

As a fully powered randomised futility study, there are elements of a number of the CONSORT extensions that we can draw upon in our reporting, in addition to the ‘main’ CONSORT guidance. We have updated the manuscript to include reference to the suggested non-inferiority extension as well as the extension for patient reported outcomes, feasibility studies and harms; it is anticipated that the most appropriate CONSORT checklist will be that from the main guidance.

- The statistical analysis states the primary analysis will be on an intention to treat basis. Given participants must comment the higher dose to be included, it may be better to describe this as a modified intention to treat.
We thank the reviewer for this suggestion and have edited the text to state “modified intention to treat”.

- Is it worth considering a planned secondary analysis of the primary outcome with adjustment for change in LED?
As the primary outcome is assessed in the OFF state, we are effectively controlling for any change in LED. However, the reviewer’s suggestion will be raised with the trial oversight committees as part of

the discussion of the draft statistical analysis plan; for example, exploring the relationship between change in LED and change in the primary outcome may be informative.

Reviewer: 2
Reviewer Name: Sarah Pirio Richardson
Institution and Country: University of New Mexico Health Sciences Center, Department of Neurology, USA
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
This study protocol describes an ongoing study assessing simvastatin as a neuroprotective agent in Parkinson disease. The manuscript is written clearly with fully delineated rationale, methods and statistical approach. There are no results presented consisted with the aim of publishing a study protocol.
We thank the reviewer for her positive feedback.

Reviewer: 3
Reviewer Name: Jordan Elm
Institution and Country: Medical University of South Carolina, USA
Please state any competing interests or state 'None declared': none

Please leave your comments for the authors below
The protocol is thorough and well written. This is a phase II trial, but it is being rigorously conducted with double-blinding, randomization, and a control group.
We thank the reviewer for her positive feedback.

VERSION 2 – REVIEW

REVIEWER	Kate Maclagan The Comprehensive Clinical Trials Unit at UCL UK Co-applicant on NIHR EME grant (grant no.16/167/19) with Camille Carroll.
REVIEW RETURNED	23-Jul-2019

GENERAL COMMENTS	Thank you for your replies to my original comments. I don't have any further comments.