PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Multiple Sclerosis-Secondary Progressive Multi-Arm Randomisation Trial (MS-SMART). A multi-arm phase 2b randomised, double blind, placebo-controlled clinical trial comparing the efficacy of three neuroprotective drugs in secondary progressive multiple sclerosis.
AUTHORS	Connick, Peter; De Angelis, Floriana; Parker, Richard; Plantone, Domenico; Doshi, Anisha; John, Nevin; Stutters, Jonathan; MacManus, David; Prados Carrasco, Ferran; Barkhof, Frederik; Ourselin, Sebastien; Braisher, Marie; Ross, Moira; Cranswick, Gina; Pavitt, Sue; Giovannoni, Gavin; Gandini Wheeler-kingshott, Claudia; Hawkins, Clive; Sharrack, Basil; Bastow, Roger; Weir, Christopher; Stallard, Nigel; Chandran, Siddharthan; Chataway, Jeremy

VERSION 1 – REVIEW

REVIEWER	Arianna Sartori Neurology Unit, ASUITs, Trieste, Italy
REVIEW RETURNED	12-Mar-2018

GENERAL COMMENTS	The authors are trying to give an answer to the unmet need of SPMS treatment with repurposed drugs strategy, in a trial involving simultaneously 3 very well known compounds, with good safety profile. This strategy is extremely welcomed, in order to allows a quicker and less expensive process of drug approval. The study protocol is well planned and extremely well written. The authors offer a complete and concise review of the literature, clear study design and statistical considerations. The primary endpoint is adequately selected and powered, and the secondary and exploratory endpoints are complete and could give interesting hints for future studies. All study procedures are explained in detail, with particular attention for safety issues. I have no major revision or comments, just some minor revisions. - page 8, line 3: please delete the extra blank space page 9, line 26: delete “such as” (“…trial design such as such as subject and disease heterogeneity, and the selection of…”) page 10, line 44: please delete the extra blank space page 15, line 40: delete “e” (“… licensed for motor neurone disease/amyotrophic…”) page 17, line 35: change “Follow up” with “Follow-up” Page 17, line 53: please delete the extra blank space page 18, line 24: change “mirtazapine.” with “mirtazapine,” page 18, line 31: change “week 24 and” with “week 24, and” page 21 line 31: change “45yrs” with “45 yrs” page 23, line 12, 19, 28: please delete the extra blank spaces page 24, line 42: please delete the extra blank spaces page 29, line 10: please change “ɣGT” with “gamma-GT” page 31, line 49: please delete the extra blank space

	page 37: please review the layout of references n 6 and n 9. page 38, line 15: change “Lancet” with “Lancet” page 39: please review the layout of reference n 21 page 40, line 35: reference n 35 is not correct. The title “T2 lesions and rate of progression of disability in multiple sclerosis” refers to “Eur J Neurol 2010;17:1471-5” and not to “Eur J Neurol 2011;17:1471–5.” Please review and delete the extra blank spaces page 40, line 41: please delete the blank line page 41, line 27: please delete “]” page 48, figure 1, line 11: please delete the vertical line after the word “appointment”

REVIEWER	Daniel Ontaneda Cleveland Clinic
REVIEW RETURNED	13-Mar-2018

GENERAL COMMENTS	The authors present the plan for a large multi-arm phase 2 study of neuro-protective medications in SPMS. The study is of interest and this type of paper is useful for increasing awareness of the trial. I have some minor comments. -The authors should clarify why they selected fluoxetine, given a trial of similar size which has already been conducted in progressive MS. -Page 7 line 40, the authors fail to mention ocrelizumab as a therapy with prvoven efficacy in progressive MS (PPMS). -The duration of the proposed MRI protocol should be included. -could the authors provide a justification of how they picked the effect size for sample size calculation of 35%? -It is of note that the ethics approval for the study was completed in 2013 in Scotland, is there a reason for the delay in study start -the reasons for the protocol amendments should be listed. -what is the timeline for the study completion

VERSION 1 – AUTHOR RESPONSE

Reviewer(s) Comments to Author:
Reviewer: 1
Reviewer Name: Arianna Sartori
Institution and Country: Neurology Unit, ASUITs, Trieste, Italy
Please state any competing interests or state ‘None declared’: AS received travel and/or speaking honoraria form Novartis, Teva, Merk, Genzyme, Roche, Almirall.

Please leave your comments for the authors below.

The authors are trying to give an answer to the unmet need of SPMS treatment with repurposed drugs strategy, in a trial involving simultaneously 3 very well known compounds, with good safety profile. This strategy is extremely welcomed, in order to allows a quicker and less expensive process of drug approval.

The study protocol is well planned and extremely well written. The authors offer a complete and concise review of the literature, clear study design and statistical considerations. The primary endpoint is adequately selected and powered, and the secondary and exploratory endpoints are complete and could give interesting hints for future studies. All study procedures are explained in detail, with particular attention for safety issues.
I have no major revision or comments, just some minor revisions (see attached file).
Thank you to the reviewer for the comments made. The minor revisions are answered below.

Reviewer: 2
Reviewer Name: Daniel Ontaneda
Institution and Country: Cleveland Clinic

Please state any competing interests or state 'None declared': None.

Please leave your comments for the authors below

The authors present the plan for a large multi-arm phase 2 study of neuro-protective medications in SPMS. The study is of interest and this type of paper is useful for increasing awareness of the trial. I have some minor comments.

-The authors should clarify why they selected fluoxetine, given a trial of similar size which has already been conducted in progressive MS.
The MS-SMART trial was commenced in December 2014 and the results of reference xx 2006 were only available. Subsequently the study FLUOX-PMS reported orally at ECTRIMS in 2016, which showed a trend in favour of Fluoxetine versus placebo in time to progression (p=0.07), though more data is awaited. In fact because of that result, we feel that the choice of fluoxetine becomes even more valuable to confirm or refute its potential utility.

-Page 7 line 40, the authors fail to mention ocrelizumab as a therapy with proven efficacy in progressive MS (PPMS).
Thank you. This phase 3 study was published in Dec 2016 and this is now inserted with the appropriate reference, as is the study on siponimod which has been published in March 2018 (page 6)

-The duration of the proposed MRI protocol should be included.
The duration of the core MRI protocol is 25 minutes and this has been included in the text (page 22)

-could the authors provide a justification of how they picked the effect size for sample size calculation of 35%?
We choose a 35% effect size from the results of the phase 2 MS-STAT trial which showed a 43% reduction in atrophy rate was accompanied by clinical benefit seen in some (secondary) clinical, patient-reported and cognitive outcomes.

-It is of note that the ethics approval for the study was completed in 2013 in Scotland, is there a reason for the delay in study start.
Yes we had planned to commence in 2013, but as mentioned on page 12 due to drug supply issues, ibudilast had to be replaced by fluoxetine, which meant there was a delay in study commencement.

-the reasons for the protocol amendments should be listed.
We have inserted Table 4 which lists them.

-what is the timeline for the study completion.
The Last Patient List Visit is 23rd May 2018.

Formatting instructions (all done and tracked, unless note)

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of_")
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References
Two additional suggested references above inserted (6 and 7). References from Box 1 now incorporated into the text (24-26).

17th April 2018

I thank the Editor for their further recommendations which I have annotated

1.Figure legends are added to the end of the document
2.A new copy for Figure 1 is attached
3.A full PPI section is incorporated
4. The contributorship;competing interest; funding statements are given before the references

A fully tracked and clean V3 are enclosed

VERSION 2 – REVIEW

REVIEWER	Daniel Ontaneda Cleveland Clinic
REVIEW RETURNED	04-May-2018

GENERAL COMMENTS	The authors have addressed all my comments