PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A Prospective Observational Cohort Study of Factors Influencing Trial Participation in People with Motor Neuron Disease (FIT-Participation-MND): A Protocol
AUTHORS	Beswick, Emily; Glasmacher, Stella; Dakin, Rachel; Newton, Judith; Carson, Alan; Abrahams, Sharon; Chandran, Siddharthan; Pal, Suvankar

VERSION 1 – REVIEW

REVIEWER	Steve Vucic University of Sydney, Australia.
REVIEW RETURNED	30-Sep-2020

GENERAL COMMENTS	This is a well written protocol pertaining to an important topic for MND. The outcome measures are appropriate. Ethics are in place. This study has the potential to impact on trial selection/recruitment of MND patients. I have no additional comments/suggestions.

REVIEWER	Ruben van Eijk UMC Utrecht, The Netherlands
REVIEW RETURNED	13-Oct-2020

GENERAL COMMENTS	This work describes a protocol for a study to investigate which patient factors are associated with trial participation. This is an important challenge in ALS and, therefore, the results of this study may significantly add to our current knowledge. The rationale for the study and its aim are clear, my main comments are related to clarify/supplement the methodology: 1. The authors introduce in section 3.3 the concept of attrition. It would strength this part of the manuscript if a clearer definition of attrition is given. In addition, from the manuscript it is unclear if and how different reasons for attrition are handled. For example, attrition related to adverse events may have different underlying patient factors than attrition due to disease progression, or withdrawal of concept. 2. The manuscript could be clarified in what are 'study participants', are these patients diagnosed with MND that are participating in CARE-MND and in the study, or are these patients in the MND-SMART trial. I think clarifying what and from whom data is collected would strength the manuscript. As a suggestion, there seems to be two aims: 1, who is deciding to participate in the trial and 2, if they do participate, who is completing follow-up. Clarifying this structure may help the reader and structure the study design. 3. There is very little to no information about the MND-SMART trial, are there any inclusion criteria from the trial itself that may lead to some selection who can and who can't participate? Second, it would

	help the reader if some background is available about the MND SMART design, is this a 2 month or 18 month trial? If the latter, is there not already about 30-40% attrition due to death and may this affect the study results? 4. It is not completely clear how 'study participants' are selected. They seem to come from the CARE-MND register. Are these patients just randomly selected and send the questionnaire, or will there some advertisement and patients need to approach the researcher to participate. If the latter, will this not cause some selection bias? 5. The 'convenience sample size' of 100 patients seem low for the number of variables collected. If I understand correctly, the authors will group patients to who did or did not enrol in the trial. If 25% of the patients decides to participate in MND-SMART, the sample size would be 25 vs 75 patients, would this be sufficient for the number of factors? Could the authors provide some estimates about the expected enrolment %. Second, if 25 patients participate in the trial, and about 30% would dropout, is this enough to evaluate patient factor associated with retention? Or are the authors planning to evaluate all patients in MND-SMART. Please clarify. 6. Based on reference #9, I would expect that disease severity will be the most prominent factor in why a patient does or does not participate in research. In the questionnaire package, the ALSFRS-R is not part of the collected data (except for those also participating in SMART-MND). I would suggest to collect ALSFRS-R together with the 'Study Assessment Questionnaires'. 7. Could the authors provide timelines for the study. 8. Missing data, suggest to use multiple imputation for missing at random rather than complete-case analysis.

REVIEWER	Fleur Garton University of Queensland, Australia
REVIEW RETURNED	15-Oct-2020

GENERAL COMMENTS	Beswick et al. have presented a study design to determine factors influencing trial participation in MND. MND is a progressive and fatal condition and there is only one approved treatment available which has a small impact in prolong disease. This will be a Scotland-based research project and the results will be used to improve clinical trial participation across the UK in the future. Some comments are below, hopefully these can be considered in future updates to the paper. Abstract: • Given significant changes in human research ethics (under-pinned by principles of GCP) – it is worth updating the background and references on trial participation – references are almost 20 years old? • Clarify that the CARE-MND population is also Scotland based? • Planned recruitment number and source is needed • A number of acronyms that are not defined i.e. ‘pwMND’ • Might be useful to label the questionnaires into what they are assessing i.e. neuropsychiatric symptoms, cognitive impairment, behavioural change, phenotype, quality of life, and physical functioning • Limitations – the population of the study is only Scotland-based, could there be other factors influencing participation in the rest of the UK. • The ACT-Q could be highlighted

	Introduction • There is a more up to date reference about the impact of riluzole • Line 38- Reference needed for multi-stage, multi-arm, adaptive design reducing patient numbers and time for >1 candiate in phase 2/3. • NO mention of any of the updated Airlie House guidelines to improve outcomes in MND clinical trials. • 3.3. 25% is incredibly low and not consistent with the experience in our neurology clinics. Additional detail about the MND trials that have been carried out, i.e. enrolment percentage is incredibly relevant & would be useful (i.e. location/type – e.g. was this an IV drug study requiring significant time/travel needs) • Reference needed - Historically many trials have focussed on specific subgroups, utilising narrow inclusion criteria. Methods • Given recruitment of n=100, a power calculation is needed to assess if this is an appropriate number to test the proposed hypothesis. • How long does the full-set of six questionnaires take to complete, and are they interactive. • How will partially finished questionnaires be treated. Better clarity could be included in the missing data section. Ten percent could be relatively strict if one (out of six questionnaires) is not completed (16% missing data) – or is this per question asked? Additionally, if the carer doesn't complete a questionnaire – then this is also >10%? Additional detail on the reference provided regarding bias might be helpful for justification – are these based on this type of questionnaires. Will the questionnaires be checked and sent back if detail is missed? • For the ALSFRS score – what date/time will this be linked with? Can an ALSFRS-rate be considered to capture fast/slow progressors into the analysis? • ACT-Q does not contain any question regarding data privacy. This can be very important to some people. • Clinical phenotype doesn't seem to include reference to Edinburgh Cognitive and Behavioural ALS Screen scores – mentioned on page 6. • Analysis plan could include simulated data. • Given the seven or eight? categories – it is unclear on whether n=100 will have the appropriate power to detect an effect. How will multiple testing be controlled for, what is the adjusted-alpha level? • 5.5 "Twelve"

VERSION 1 – AUTHOR RESPONSE

Reviewer 1	
R1.1 This is a well written protocol pertaining to an important topic for MND. The outcome measures are appropriate. Ethics are in place. This study has the potential to impact on trial selection/recruitment of MND patients. I have no additional comments/suggestions.	Thank you for your kind and positive feedback.

Reviewer 2	
R2.1. The authors introduce in section 3.3 the concept of attrition. It would strength this part of the manuscript if a clearer definition of attrition is given. In addition, from the manuscript it is unclear if and how different reasons for attrition are handled. For example, attrition related to adverse events may have different underlying patient factors than attrition due to disease progression, or withdrawal of concept.	In Section 3.3. we have defined the concept of attrition and in Section 3.4 discussed how we will categorise attrition using descriptive statistics and death will be included as a reason for attrition. Death will not be included in the logistic regression as a competing risk as this focuses on the binary outcome of Participation vs Non-Participation.
R2. 2. The manuscript could be clarified in what are 'study participants', are these patients diagnosed with MND that are participating in CARE-MND and in the study, or are these patients in the MND-SMART trial. I think clarifying what and from whom data is collected would strength the manuscript. As a suggestion, there seems to be two aims: 1, who is deciding to participate in the trial and 2, if they do participate, who is completing follow-up. Clarifying this structure may help the reader and structure the study design.	Clarification of the differentiation between FIT-Participation-MND and MND-SMART participants added in throughout the manuscript. Addition of the aim definition as suggested by R2 in a new Section 3.5 on Aims.
R2. 3. There is very little to no information about the MND-SMART trial, are there any inclusion criteria from the trial itself that may lead to some selection who can and who can't participate? Second, it would help the reader if some background is available about the MND SMART design, is this a 2 month or 18 month trial? If the latter, is there not already about 30-40% attrition due to death and may this affect the study results?	Due to word limit restrictions full details of MND-SMART could not be included in this protocol, however references to the trial record on Clinicaltrials.gov and EudraCT have been signposted and details of trial expanded on in Section 3.2.
R2. 4. It is not completely clear how 'study participants' are selected. They seem to come from the CARE-MND register. Are these patients just randomly selected and send the questionnaire, or will there some advertisement and patients need to approach the researcher to participate. If the latter, will this not cause some selection bias?	Study participants are invited from the CARE-MND register. Every eligible person on CARE-MND will be invited to participate, this has been clarified in Section 4.2.
R2. 5. The 'convenience sample size' of 100 patients seem low for the number of variables collected. If I understand correctly, the authors will group patients to who did or did not enrol in the trial. If 25% of the patients decides to participate in MND-SMART, the sample size would be 25 vs 75 patients, would this be	In Section 3.2. we have expanded upon the decision to focus on Scottish pwMND and how MND-SMART beginning with opening Scottish sites aligns with the timeline of FIT-P-MND. Table 3 of exclusion/inclusion criteria reiterates that the two participant groups of FIT-P-MND and MND-SMART are designed to be as overlapping as

sufficient for the number of factors? Could the authors provide some estimates about the expected enrolment %. Second, if 25 patients participate in the trial, and about 30% would dropout, is this enough to evaluate patient factor associated with retention? Or are the authors planning to evaluate all patients in MND-SMART. Please clarify.	possible, to ensure the decision not to participate rather than ineligibility is the reason for not joining the trial. Due to the broad inclusion criteria for MND-SMART, exclusion is unlikely.
R2. 6. Based on reference #9, I would expect that disease severity will be the most prominent factor in why a patient does or does not participate in research. In the questionnaire package, the ALSFRS-R is not part of the collected data (except for those also participating in SMART-MND). I would suggest to collect ALSFRS-R together with the 'Study Assessment Questionnaires'.	Agreed, we also think disease progression will be extremely impactful. We have clarified in Table 1 and Section 4.4. that ALS-FRS and ECAS data will be taken from either CARE-MND or MND-SMART (if a participant) depending upon which assessment was completed closest to the date of the FIT-Participation-MND questionnaires.
R2. 7. Could the authors provide timelines for the study.	Additional section added in 4.2. with timeline of key dates and projected timeline.
R2. 8. 8. Missing data, suggest to use multiple imputation for missing at random rather than complete-case analysis.	Revised in Section 5.3. to reflect that multiple imputation will be used.

Reviewer 3	
Abstract	
R3. 1. Given significant changes in human research ethics (under-pinned by principles of GCP) – it is worth updating the background and references on trial participation – references are almost 20 years old?	Updated with 2020 reference; Yu, M., Lin, Z., Liang, C., Li, C., Zhang, Z., Liu, K., ... & Fei, Y. (2020). How to improve participant compliance in clinical trials: A Scoping Review of process factors.
R3. 2. Clarify that the CARE-MND population is also Scotland based?	Additional sentence added to abstract methods to clarify this is Scotland only.
R3. 3. Planned recruitment number and source is needed	Added into Aim section.
R3. 4. A number of acronyms that are not defined i.e. 'pwMND'	Acronym defined in Abstract and Section 3.3. of Introduction.
R3. 5. Might be useful to label the questionnaires into what they are assessing i.e. neuropsychiatric symptoms, cognitive impairment, behavioural change, phenotype, quality of life, and physical functioning	Labelled each assessment tool as the area of functioning it is assessing.
R3. 6. Limitations – the population of the study is only Scotland-based, could there be other factors influencing participation in the rest of the UK.	Added as an additional limitation.
R3. 7. The ACT-Q could be highlighted	Reiterated in the abstract that this is a novel questionnaire designed specifically for this study.

Introduction	
R3. 8. There is a more up to date reference about the impact of riluzole	Revised reference to Andrews, J. A., Jackson, C. E., Heiman-Patterson, T. D., Bettica, P., Brooks, B. R., & Pioro, E. P. (2020). Real-world evidence of riluzole effectiveness in treating amyotrophic lateral sclerosis. *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration*, 1-10
R3. 9. Line 38- Reference needed for multi-stage, multi-arm, adaptive design reducing patient numbers and time for >1 candidate in phase 2/3.	Added references for the impact of MAMS design in stroke and cancer.
R3. 10. NO mention of any of the updated Airlie House guidelines to improve outcomes in MND clinical trials.	Airlie house guidelines have been acknowledged in Section 3.2.
R3. 11. 3.3. 25% is incredibly low and not consistent with the experience in our neurology clinics. Additional detail about the MND trials that have been carried out, i.e. enrolment percentage is incredibly relevant & would be useful (i.e. location/type – e.g. was this an IV drug study requiring significant time/travel needs)	We have clarified that this figure is based on clinician survey estimates reported in Bedlack, R. S., Pastula, D., Welsh, E., Pulley, D., & Cudkowicz, M. E. (2008). Scrutinizing enrollment in ALS clinical trials: room for improvement?. *Amyotrophic Lateral Sclerosis*, *9*(5), 257-265.
R3. 12. Reference needed - Historically many trials have focussed on specific subgroups, utilising narrow inclusion criteria.	Added a discussion of exclusion criteria on trial outcomes and patient engagement to 3.3.
Methods	
R3. 13. Given recruitment of n=100, a power calculation is needed to assess if this is an appropriate number to test the proposed hypothesis.	This is considered in Section 4.2. and further information on sample size calculations, prevalence and estimated recruitment to MND-SMART has been added.
R3. 14. How long does the full-set of six questionnaires take to complete, and are they interactive.	Time taken to complete the questionnaire series has been added to the 4.4. Study Assessments section.
R3. 15. How will partially finished questionnaires be treated. Better clarity could be included in the missing data section. Ten percent could be relatively strict if one (out of six questionnaires) is not completed (16% missing data) – or is this per question asked? Additionally, if the carer doesn't complete a questionnaire – then this is also >10%? Additional detail on the reference provided regarding bias might be helpful for justification – are these based on this type of questionnaires. Will the questionnaires be checked and sent back if detail is missed?	Questionnaires will not be sent back if incomplete and individuals without a caregiver are still able to be included. Behavioural data from caregiver questionnaires will be included where obtained, this has been clarified in Section 5.6.
R3. 16. For the ALSFRS score – what date/time will this be linked with? Can an ALSFRS-rate be considered to capture fast/slow progressors into the analysis?	ALSFRS score will be linked with the date of completion in MND-SMART or on CARE-MND. The score closest to the date of the participant questionnaires will be selected. The authors agree, ALS-FRS progression and

	association would be of interest for future studies, however as this is a snapshot study linking trial data in 12 months it is beyond the scope of the current study.
R3. 17. ACT-Q does not contain any question regarding data privacy. This can be very important to some people.	This was not an issue raised by our PPI discussion, however, the authors agree that it is potentially an important consideration and will be worthwhile including in future research projects.
R3. 18. Clinical phenotype doesn't seem to include reference to Edinburgh Cognitive and Behavioural ALS Screen scores – mentioned on page 6.	This has been clarified in response to R2. 6. That ECAS and ALSFRS will be obtained from CARE-MND or MND-SMART depending on which is closest to the time of FIT-P-MND questionnaire completion and if the study participant joined the trial.
R3. 19. Analysis plan could include simulated data.	Whilst the authors agree that simulated data could be of interest, we believe it may be outside the scope of this study and expected sample size.
R3. 20. Given the seven or eight? categories – it is unclear on whether n=100 will have the appropriate power to detect an effect. How will multiple testing be controlled for, what is the adjusted-alpha level?	As this in exploratory study, with each variable being of interest in the analysis, correction techniques will not be employed. Justification and more detailed explanation is provided in Section 5.2.
R3. 21. 5.5 “Twelve”	Amended

Formatting Amendments	
1. Funding Information: - You have indicated a funder/s for your paper. Please ensure to provide an award/grant number for your funder/s in the main document file and in ScholarOne.	Funding information added to the main document file and ScholarOne.
2. Embedded figure: - Please remove all your figures in your main document and upload each of them separately under file designation ‘Image' (except tables and please ensure that Figures are of better quality or not pix-elated when zoom in). NOTE: They can be in TIFF, JPG or PDF format and make sure that they have a resolution of at least 300 dpi. Figures in DOCUMENT, EXCEL and POWERPOINT format are not acceptable.	Figure 1 added at JPG additional file, removed from main document.
3. Table 2 citation missing: - The in-text citation for “Table 2” is missing in the main text of your main document file. Please amend accordingly.	Included in Section 4.5.

VERSION 2 – REVIEW

REVIEWER	Ruben van Eijk UMC Utrecht, the Netherlands
REVIEW RETURNED	10-Dec-2020

GENERAL COMMENTS	I would like to thank the authors for their rebuttal, all my comments have been addressed sufficiently.

REVIEWER	Fleur Garton University of Queensland, Australia
REVIEW RETURNED	26-Nov-2020

GENERAL COMMENTS	The authors have sufficiently responded to reviewer questions.