Author's response to reviews

Title: Assessment of bone marrow-derived cellular therapy in progressive multiple sclerosis (ACTiMuS): study protocol for a randomized controlled trial

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Author's response to reviews: see over
Dear Professor Furberg and colleagues,

Thank you for giving us the opportunity to respond to the reviewer’s comments regarding our manuscript entitled ‘Assessment of bone marrow-derived cellular therapy in progressive multiple sclerosis (ACTiMuS): study protocol for a randomized controlled trial’.

We have uploaded a version with tracked changes to the submission website but have also provided a point-by-point response below.

Reviewer's report:

The manuscript is well written with a brief but clear explanation of the background and purpose of the study.

We thank Dr Palmer for her kind comments.

I have noted just a few points where clarity and thus replicability could be improved:

Randomisation and blinding: the second paragraph states that the trial product will be shielded from participants. Could the authors provide additional detail on how this will be achieved?

Manuscript updated as follows:

During infusion, the trial product (blood or marrow) will be shielded from the participants using covered giving sets and obscuring the cannula site from the
participant. Trial assessors do not have access to information regarding the order in which blood and marrow are infused.

Trial interventions: could the authors provide a brief description of venesection.

Manuscript updated as follows:

Venesection of approximately 500ml will be performed at entry and at 1 year. Blood donation will be performed in accordance with NHS Blood and Transplant standard operating procedures for blood donation which are fully described in the ‘Red Book’ [5]. Briefly, a cannula is inserted in the antecubital fossa and venesection is performed with a sphygmomanometer cuff inflated to 60mmHg.


Also in the final paragraph of this section, the authors state that bone marrow trephine and a sample of bone marrow aspirated will be retained for research. Could the authors make it clear whether it is for this research study or future research in this area?

The manuscript has been updated as follows:

Bone marrow trephines and a small sample of the bone marrow aspirate will be retained for back-translational laboratory research studies running in parallel with the clinical trial if specific written informed consent is given. Blood samples for research purposes may be requested throughout the duration of the study.

Trial analyses:
Paragraph 1 - the authors state that a statistical analysis plan will be written prior to data collection. As data collection has already started, do the authors mean a SAP will be written prior to completion of data collection? Or that a SAP has been written? Please clarify.

A statistical analysis plan will be written prior to completion of data collection. Text updated to clarify.

A full statistical analysis plan will be written prior to completion of data collection and analyses.
Paragraph 2 - change in GEP is the primary outcome measure. Please state between which time points change is measured for the primary outcome.

Thank you. The manuscript has been updated with clear specification of the primary outcome measure in the relevant section.

The primary outcome measure is change in GEP in the 12 month period after infusion of autologous marrow.

Paragraph 4 - secondary outcomes will be scored according to standard methodology. Details are required to enable replication.

The appropriate references are already listed earlier in the text in the section on secondary outcome measures.

Finally just one typo has been identified in the eligibility and enrolment paragraph - ‘entry’ should read ‘enter’. Also the acronym FBC needs to be added to the abbreviations list.

Text corrected. Thank you.

Editorial requests

1. Please clearly explain that you will obtain informed consent from all participants in the Methods section.

This information is given in the ‘Eligibility and Enrolment’ section.

Please let us know if there are additional queries.

With thanks and best wishes,

Yours sincerely,

Dr Claire Rice
Consultant Senior Lecturer in Neurology