Author's response to reviews

Title: The Mesenchymal Stem Cells in Multiple Sclerosis (MSCIMS) Trial protocol and baseline cohort characteristics: an open-label pre-test : post-test study with blinded outcome assessments.

Authors:

Peter Connick (pc349@cam.ac.uk)
Madhan Kolappan (mkolappan@gmail.com)
Rickie Patani (rp349@cam.ac.uk)
Michael A Scott (mas59@cam.ac.uk)
Charles Crawley (charles.crawley@addenbrookes.nhs.uk)
Xiao-ling He (xlh20@cam.ac.uk)
Karen Richardson (karen.richardson@addenbrookes.nhs.uk)
Kelly Barber (kelly.barber@addenbrookes.nhs.uk)
Daniel J Webber (djw74@cam.ac.uk)
Claudia AM Wheeler-Kingshott (c.wheeler-kingshott@ion.uck.ac.uk)
Daniel J Tozer (d.tozer@ion.ucl.ac.uk)
Rebecca S Samson (r.samson@ion.ucl.ac.uk)
David L Thomas (thomas@medphys.ucl.ac.uk)
Ming Q Du (mqd20@cam.ac.uk)
Shi L Luan (sl470@cam.ac.uk)
Andrew W Michell (andrew.michell@addenbrookes.nhs.uk)
Daniel R Altmann (dan.altmann@lshtm.ac.uk)
Alan J Thompson (a.thompson@ion.ucl.ac.uk)
David H Miller (d.miller@ion.ucl.ac.uk)
Alastair Compston (alastair.compston@medschl.cam.ac.uk)
Siddharthan Chandran (siddharthan.chandran@ed.ac.uk)

Version: 2 Date: 18 February 2011

Author's response to reviews: see over
Response to reviewers’ comments

Title: The Mesenchymal Stem Cells in Multiple Sclerosis (MSCIMS) Trial protocol and baseline cohort characteristics: an open-label pre-test: post-test study with blinded outcome assessments.

Dear Editors,

We are encouraged by the helpful and positive comments provided by Drs. Mazzini and Fagioli. Both reviewers provide thoughtful and helpful insights that have allowed us to improve our manuscript through this revision.

Our response to the specific comments made is shown below.

A) Response to Dr Mazzini’s comments

1. We completely agree with Dr Mazzini’s view that studies such as ours are important in order to determine the optimum methodological approach for informative clinical trials of advanced therapies. In this context, our manuscript describes both the detailed methodology and the rationale for the novel approach we describe.

2. We thank Dr Mazzini for identifying that clarification of the objective of our manuscript would aid the reader. We agree that it is helpful to make an explicit distinction between the primary and secondary objectives of the trial (to assess safety and efficacy of the intervention respectively), and the objectives of the manuscript (describing the detailed methodology and rationale in order to inform the design of subsequent studies assessing this and/or similar interventions). We have revised the text and abstract accordingly.

3. We thank Dr Mazzini for identifying the possibility for confusion regarding our reporting of the effects of intervention. As the study is ongoing, we have not reported interim results in this manuscript. We have therefore clarified this in the text.

4. Dr Mazzini raises an important issue regarding the approach to assessment of safety for trials involving advanced therapies. Our own systematic review indicates that around 500 people having been treated with intravenously administered Mesenchymal Stem Cells (MSCs) - both autologous and allogeneic. The main adverse events fall into two groups: immediate type 1 hypersensitivity reactions (seen in around 10%), and a theoretical medium to long-term risk of infection or neoplasia (not reported to date). In addition to allowing the recording of unexpected adverse reactions, our trial has
therefore been specifically designed to actively screen for hypersensitivity reactions (immediate monitoring around intervention), evidence of infection (weekly [x4] assessments), and neoplasia (through longer term assessment). We have revised the text in order to clarify this point.

5. We thank Dr Mazzini for suggesting that we develop our discussion to include the context of recent studies evaluating intrathecally delivered mesenchymal stem cells in neurological diseases (e.g. Karussis et al.). We have revised the text accordingly.

A) Response to Dr Fagioli’s comments

1. We thank Dr Fagioli for the suggestion to develop our discussion with reference to the existing literature. We have revised the text accordingly.

2. Dr Fagioli also raises a fascinating issue around length of follow up. We have sought to address this in the discussion, with particular regard to the challenge of achieving adequate power to detect efficacy in early phase neuroprotective trials.

3. Dr Fagioli’s suggested corrections as minor comments have all been revised in the text.

Yours sincerely,

Peter Connick
(For and on behalf of the MSCIMS Trial authors)