Repeat infusion of autologous bone marrow cells in multiple sclerosis – protocol for a phase I extension study (SIAMMS-II)

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<td>Complete List of Authors:</td>
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Repeat infusion of autologous bone marrow cells in multiple sclerosis – a phase I extension study (SIAMMS-II)

Claire M. Rice\textsuperscript{1,2*}, David I. Marks\textsuperscript{3}, Peter Walsh\textsuperscript{2}, Nick M. Kane\textsuperscript{2}, Martin G. Guttridge\textsuperscript{4}, Juliana Redondo\textsuperscript{1}, Pamela Sarkar\textsuperscript{1,2}, Denise Owen\textsuperscript{2}, Alastair Wilkins\textsuperscript{1,2}, and Neil J. Scolding\textsuperscript{1,2}

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Keywords: cell therapy
bone marrow
multiple sclerosis
reparative therapy
Abstract

Introduction: The ‘Study of Intravenous Autologous Marrow in Multiple Sclerosis (SIAMMS)’ trial was a safety and feasibility study which examined the effect of intravenous infusion of autologous bone marrow without myeloablative therapy. This trial was well-tolerated and improvement was noted in the global evoked potential (GEP) - a neurophysiological secondary outcome measure recording speed of conduction in central nervous system pathways. The efficacy of intravenous delivery of autologous marrow in progressive MS will be examined in the phase II study the ‘Assessment of Bone Marrow-Derived Cellular Therapy in Progressive Multiple Sclerosis (ACTiMuS; NCT01815632)’. In parallel with the ‘ACTiMuS’ study, the current study ‘SIAMMS-II’ will explore the feasibility of repeated, non-myeloablative autologous bone marrow-derived cell therapy in progressive MS. Furthermore, information will be obtained regarding the persistence or otherwise of improvements in conduction in central nervous system pathways observed in the original ‘SIAMMS’ study and whether these can be reproduced or augmented by a second infusion of autologous bone marrow-derived cells.

Methods and analysis: An open, prospective, single centre phase I extension study. The 6 patients with progressive MS who participated in the ‘SIAMMS’ study will be invited to undergo repeat bone marrow harvest and receive an intravenous infusion of autologous, unfractionated bone marrow as a day-case procedure. The primary outcome measure is the number of adverse events and secondary outcome measures will include change in clinical rating scales of disability, global evoked potential and cranial MRI.

Ethics and dissemination: The study has UK National Research Ethics Committee approval (13/SW/0255). Study results will be disseminated via peer-reviewed publications and conference presentations.

Trial Registration: ClinicalTrials.gov registry NCT01932593

Strengths and limitations of this study

Strengths:
Regulated clinical trial of cell therapy for progressive MS
Extension data for phase I clinical trial

Limitations:
Open label trial
Small sample size
Introduction

Although effective treatments for relapsing remitting multiple sclerosis (MS) are available, there are no proven therapies available to halt or reverse the progressive phase of the disease which ultimately affects the majority of people with MS. There is preclinical evidence to support a reparative role for bone marrow-derived cells in demyelinating disease and, following on from this, we have begun to explore the potential of autologous, unselected bone marrow cells for repair in progressive MS. ‘SIAMMS’ was a safety and feasibility study of intravenous autologous bone marrow (BM) infusion in patients with progressive MS 1. This study was well tolerated and also raised the possibility of partial repair; conduction times in multiple central nervous system (CNS) pathways collated as a composite score (GEP) 2,3 improved in all patients studied (n=6) 1. A randomised, placebo-controlled trial will determine whether autologous bone marrow infusion exerts genuine reparative effects in progressive MS (‘ACTiMuS’; NCT01815632) 4 but the purpose of ‘SIAMMS-II’ is to explore whether the improvements observed in the initial study performed over 5 years ago have persisted and whether these can be repeated or augmented.

Methods and design

Objective and hypothesis

Our hypothesis is that intravenously-delivered autologous bone marrow cell therapy in chronic MS has reparative properties. We postulate that bone marrow-derived cells contribute to repair within the CNS via a multiplicity of mechanisms including immunomodulation and reparative and/or neuroprotective effects. Furthering our understanding of these processes will enable development and refinement of cell therapy for progressive MS.

The phase II ‘ACTiMuS’ trial will explore the efficacy of intravenous infusion of autologous bone marrow-derived cell therapy in progressive MS and its laboratory arm will explore the underlying mechanisms of any observed effect. ‘SIAMMS-II’ will run in parallel with ‘ACTiMuS’ and will investigate whether the previously observed effects can be replicated and/or augmented.

Trial design

‘SIAMMS-II’ is an open, prospective, single centre, safety and feasibility extension study. The study schema is presented in figure 1. The study has UK National Research Ethics Committee approval (13/SW/0255).

Sample size, eligibility & enrolment

The study is limited to the 6 people who participated in the original ‘SIAMMS’ study, all of whom are under active follow up at the Bristol and Avon Multiple Sclerosis (BrAMS) Unit, North Bristol NHS Trust, Bristol, UK. All participants have progressive MS and must fulfil the inclusion and exclusion criteria as detailed in table 1.
Trial interventions

Participants will have a bone marrow harvest and re-infusion of autologous marrow as a daycase procedure. A short general anaesthesia will be given for the bone marrow harvest which will be taken from the posterior iliac crests. Approximately 600ml marrow will be collected together with a single bone marrow trephine. The marrow aspirate will be processed by NHSBT (filtered, bagged and labelled) prior to intravenous infusion.

Assuming specific written informed consent is granted, a bone marrow trephine and a small sample of the bone marrow aspirate will be retained for research. Additional blood samples for research purposes may be requested throughout the duration of the study.

Outcome Measures

Primary outcome measure

The primary outcome measure is the number of adverse events (AE). For the purposes of the study, an AE is defined as any unfavourable and unintended sign, symptom or illness that develops or worsens during the period of the study. This is irrespective of the likelihood that the AE is related to study interventions. AEs may be expected or unexpected and include unwanted side effects, toxicity or sensitivity reactions, as well as abnormal laboratory results, injury or intercurrent illnesses.

A serious adverse event (SAE) is defined as an AE which results in death, is life threatening or requires hospitalisation or prolongation of in-patient stay or which results in persistent or significant disability or incapacity. Any congenital anomaly or birth defect or any event considered to be a medical event of importance will be also be classified as a SAE. All SAEs must be reported to the trial co-ordinating centre as soon as possible. Those hospital admissions that were planned prior to trial entry will not be recorded as SAEs.

As per the ‘ACTiMuS’ trial, expected AEs include:

- Local bruising and discomfort following bone marrow harvest
- Increase in lower limb spasticity following bone marrow harvest
- Acute urinary retention following bone marrow harvest
- Temporary exacerbation of MS following general anaesthesia
- Hypovolaemia or anaemia following blood and marrow donation
- Exacerbation of MS due to sepsis e.g. urinary tract infection or chest infection
- Assessment at or admission to hospital following fall

Bloods taken for safety analyses will be screened as follows: urea and electrolytes, liver function tests, full blood count with differential white cell count, coagulation, group and save, C-reactive protein, glucose, calcium, magnesium, chloride, bicarbonate, phosphate, viral serology (including cytomegalovirus, Epstein-Barr virus, herpes simplex virus, varicella zoster virus, toxoplasmosis, Hepatitis B&C, human immunodeficiency virus, human T cell lymphoma virus and syphilis screening. Urinalysis (microscopy and culture) will also be performed.
Secondary outcome measures

Change in clinical measures of disability, GEP and cranial MRI findings are included as secondary outcome measures.

Clinical outcomes will be assessed at entry and at 6 months and 1 year. The clinical rating scales will include the widely used Expanded Disability Status Scale (EDSS)\(^5\) together with the Multiple Sclerosis Functional Composite (MSFC)\(^6\). The latter is a three-part quantitative assessment including a timed walk, nine-hole peg test and Paced Auditory Serial Addition Test (PASAT). In addition, participants will be asked to complete the MS Impact Scale (MSIS-29) which is a well-validated patient-completed rating scale\(^7-10\). The measures taken for clinical secondary outcome measures will be:

1. Physician-based EDSS: time to EDSS progression of at least one point from a baseline EDSS of 4.0, 4.5 or 5.0 or at least 0.5 points from a baseline EDSS ≥5.5.
2. Patient-based MSIS-29 physical impact scale version 2: overall mean change from baseline to end of study
3. MSFC: overall mean change of z-scores, from baseline to final visit

Multimodal evoked potentials will be examined at 0, 6 and 12 months. Evoked potential abnormalities will be quantified according to a 4-point graded ordinal score modified from Leocani et al (0=normal; 1=increased latency; 2=increased latency and abnormal amplitude; 3=absent) and the composite GEP score calculated\(^3\).

The recording of the evoked potentials shall be in accordance with the Guidelines of the International Federation of Clinical Neurophysiology\(^11\) and analysis will be performed using standard methods\(^12\) (box 1). Electrophysiological responses shall be considered abnormal if they exceed 2.5 standard deviations of the normal values or cannot be detected.

Participants will undergo cranial MRI at entry and at 6 months after bone marrow infusion. The secondary MRI outcome measures will relate to lesion load and atrophy measures of the brain.

Annual subjective patient and treating physician assessments of efficacy will also be recorded.

**Trial status**

‘SIAMMS-II’ opened to recruitment in March 2014 and is ongoing.

**Analysis**

A full statistical analysis plan will be written prior to data collection. The null hypothesis is that there will be no significant difference in the primary and secondary outcomes between intervention and control arms at 12 months.
Secondary outcomes will be scored according to standard methodology but the limitations of the small sample size are acknowledged.

Conclusion

On the background of extensive pre-clinical studies and anticipated low risk of significant harm, we commenced a phase I trial intravenous delivery of filtered but otherwise unmodified autologous bone marrow in 2006. The successful completion of this early trial and the suggestion that electrophysiological improvement may have occurred, made further exploration of the reparative potential of autologous marrow in MS mandatory. We have begun to assess the efficacy of this approach in the randomised, double-blind ‘ACTiMuS’ trial. However, ‘SIAMMS-II’ will give some preliminary information about the value of retreating progressive MS with repeat infusion of autologous bone marrow.

A number of clinical trials are now beginning to explore the safety and therapeutic effectiveness of bone marrow-derived cell therapy for MS using specific sub-populations of bone marrow cells such as multipotent mesenchymal stromal cells (reviewed in 13). We have set out our rationale for using unfractionated marrow in an accompanying manuscript 4 but, in essence, our approach utilises the potential reparative effects of multiple cell populations and has not be shown to be associated with increased clinical risk.

There is now a wealth of pre-clinical data which supports a clear scientific rationale for bone marrow-derived cell therapy in MS. This, together with the extensive clinical experience of bone marrow transplantation which has been acquired over several decades, justifies the examination of the putative clinical benefit of bone marrow-derived cell therapy for MS in clinical trials.

‘SIAMMS-II’, the ‘ACTiMuS’ trial and other on-going studies 13 will determine whether bone marrow-derived cell therapy genuinely effects neurological repair in MS and will further understanding of the potential multiplicity of reparative mechanisms. Optimisation of treatment is likely to be an iterative process which is dependent on efficient back-translation of information gained from carefully designed clinical trials and it is hoped that future refinements will exploit more efficiently the therapeutic potential of bone marrow cell therapy for the treatment of progressive MS.

Acknowledgements

We are very grateful to all those providing financial support for the ‘SIAMMS-II’ trial as listed above.

Contributors

CMR and NJS were responsible for overall study design. NMK and PW are involved in the neurophysiological outcome measures. GM has co-ordinated NHSBT involvement. AW has contributed to protocol review and refinement. PS, DO, CMR,
AW and NJS are involved in the clinical trial processes. JR, PS, CMR, AW and NJS are responsible for the laboratory analyses. CMR drafted the manuscript, the final version of which all authors read and approved.

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**Competing interests**

The authors declare that they have no competing interests.

**Abbreviations**

'ACTiMuS' Assessment of Cellular Therapy in progressive Multiple Sclerosis

AE adverse event

BM bone marrow

BSAEP brainstem auditory evoked potential

CNS central nervous system

CXR chest X-ray

EDSS expanded disability status scale

GEP global evoked potential

GMP good manufacturing practice

Hb haemoglobin

MEP motor evoked potential

MMEP multimodal evoked potential

MRI magnetic resonance imaging

MS multiple sclerosis

MSFC multiple sclerosis functional composite

MSIS-29 multiple sclerosis impact scale-29

NHSBT National Health Service Blood and Transplant

OCT optical coherence tomography

PPMS primary progressive multiple sclerosis

PASAT paced auditory serial addition

SAE serious adverse event

SEP sensory evoked potential

'SIAMMS' Study of Intravenous Autologous Marrow in Multiple Sclerosis

'SIAMMS-II' Repeat infusion of autologous bone marrow cells in multiple sclerosis – a phase I extension study

SPMS secondary progressive multiple sclerosis

VEP visual evoked potential
References


Figure legends

Table 1 Eligibility criteria for the ‘SIAMMS’ trial

Figure 1 Study schema for the ‘SIAMMS-II’ trial

Box 1 Method for recording of multimodal evoked potentials
Figure 1 Study schema for the ‘SIAMMS-II’ trial
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<td>Participation in another experimental study or treatment within previous 24 months</td>
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Box 1 Method for recording of multimodal evoked potentials

VEPs will be evoked with a rear-projected checkerboard pattern using an optomechanical device subtending 30 degrees at the retina, check-size 1 degree, white brightness of 150cdm⁻² and contrast 87.5%.

Monaural stimulation will be delivered via earphones to each side with rarefaction click stimuli of 0.1ms duration at an intensity of 75dB above the subjective hearing threshold whilst the contralateral ear was masked with white noise.

SEPs will be obtained by delivering electrical stimulation with square wave pulses of 0.2ms duration to the median and the posterior tibial nerves, at the wrist and ankle respectively.

Motor evoked potentials (MEPs) will be recorded from electrodes situated over the abductor pollicis brevis muscle in the hand and the abductor hallucis in the foot using a 9cm circular coil held over the vertex. The central motor conduction time (CMCT) was calculated by subtracting ½(M+F+1) from the MEP latency where M is the distal motor latency and F is the minimum F wave latency.

The GEP score will then be calculated as the sum of left and right BSAEP and VEP scores (0-12) and left and right upper and lower SEPs (0-12) and CMCTs (0-12).
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Keywords: cell therapy bone marrow multiple sclerosis reparative therapy
Abstract

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**Strengths:**
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Extension data for phase I clinical trial

**Limitations:**
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Small sample size
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Our hypothesis is that intravenously-delivered autologous bone marrow cell therapy in chronic MS has reparative properties. We postulate that bone marrow-derived cells contribute to repair within the CNS via a multiplicity of mechanisms including immunomodulation and reparative and/or neuroprotective effects. Furthering our understanding of these processes will enable development and refinement of cell therapy for progressive MS.

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participants had had no exposure to disease modifying treatment. One had received prior treatment with azathioprine and methotrexate and another participant had been previously been treated with glatiramer and Avonex. In the intervening period since receiving the first infusion of autologous bone marrow, none of the 6 participants have received additional disease modifying therapy.

**Trial interventions**

Participants will have a bone marrow harvest and re-infusion of autologous marrow as a daycase procedure. A short general anaesthesis will be given for the bone marrow harvest which will be taken from the posterior iliac crests. Approximately 600ml marrow will be collected together with a single bone marrow trephine. The marrow aspirate will be processed by NHSBT (filtered, bagged and labelled) prior to intravenous infusion.

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Primary outcome measure

The primary outcome measure is the number of adverse events (AE). For the purposes of the study, an AE is defined as any unfavourable and unintended sign, symptom or illness that develops or worsens during the period of the study. This is irrespective of the likelihood that the AE is related to study interventions. AEs may be expected or unexpected and include unwanted side effects, toxicity or sensitivity reactions, as well as abnormal laboratory results, injury or intercurrent illnesses.

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Conclusion

On the background of extensive pre-clinical studies and anticipated low risk of significant harm, we commenced a phase I trial intravenous delivery of filtered but otherwise unmodified autologous bone marrow in 2006. The successful completion of this early trial and the suggestion that electrophysiological improvement may have occurred,¹ made further exploration of the reparative potential of autologous marrow in MS mandatory. We have begun to assess the efficacy of this approach in the randomised, double-blind ‘ACTiMuS’ trial.⁴ However, ‘SIAMMS-II’ will give some preliminary information about the value of retreating progressive MS with repeat infusion of autologous bone marrow.

There is now a wealth of pre-clinical data which supports a clear scientific rationale for bone marrow-derived cell therapy in MS. This, together with the extensive clinical experience of bone marrow transplantation which has been acquired over several decades, justifies the examination of the putative clinical benefit of bone marrow-derived cell therapy for MS in clinical trials. Indeed, in addition to our own studies using filtered but otherwise unselected bone marrow, a number of clinical trials are now exploring the safety and therapeutic effectiveness of bone marrow-derived cell therapy for MS using specific sub-populations of bone marrow cells. We and others have recently reviewed the approaches being explored¹³¹⁴¹⁵ but, whilst candidates certainly include multipotent mesenchymal stromal cells, the cell population(s) of greatest therapeutic potential have not been definitively identified. The rationale for our use of unfractionated marrow has been set out in detail elsewhere¹⁴ but in essence our approach utilises the potential reparative effects of multiple cell populations and has not be shown to be associated with increased clinical risk.

‘SIAMMS-II’, the ‘ACTiMuS’ trial and other on-going studies will determine whether bone marrow-derived cell therapy genuinely effects neurological repair in MS and will further understanding of the potential multiplicity of reparative mechanisms. Optimisation of treatment is likely to be an iterative process dependent on efficient back-translation of information gained from carefully designed clinical trials but it is hoped that future refinements will exploit more efficiently the therapeutic potential of bone marrow cell therapy for the treatment of progressive MS.

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Contributors

CMR and NJS were responsible for overall study design. NMK and PW are involved in the neurophysiological outcome measures. GM has co-ordinated NHSBT involvement. AW has contributed to protocol review and refinement. PS, DO, CMR, AW and NJS are involved in the clinical trial processes. JR, PS, CMR, AW and NJS are responsible for the laboratory analyses. CMR drafted the manuscript, the final version of which all authors read and approved.

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Competing interests

The authors declare that they have no competing interests.

Abbreviations

‘ACTiMuS’ Assessment of Cellular Therapy in progressive Multiple Sclerosis
AE adverse event
BM bone marrow
BSAEP brainstem auditory evoked potential
CNS central nervous system
CXR chest X-ray
EDSS expanded disability status scale
GEP global evoked potential
GMP good manufacturing practice
Hb haemoglobin
MEP motor evoked potential
MMEP multimodal evoked potential
MRI magnetic resonance imaging
MS multiple sclerosis
MSFC multiple sclerosis functional composite
MSIS-29 multiple sclerosis impact scale-29
NHSBT National Health Service Blood and Transplant
OCT optical coherence tomography
PPMS primary progressive multiple sclerosis
PASAT paced auditory serial addition
SAE serious adverse event
SEP sensory evoked potential
‘SIAMMS’ Study of Intravenous Autologous Marrow in Multiple Sclerosis
‘SIAMMS-II’ Repeat infusion of autologous bone marrow cells in multiple sclerosis – a phase I extension study
SPMS secondary progressive multiple sclerosis
VEP visual evoked potential
References


**Tables**

Table 1 Eligibility criteria for the ‘SIAMMS-II’ trial

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participation in the phase I safety and feasibility ‘Study of Intravenous Autologous Marrow in Multiple Sclerosis’ (SIAMMS) (REC reference number number 05/Q1704/137)³</td>
<td>Pregnancy, breastfeeding or lactation</td>
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<tr>
<td></td>
<td>History of autologous/allogeneic bone marrow transplantation or peripheral blood stem cell transplant other than in SIAMMS</td>
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<td></td>
<td>Bone marrow insufficiency</td>
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<td>History of lymphoproliferative disease or previous total lymphoid irradiation</td>
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<td>Immune deficiency</td>
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<td></td>
<td>History of current or recent (&lt;5 years) malignancy</td>
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<td>Chronic or frequent drug-resistant bacterial infections or presence of active infection requiring antimicrobial treatment</td>
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<td></td>
<td>Frequent and/or serious viral infection</td>
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<td></td>
<td>Systemic or invasive fungal disease within 2 years of entry to study</td>
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<td></td>
<td>Significant renal, hepatic, cardiac or respiratory dysfunction</td>
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<td></td>
<td>Contraindication to anaesthesia</td>
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<tr>
<td></td>
<td>Bleeding or clotting diathesis</td>
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<td></td>
<td>Current or recent (within preceding 12 months) immunomodulatory therapy other than corticosteroid therapy</td>
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<td>Treatment with corticosteroids within the preceding 3 months</td>
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<td>Radiation exposure in the past year other than chest / dental x-rays</td>
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<td>Previous claustrophobia</td>
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<td></td>
<td>The presence of any implanted metal or other contraindication to MRI</td>
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<tr>
<td></td>
<td>Participation in another experimental study or treatment within previous 24 months</td>
</tr>
</tbody>
</table>
Box 1 Method for recording of multimodal evoked potentials

VEPs will be evoked with a rear-projected checkerboard pattern using an opto-mechanical device subtending 30 degrees at the retina, check-size 1 degree, white brightness of 150cd m⁻² and contrast 87.5%.

Monaural stimulation will be delivered via earphones to each side with rarefaction click stimuli of 0.1ms duration at an intensity of 75dB above the subjective hearing threshold whilst the contralateral ear was masked with white noise.

SEPs will be obtained by delivering electrical stimulation with square wave pulses of 0.2ms duration to the median and the posterior tibial nerves, at the wrist and ankle respectively.

Motor evoked potentials (MEPs) will be recorded from electrodes situated over the abductor pollicis brevis muscle in the hand and the abductor hallucis in the foot using a 9cm circular coil held over the vertex. The central motor conduction time (CMCT) was calculated by subtracting ½(M+F+1) from the MEP latency where M is the distal motor latency and F is the minimum F wave latency.

The GEP score will then be calculated as the sum of left and right BSAEP and VEP scores (0-12) and left and right upper and lower SEPs (0-12) and CMCTs (0-12).
Figure Legend

Figure 1 Study schema for the 'SIAMMS-II' trial
Recruitment

Participants in the phase I safety and feasibility ‘Study of Intravenous Autologous Marrow in Multiple Sclerosis’

n=6

Assessment for suitability

Baseline assessment – EDSS, MSFC, MSIS-29, bloods, ECG, GEPs & MRI brain

Bone marrow harvest

Infusion of bone marrow

6mths – EDSS, MSFC, MSIS-29, blood, MRI brain & GEPs

12mths – EDSS, MSFC, MSIS-29, blood & GEPs
Repeat infusion of autologous bone marrow cells in multiple sclerosis: protocol for a phase I extension study (SIAMMS-II)

Claire M Rice, David I Marks, Peter Walsh, Nick M Kane, Martin G Guttridge, Juliana Redondo, Pamela Sarkar, Denise Owen, Alastair Wilkins and Neil J Scolding

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