Autologous Stem Cell Transplantation versus Alemtuzumab or Ocrelizumab in Relapsing Remitting Multiple Sclerosis

StarMS

A multicentre, randomised controlled trial to evaluate the efficacy and safety of autologous haematopoietic stem cell transplantation versus alemtuzumab or ocrelizumab in relapsing remitting multiple sclerosis.

RESEARCH PROTOCOL
Version 3.0, 17Jun2020

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REC:	20/YH/0061
Sponsor:	STH19379
ISRCTN:	TBC
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Chief Investigator Agreement Page

The clinical study as detailed within this research protocol (Version 3.0, dated 17Jun2020), or any subsequent amendments, involves the use of an investigational medicinal product and will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996), Principles of ICH-GCP, and the current regulatory requirements, as detailed in the Medicines for Human Use (Clinical Trials) Regulations 2004 (UK S.I. 2004/1031) and any subsequent amendments of the clinical trial regulations.

Chief Investigator Name: Professor John Snowden

Chief Investigator Site: Sheffield

Signature and Date:

17/06/2020

Print name: John Snowden

Statistician Agreement Page

The clinical study as detailed within this research protocol (Version 3.0, dated 17Jun2020), or any subsequent amendments, involves the use of an investigational medicinal product and will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996), Principles of ICH-GCP, and the current regulatory requirements, as detailed in the Medicines for Human Use (Clinical Trials) Regulations 2004 (UK S.I. 2004/1031) and any subsequent amendments of the clinical trials regulations.

Statistician Name: Professor Stephen Walters

Statistician Job Title: Senior Statistician

Organisation: Sheffield Clinical Trials Research Unit

Signature and Date:

18/06/2020

Print name: Stephen Walters

Sheffield Clinical Trials Research Unit (CTRU)

Autologous Stem Cell Transplantation versus Alemtuzumab or Ocrelizumab in Relapsing Remitting Multiple Sclerosis (StarMS)

This document describes a clinical trial, and provides information about procedures for entering participants. The protocol is not intended for use as a guide to the treatment of other patients. Amendments may be necessary; these will be circulated to known participants in the trial.

Contents

Abbreviations

ABN	Association of British Neurologists
ADWP	Autoimmune Diseases Working Party
AE	Adverse Event
aHSCT	Autologous Haematopoietic Stem Cell Transplant
AR	Adverse Reaction
AST	Aspartate transaminase
ATG	Anti-thymocyte globulin
BCR	B Cell Receptor
BICAMS	Brief International Cognitive Assessment for Multiple Sclerosis
BRC	Biomedical Research Centre
BSMBT	British Society of Blood and Marrow Transplantation
CANTAB	Cambridge Neuropsychological Test Automated Battery
CCR6	C-C Chemokine Receptor Type 6
CI	Chief Investigator
CMV	Cytomegalovirus
CMV Ab	CMV Antibody
CNS	Central Nervous System
Co-CI	Co-Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CSF	Cerebrospinal Fluid
CT	Computerised Tomography
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTRU	Clinical Trials Research Unit
CV	Curriculum Vitae
DLCO	Diffusing capacity of the lung for carbon monoxide
DMEC	Data Monitoring and Ethics Committee
DMP	Data Management Plan
DMT	Disease Modifying Therapy
EBMT	European Society for Blood and Marrow Transplantation
EBV	Epstein-Barr Virus
EBV-PTLD	EBV-Driven Post-transplant Lymphoproliferative Disorder
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDSS	Expanded Disability Status Scale
EDTA	Ethylenediaminetetraacetic acid
EQ-5D-5L	EuroQol Five Dimensions Questionnaire
EQ-VAS	EuroQol Visual Analog Scale
EU	European Union
EudraCT	European Union Drug Regulatory Agency Clinical Trial
FBC	Full Blood Count
FDA	Food and Drug Administration
FEV1	Forced Expiratory Volume in 1 second
FLAIR	Fluid-Attenuated Inversion Recovery
FSH	Follicle Stimulating Hormone
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
G-CSF	Granulocyte-colony stimulating factor
GDPR	General Data Protection Regulation

GP	General Practitioner
HbA1c	Haemoglobin A1C (glycated haemoglobin)
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIB	*Haemophilus influenzae* type B
HIV	Human Immunodeficiency Virus
HRA	Health Research Authority
HSCT	Haematopoietic stem cell transplantation
HSV 1	Herpes Simplex Virus Type 1
HSV 2	Herpes Simplex Virus Type 2
HTVL 1	Human T-Cell Lymphotropic Virus Type 1
HTVL 2	Human T-Cell Lymphotropic Virus Type 2
IB	Investigator's Brochure
ICH-GCP	International Conference on Harmonisation – Good Clinical Practice
IDSA	Infectious Diseases Society of America (IDSA)
IFNγ	Type II Interferon
IICD	Department of Infection Immunity and Cardiovascular Disease
IMGT/GENE-DB	ImMunoGeneTics Genome Database
IMP	Investigational Medicinal Product
ISF	Investigator Site File
ITT	Intention to Treat
IV	Intravenous
JACIE	Joint Accreditation Committee-ISCT & EBMT
JCV	John Cunningham Virus
LDH	Lactate Dehydrogenase
LH	Luteinising Hormone
LPLV	Last patient last visit
MAIT	Mucosal-Associated Invariant T
MDT	Multidisciplinary Team
MHRA	Medicines and Healthcare products Regulatory Agency
MICE	Multiple Imputation using Chained Equations
MMR	Mumps, Measles and Rubella
MRI	Magnetic resonance imaging
MS	Multiple Sclerosis
MSFC	Multiple Sclerosis Functional Composite
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NEDA	No Evidence of Disease Activity
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NIHR EME	National Institute for Health Research Efficacy and Mechanism Evaluation
NIMP	Non-Investigational Medicinal Product
NMR	Nuclear Magnetic Resonance
PB CD34	Peripheral Blood CD34
PBMC	Peripheral blood mononuclear cell
PBSC	Peripheral Blood Stem Cell
PCR	Polymerase Chain Reaction
PET-CT	Positron Emission Tomography and Computed Tomography
PI	Principal Investigator
PML	Progressive Multifocal Leukoencephalopathy

PO	Oral Administration (Per os)
QoL	Quality of Life
RCT	Randomised Controlled Trial
rATG	Rabbit Anti-thymocyte Globulin
REC	Research Ethics Committee
RRMS	Relapsing Remitting Multiple Sclerosis
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SDV	Source Data Verification
RAND SF-36	36-Item Short Form Health Survey
SMP	Site Monitoring Plan
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCR	T Cell Receptor
TCRB	T Cell Receptor Beta
TMF	Trial Master File
TMG	Trial Management Group
TRM	Transplant-Related Mortality
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction
UCL	University College London
UK	United Kingdom
US	United States
VPD	Vaccine Preventable Diseases
VZV	Varicella-zoster Virus
WOCBP	Woman of childbearing potential

1. General information

1.1 Investigator Details

Chief Investigator:
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Mrs Colette Beecher
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Professor Neil Scolding
Professor at Neurology Department
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Professor Carolyn Young
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Ms Diana Papaioannou
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Professor Stephen Walters
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Emergency contacts

In the event of the Chief Investigator (CI) becoming unavailable during the trial, the emergency contact will be either Professor Basil Sharrack or Professor Paolo Muraro.

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1.2 Central Review Team

Neurologists*
Professor Basil Sharrack
Professor Paolo Muraro
Dr David Paling

Haematologists*
Professor John Snowden
Dr Majid Kazmi
Dr Andy Peniket

* Note that only the core members of the central review team are listed above. Additional members of staff may be included in the central review team if needed due to absence etc. Full membership will be documented in a study-specific SOP.

1.3 Clinical Trials Research Unit

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1.4 Sponsor Details

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Sponsor Representative: Name: Luke Barron
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1.5 Committees

Trial Steering Committee:

Name	Role	Affiliation
Dr Kavita Raj (Chair)	Consultant Haematologist	Guys and St Thomas' NHS Foundation Trust
Dr Murray Martin	Consultant Haematologist	University Hospitals of Leicester NHS Trust
Dr Orla Gray	Consultant Neurologist	South Eastern Health and Social Care Trust
Dr Jonathon O'Riordan	Consultant Neurologist	NHS Tayside
Ms Cassandra Brooks	Principal Statistician	University of Leicester
Dr Shaun Barber	Medical Statistician	University of Leicester
Mrs Helen Day	PPI Representative	NA
Mr Brian Day	PPI Representative	NA
Mr Howard Caplin	PPI Representative	NA

Data Monitoring and Ethics Committee:

Name	Role	Affiliation
Dr Riccardo Saccardi (Chair)	Director of Department of Cellular Therapies and Transfusion Medicine	Careggi University Hospital, Florence
Professor Gianluigi Mancardi	Consultant Neurologist	University of Genoa
Dr Dominic Culligan	Consultant Haematologist	Aberdeen Royal Infirmary
Professsor Gianvito Martino	Consultant Neurologist	San Raffaele Hospital, Milan
Dr Nuria Porta	Senior Medical Statistician	Institute of Cancer Research, London

1.6 Participating Centres

Site	Lead Neurologist	Lead Haematologist
Sheffield Teaching Hospitals NHS Foundation Trust	Prof Basil Sharrack	Prof John Snowden
Imperial College Healthcare NHS Trust	Prof Richard Nicholas	Dr Ian Gabriel
King's College Hospital NHS Foundation Trust	Dr Eli Silber	Dr Majid Kazmi
Bart's and the London NHS Trust	Dr Ben Turner	Prof John Gribben

Site	Lead Neurologist	Lead Haematologist
Cambridge University Hospitals NHS Foundation Trust	Prof Alasdair Coles	Dr Charles Crawley
The Walton Centre NHS Foundation Trust **Associated Treatment Centre:** The Clatterbridge Cancer Centre NHS Foundation Trust	Prof Carolyn Young	Dr Arpad Toth
Oxford University Hospitals NHS Foundation Trust	Prof Gabriele DeLuca	Dr Andy Peniket
North Bristol NHS Trust **Associated treatment centre:** University Hospitals Bristol NHS Trust	Dr Claire Rice	Prof David Marks
University Hospitals Birmingham NHS Foundation Trust	Dr Gordon Mazibrada	Dr Ram Malladi
University Hospital Southampton NHS Foundation Trust	Dr Ian Galea	Dr Kim Orchard
University Hospitals Plymouth NHS Trust	Prof Jeremy Hobart	Dr Hannah Hunter
Salford Royal NHS Foundation Trust **Associated treatment centre:** Manchester University NHS Foundation Trust	Dr David Rog	Dr Eleni Tholouili
The Newcastle upon Tyne Hospitals NHS Foundation Trust	Dr Martin Duddy	Dr Amy Publicover
Leeds Teaching Hospitals NHS Trust	Dr Maruthi Vinjam	Dr Jennifer Clay
Nottingham University Hospitals NHS Trust	Prof Cris Constantinescu	Dr Jenny Byrne
University College London Hospitals NHS Foundation Trust	Prof Olga Cicarelli	Dr Charalampia Kyriakou
NHS Greater Glasgow and Clyde	Dr Stewart Webb	Dr Anne Parker
NHS Lothian	Prof Anna Williams	Dr Chun Huat Teh
Cardiff & Vale University Health Board	Prof Neil Robertson	Dr Keith Wilson

1.7 Laboratory Details

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1.8 Role of the Funder

The funder has reviewed the research protocol but will have no role in data collection, analysis, data interpretation, report writing or in the decision to submit the report for publication. The funder has approved the selection of members for oversight committees.

1.9 Protocol amendments

Protocol version	Changes made
v2.0	Updates made following MHRA review: • Exclusion criteria 14-18 added/amended (section 6.3) • Contraception guidance updated to include specific requirements for continued use of contraceptive measures following discontinuation of Alemtuzumab, Ocrelizumab and Cyclophosphamide (section 6.7) • Concomitant treatment guidance updated with regard to live vaccines and anti-coagulant or anti-platelet therapy (section 8.10) • Alemtuzumab monitoring requirements updated to include LFTs and platelet counts (sections 8.3.1 & 9.1) • Updated to clarify that AEs and SAEs will be recorded from the date of informed consent (sections 9.1, 10.2 & 10.4) • Study assessments schedule updated to include thyroid function tests in the list of safety bloods (sections 9.1 & 9.6)
V3.0	Updates made for Substantial Amendment 1 • Associated treatment centres added (section 1.6) • Time points of CANTAB assessments updated to only be required at baseline, month 12 and month 24 (sections 1.10, 3.5.2, 4.4 & 11, table 6 and figure 2) • Sections 1.10, 3.5.2, 4.4, 9.8 and 11, table 6 and figure 2 have been updated to include the Brief International Cognitive Assessment for MS (BICAMS) at baseline, month 12 and month 24. • Removed reference to MRI at month 18 (section 4.2.3) • Exclusion criteria 8 has been updated for consistency with section 6.7 (section 6.3) • Statement regarding COVID-19 added (section 8) • Updated to clarify that specific trial involvement from pharmacy is not required (section 8) • Reference to testing vaccinations samples for pneumococcal serotype-specific antibodies, DTP, HIB and polio titres has been removed (section 8.2.5) • Clarify that immunoglobulin levels and serum protein electrophoresis is only required for the trial at baseline and not at follow up (table 5) • Clarify that haematinics are not required for the trial (table 5) • Mechanistic blood samples not required at month 18 (figure 2) • Updated low contrast sensitivity assessments to only assess binocular vision (section 9.5) • Updated to clarify the events that are exempt from expedited reporting (section 10.5) • Updated to clarify the reporting requirements for pregnancy in female partners of male participants (section 10.8)

1.10 Trial Summary

Study Title:	Autologous Stem Cell Transplantation versus Alemtuzumab or Ocrelizumab in Relapsing Remitting Multiple Sclerosis
EudraCT no:	2019-001549-42
Sponsor:	Sheffield Teaching Hospitals NHS Foundation Trust
Funder:	National Institute for Health Research Efficacy and Mechanism Evaluation (EME)
ISRCTN no:	TBC
Project start date:	1st January 2019
Project end date:	31st July 2024
Study Design:	Multicentre parallel-group rater-blinded RCT
Participants:	198 participants with highly active relapsing and remitting MS
Setting:	Participants will be recruited from 19 secondary care centres, and HSCT will be carried out within centres JACIE accredited for allogeneic HSCT, or for autologous HSCT if they have previous experience of autologous HSCT for autoimmune diseases
Inclusion/exclusion criteria (see section 6.2 & 6.3)	**Inclusion Criteria:** 1. Diagnosis of MS using the 2017 McDonald criteria (51). 2. Age 16-55 inclusive. 3. EDSS 0-6.0 inclusive*. If the EDSS score is 6.0 this must be due to confirmed relapse rather than progressive disease. 4. Severe inflammatory disease defined as RRMS course with 2 or more protocol defined relapses**, or 1 such a relapse and evidence of MRI disease activity >3 months before or after its onset, in last 12 months despite being on a DMT*. 5. Clinical stability for >30 days following last relapse at time of screening. 6. Satisfactory EBMT Autoimmune Disease Working Party (ADWP) recommended screening assessment prior to aHSCT (1) 7. Participants who have been reviewed by the central neurology team and confirmed as eligible. 8. Participants who, in the opinion of the local haematology lead or delegate, are fit enough to undergo treatment. 9. Able to undergo MRI examination ** Patients with EDSS scores of 0-1.5 or those who failed only first line treatments must also fulfil following criteria: short illness duration (<5 years), active disease clinically and radiologically (i.e. at least 2 relapses in the last 12 months and evidence of multiple Gad enhancing MRI lesion), high brain lesion load and brain or spinal cord atrophy (2).* ***see section 6 for details* **Exclusion criteria** 1. Diagnosis of primary or secondary progressive MS. 2. Disease duration of >10 years from symptom onset (note: symptoms must be clearly attributable to MS). 3. Previous use of Alemtuzumab, Ocrelizumab or Cladribine.

	4. Previous HSCT for any reason, or any previous experimental or commercial stem cell therapy. 5. JCV antibody Index of >1.5 in patients previously treated with Natalizumab (unless they are CSF JCV PCR negative). 6. Prior diagnosis of Hepatitis B, Hepatitis C or HIV infection or current TB infection. 7. Pregnant or breast-feeding females. 8. Unwilling to use adequate contraception during the trial. Female participants of child-bearing potential must use adequate contraception for the duration of the trial (24 months), and for 12 months after discontinuation of Cyclophosphamide or Ocrelizumab, or 4 months after the last dose of Alemtuzumab. Male participants with female partners of child-bearing potential must use adequate contraception if they are randomised to the aHSCT arm during treatment and for at least six months following discontinuation (i.e. the last dose) of cyclophosphamide. See section 6.7 for more details. 9. Unable to comply with treatment protocol. 10. Contraindication to the use of Cyclophosphamide, G-CSF (Filgrastim or Lenograstim), or Rabbit ATG. 11. Participants with significant medical co-morbidity that precludes aHSCT as assessed by the local haematology team. 12. Significant language barriers, which are likely to affect the participant's understanding of the study, or ability to complete outcome questionnaires. 13. Concurrent participation in another interventional clinical trial. 14. AST and ALT >2.5 x upper limit of normal (ULN), bilirubin > 1.5 x ULN or direct bilirubin >ULN for participants with total bilirubin levels >1.5 x ULN 15. Current diagnosis of a clinically defined bleeding disorder (patients with platelet counts of $100x10^9$/l or above up to normal range are not excluded, as per section 18d. Persistently abnormal coagulation tests should be addressed to determine whether they constitute a defined bleeding disorder). 16. Diagnosis of a clinically defined autoimmune disorder other than multiple sclerosis. (i.e. meeting full current international clinical and laboratory criteria for a specific autoimmune disorder). 17. Patient with history of myocardial infarction, angina pectoris, stroke or arterial dissection 18. Participants who are not considered medically fit for aHSCT defined by any of the following. Note that these criteria are not automatic exclusion criteria but if any of these are met, and in the opinion of the PI, the participant is medically fit enough to undergo aHSCT, the case may be put forward to the central team for discussion about eligibility: a. Renal: creatinine clearance <40ml/min (measured or estimated) b. Cardiac: clinical evidence of refractory congestive heart failure, left ventricular ejection fraction <45% by cardiac echo; uncontrolled ventricular arrhythmia;

	pericardial effusion with haemodynamic consequences as evaluated by an experienced echocardiographer c. Concurrent neoplasms or myelodysplasia d. Bone marrow insufficiency defined as neutropenia with an absolute neutrophil count $<1x10^9$/l, or thrombocytopenia with a platelet count $<100x10^9$/l, or anaemia with a haemoglobin <100g/l e. Diagnosis of hypertension, which is uncontrolled despite at least 2 anti-hypertensive agents. f. Uncontrolled acute or chronic infection with any infection the investigator or central team consider a contraindication to participation. (N.B. Baseline JC virus serology will be recorded, but positivity will not be an exclusion criterion). g. Other chronic disease causing significant organ failure, including established cirrhosis with evidence of impaired synthetic function on biochemical testing. This also includes known respiratory disease which, in the opinion of the local haematologist would represent a significant risk to the safe administration of aHSCT. Patients for whom there is concern about potential respiratory disease must undergo formal evaluation by a respiratory physician, including pulmonary function and blood gas measurement.
Intervention Treatment Summary:	For those randomised to aHSCT Mobilisation and stem cell harvest • Cyclophosphamide $2g/m^2$ from baseline date of mobilisation • Mesna with hydration in line with local clinical practice • G-CSF (Filgrastim 5-10µg/kg/day or Lenograstim 5-10µg/kg/day, depending on local practice), starting from day 5 until apheresis completed • Monitoring of full blood count and peripheral blood CD34+ counts until CD34+ exceeds $10x10^6$/L • Stem cell harvest (leukapheresis) until a minimum of 2.5 $x10^6$/kg CD34+ are collected for cryopreservation Conditioning (after stem cell harvest) • Cyclophosphamide 50mg/kg on days -5, -4, -3, -2 • Rabbit ATG (Thymoglobuline) will be given on day -5 (0.5mg/kg), -4 (1.0mg/kg), -3 (1.5mg/kg), -2 (1.5mg/kg), -1 (1.5mg/kg) with prior Methylprednisolone 1g IV, Paracetamol PO or IV and Chlorpheniramine PO or IV 30 minutes before infusion. Ongoing cover with Paracetamol and Chlorpheniramine as needed. • Standard hydration and diuretics throughout administration of Cyclophosphamide, with Mesna and electrolyte replacement. • Stem cell reinfusion on day 0 • Recommended Prednisolone dosing to prevent ATG fever: Prednisolone given on days 0, 1 and 2 (60mg), days 3 and 4

	(40mg), day 5 and until engraftment (20mg) then 10mg for 2 days. • G-CSF (Filgrastim 5-10µg/kg/day rounded according to local practice to the nearest syringe or vial size or Lenograstim 5-10µg/kg/day, depending on local practice) started on day +5 and continued until the absolute neutrophil counts reach >1.0x10^9/L for 2 consecutive days. • It is recommended that platelets are transfused to maintain levels >20x10^9/L. Prophylactic broad spectrum antibiotics and tapering steroids, along with Paracetamol, will be given until neutrophil recovery to minimize fever. • Standard medical supportive care. As routine standard of care, participants will receive the necessary vaccinations, including an annual influenza vaccine. See section 8.2.5 for details For those randomised to DMT: Either Alemtuzumab: • Alemtuzumab 12mg/day on 5 consecutive days • 12 months later 12 mg/day on 3 consecutive days. • Standard medical supportive care Or Ocrelizumab: • Initial dose – 600mg administered as two separate intravenous infusions; first as a 300mg infusion, followed 2 weeks later by a second 300mg infusion • Subsequent doses – a single 600mg infusion every six months. The first subsequent dose should be administered six months after the first infusion of the initial dose. A minimum of 5 months should be maintained between each dose. • Standard medical supportive care
Randomisation:	Participants will be randomised to receive either aHSCT or DMT (Alemtuzumab or Ocrelizumab) in a 1:1 ratio
Anticipated recruitment period:	2 years
Duration of follow-up:	2 years
Hypothesis:	aHSCT is more efficacious at achieving 'No Evidence of Disease Activity' than treatment with a DMT (Alemtuzumab or Ocrelizumab) and has an acceptable safety profile in patients with highly active RRMS.
Primary Objective:	To assess the clinical efficacy, as measured by the no evidence of disease activity (NEDA) outcome rate at 2-years post-randomisation, of aHSCT delivered using non-myeloablative conditioning with the Cy/ATG regimen (as used in the MIST trial) compared with treatment with a highly effective DMT (Alemtuzumab or Ocrelizumab) administered and monitored as per licence in patients with highly active RRMS.

Secondary Objectives:	1. To determine whether the relative safety & toxicity profile (as measured by adverse events (AEs) and serious adverse events (SAEs)) of aHSCT compared with a DMT (Alemtuzumab or Ocrelizumab) is acceptable. 2. To assess the impact of aHSCT compared to DMT (Alemtuzumab or Ocrelizumab) on quality of life (as measured by the EQ-5D-5L, RAND SF-36, WHO-QOL-Bref and Global rating of change outcomes at 3, 6, 9, 12 ,18 and 24 months post-randomisation). 3. To assess the impact of aHSCT compared to highly effective DMTs (Alemtuzumab or Ocrelizumab) on other clinical outcomes (time to evidence of disease activity; EDSS, MSFC, Low contrast visual acuity).
Exploratory Objectives	**Mechanistic study objectives** 1. Analyse TCR and BCR repertoires pre- (baseline before mobilisation) and post-therapy (24 months) in highly purified peripheral blood T and B cell subsets, respectively. 2. Interrogate the reconstitution in blood of candidate MS-associated B and T cell populations by immune profiling with multicolour flow-cytometry with reference to their pre-therapy profile. This will enable us to: a. Characterise immune reconstitution after aHSCT or DMT (Alemtuzumab or Ocrelizumab) b. Examine the extent of depletion of the CD8/MAIT pro-inflammatory subset of T cells c. Describe any immunological changes that precede disease recurrence post aHSCT or DMT (Alemtuzumab or Ocrelizumab) **Neuropsychology study objectives** 1. Assess the effect of aHSCT on cognitive recovery using the Cambridge Neuropsychological Test Automated Battery (CANTAB), (3) an automated battery of neuropsychological assessments (https://www.cambridgecognition.com/) and the Brief International Cognitive Assessment for MS (BICAMS) measured at 12 and 24 months (4). 2. To assess whether the two interventions differentially affect the degree of cognitive impairment after treatment using the CANTAB and BICAMS outcomes. **Optical Coherence Tomography (OCT) study objectives** 1. To compare retinal nerve fiber layer thickness as a marker axonal damage between the two study arms 2. To compare ganglion-cell layer thickness as a marker of neuronal injury between the two study arms 3. To compare the microcystic macular oedema and associated thickening of the retinal inner nuclear layer as markers of active CNS inflammatory activity in the two treatment arms

	Cost-effectiveness Although cost-effectiveness will not be addressed definitively in this application, data will be collected for future economic analyses.
Definition of end of trial	The end of the trial is defined as the end of the grant funding period, assuming that this is after last patient last visit (LPLV), to allow for ongoing study sample analysis. Where LPLV occurs after the end of the grant funding period the end of trial will be defined as LPLV. Sites will be closed once data cleaning is completed, after LPLV.

2. Introduction

2.1 Background

Multiple sclerosis (MS) is a chronic autoimmune inflammatory disease of the central nervous system (CNS) which leads to impairment in strength, sensation, balance, vision, cognition and sphincter function (5). Autologous haematopoietic stem cell transplantation (aHSCT) is being used increasingly as an intensive one-off treatment for highly active Relapsing Remitting Multiple Sclerosis (RRMS). Observational and clinical trial data suggest that aHSCT reduces relapse rates, improves disability and Quality of Life (QoL) in excess of those observed with disease modifying therapies (DMT) and is potentially more cost-effective (1,6–18). A small phase II randomised controlled trial (RCT), 'ASTIMS', supported proof of concept (17) and a larger phase III RCT, 'MIST' (ClinicalTrials.gov Identifier: NCT00273364), which finished recruitment in late 2016, showed that aHSCT resulted in prolonged time to disease progression compared to DMTs (19) . As ASTIMS and MIST did not compare aHSCT with the most efficacious currently available DMTs, Alemtuzumab or Ocrelizumab (20–22) , questions remain concerning the relative efficacy and safety of aHSCT over standard of care in the UK. Clinically important questions regarding long-term complications of aHSCT (23–26) and post-transplant immune reconstitution, in respect to its mechanism of action and recovery of normal immune responses (27–35), need answering before aHSCT is accepted as a standard of care in highly active MS. These issues have been the subject of a recent Association of British Neurologists (ABN) position statement on the use of aHSCT in MS (http://www.theabn.org/resources/abn/m/abn-statement-ms-2016.html), which has highlighted the need for a clinical trial to answer key questions.

Existing research

There is growing evidence from large registry studies and prospective trials supporting the efficacy of aHSCT in highly active MS, with long-term clinical and MRI remissions observed in a majority of patients with acceptable safety. Significantly, improvement in disability after aHSCT has been reported in patients with RRMS (7–10,15–18). A single phase II RCT, ASTIMS, has shown superior efficacy of aHSCT against the development of new MRI lesions compared to mitoxantrone, a drug rarely used in MS now, with conclusions limited by under-powering and a predominance of patients with secondary progressive MS in the trial's small cohort (17). Recently, a systematic analysis of 'No Evidence of Disease Activity' (NEDA) rates following aHSCT supported durable clinical remission in a high proportion of patients with RRMS, suggesting that potential benefit could exceed that seen after approved DMTs including those considered to be highly efficacious (9,10).

A phase III trial, MIST, which randomized patients to aHSCT employing a non-myeloablative immunosuppressive regimen versus FDA-approved DMTs, completed recruitment in December 2016 (ClinicalTrials.gov Identifier: NCT00273364) (19). This trial was open at only one site in the UK (Sheffield) and did not include Alemtuzumab in its control arm despite being shown to be the most efficacious DMT in large RCTs (21,36) because of historical factors specific to the US where Alemtuzumab has a restricted label (37–39). Ocrelizumab was also not included in the control arm for the MIST trial as this is a newer DMT (19). In summary, 110 patients with active RRMS who failed first line DMTs were randomised to receive either the best available DMTs (excluding Alemtuzumab and Ocrelizumab) or aHSCT. There were no significant side effects and no treatment related mortality in the aHSCT arm. The EDSS score of patients receiving aHSCT improved from an average of 3.4 to 2.4 whereas the scores in patients in the standard DMT arm declined from an average of 3.3 to 4. Within the first year of joining the trial, only one patient in the aHSCT arm suffered a relapse compared to 39 relapses observed in the DMT arm. With a mean follow up of 3 years, treatment failure measured by disability progression was 6% in the aHSCT arm and 60% in DMT arm. A total of 31 patients who were originally randomised into the DMT arm were moved over to the transplant arm during the trial period after reaching the primary point (6 month sustained decline of EDSS of 1 or more points). After aHSCT

their scores improved from 5.2 to 2.6. These interim results suggest that aHSCT is safe and has superior efficacy compared with currently available DMTs. However since Alemtuzumab and Ocrelizumab were not included in the control arm of MIST, the need to compare the efficacy of aHSCT against Alemtuzumab and Ocrelizumab, as part of StarMS, is now greater. The long-term results of the MIST trial will be published at the end of the trial in 2021, but there will be still unanswered questions about the relative efficacy and safety of aHSCT over Alemtuzumab and Ocrelizumab, which are approved by NICE and are widely used in the NHS albeit with significant toxicity and considerable economic costs (21,36–38,40,41).

In the interim period, aHSCT is being offered in a number of centres as a 'compassionate' treatment to a limited number of carefully selected patients who failed DMTs based on the EBMT recommendations (1). Whilst these patients are being actively registered into the database of the EBMT, there remains an unmet scientific and health service need to establish the relative benefits and toxicities of aHSCT in relation to the best currently available DMTs in RRMS, namely Alemtuzumab and Ocrelizumab. More recently, the use of aHSCT in MS has been subject of a horizon scanning appraisal and 'guidance in development' by NICE, who elected to defer the publication of any guidelines whist awaiting the outcome of the MIST trial (https://www.nice.org.uk/guidance/indevelopment/gid-ip1151).

2.2 Rationale for current study

Recent observational & clinical trial data suggest that aHSCT reduces relapse rates, improves disability and QoL in excess of those observed with licensed DMTs and is potentially more cost-effective (1,6–18). The effects appear to be long-term extending beyond 5 years (7–10,13–18). Its short-term safety, and acceptance by the neurological community, has improved in recent years, with no reports of transplant related mortality (TRM) in recent studies (10).

A recent systematic analysis of NEDA rates following aHSCT supports durable clinical remissions in a high proportion of patients with RRMS, suggesting that potential benefit could exceed that seen after approved DMTs, including the highly efficacious ones (9,10). As most data is registry based and the ASTIMS & MIST trials have not directly compared aHSCT with the most efficacious DMTs, Alemtuzumab and Ocrelizumab (20,36) questions remain concerning the relative efficacy & safety of aHSCT over this UK standard of care DMT for highly active RRMS. Equally, this question will not be answered by the forthcoming US-based NIH BEAT-MS study, which is expected to compare aHSCT (which will use a more intensive conditioning regimen, 'BEAM/ATG'), to the best available DMT, because limited number of patients are treated with Alemtuzumab in the US where it has a restricted label (37–39).

We have therefore designed a research programme to assess the safety, efficacy and long-term impact of aHSCT using the non-myeloablative 'Cy/ATG' conditioning regimen (as per the MIST trial protocol) compared with DMTs (Alemtuzumab or Ocrelizumab), the evidenced-based UK standard of care in patients with highly active RRMS. In addition to carrying over the conditioning regimen from the MIST trial, historical data suggests that the Cy/ATG conditioning regimen may have significantly less short-term toxicity than the more intensive regimens (8,42), although more recent data supports improved safety of BEAM/ATG (18) . It is notable that there were no transplant-related deaths in the MIST study.

In association with the clinical elements of this RCT, we have embedded a mechanistic study to assess baseline immune profiles and post-transplant immune reconstitution with a view to identifying predictive biomarkers of clinical response.

The study will be conducted in accordance with the protocol, GCP and the Medicines for Human Use (Clinical Trials) Regulations 2004.

Risks and benefits

MS affects approximately 120,000 people in the UK and 2.3 million people worldwide (43). It is the most common cause of non-traumatic neurological disability of young adults. Following diagnosis, patients rapidly fall out of employment, with recent UK data indicating that after 5 years only 25% of people with MS are still working. As a result MS has an economic impact disproportionate to its prevalence, with estimated annual costs of up to £33,000 per patient, related to the high cost of DMTs, the direct and indirect costs of relapses and the costs of benefits and personal care. Costs to the NHS and wider society could be reduced by effectively preventing relapses & accumulation of physical disability (44).

Most patients with RRMS respond to currently available DMTs and these have been evaluated in NICE and ABN professional guidelines with recommendations for their use sequentially based on baseline disease activity and response to treatment (45). Whilst more efficacious immunosuppressive DMTs, such as Alemtuzumab and Ocrelizumab, may lead to high level of disease control (reflected by NEDA) in patients with highly active RRMS, they are expensive and have significant documented risks including infusion associated reactions, secondary autoimmunity and infections including progressive multifocal leukoencephalopathy (45). Adverse events are routinely recognised in delivery of aHSCT, including a risk of life-threatening complications during the phase of aplasia and immune deficiency following administration of chemotherapy. There is a risk of treatment related mortality, although the recently reported studies of aHSCT in RRMS using low or intermediate intensity conditioning regimens have reported none (10). In the longer term, important questions remain regarding long-term complications of aHSCT, including 'late effects' (23–26) and post-transplant immune reconstitution (27–35).

3. Aims and objectives

3.1 Hypothesis

aHSCT is more efficacious at achieving 'No Evidence of Disease Activity' (NEDA) (10) than treatment with a highly effective disease modifying therapy (Alemtuzumab or Ocrelizumab) and has an acceptable safety profile in patients with highly active RRMS.

3.2 Aims

1. To determine whether aHSCT has superior clinical efficacy to highly effective DMT (Alemtuzumab or Ocrelizumab) with an acceptable safety profile.
2. To advance our understanding of aHSCT mechanisms of efficacy by hypothesis-driven laboratory studies.

3.3 Primary objective

To assess the clinical efficacy, as measured by the no evidence of disease activity (NEDA) outcome rate at 2-years post-randomisation, of aHSCT delivered using non-myeloablative conditioning with the Cy/ATG regimen (as used in the MIST trial) compared with treatment with a highly effective DMT (Alemtuzumab or Ocrelizumab) administered and monitored as per licence in patients with highly active RRMS.

3.4 Secondary objectives

1. To determine whether the relative safety & toxicity profile (as measured by Adverse events (AEs) and serious adverse events (SAEs)) of aHSCT compared with a highly effective DMT (Alemtuzumab or Ocrelizumab) is acceptable.
2. To assess the impact of aHSCT compared to highly effective DMTs (Alemtuzumab or Ocrelizumab) on quality of life (as measured by the EQ-5D-5L, RAND SF-36, WHO-QOL-Bref and Global rating of change outcomes at 3, 6, 9, 12 ,18 and 24 months post-randomisation).
3. To assess the impact of aHSCT compared to highly effective DMTs (Alemtuzumab or Ocrelizumab) on other clinical outcomes (time to evidence of disease activity; EDSS, MSFC, Low contrast visual acuity).

3.5 Exploratory objectives

3.5.1 Mechanistic study objectives

Previous studies have demonstrated that aHSCT induces a qualitative immune resetting, with changes in adaptive immunity that last well beyond recovery of lymphocyte numbers. However, a clearer understanding of the mechanism of the treatment is needed to strengthen the treatment rationale and refine treatment protocols.

Using deep sequencing of T cell receptor beta (TCRB) repertoires of blood samples obtained from the HALT-MS trial (18), it was demonstrated that aHSCT induced significant regeneration of circulating T cells repertoire (30). Importantly, an association was detected between early post-transplant T cells repertoire diversification and 'complete' clinical response. In another study, the effect of aHSCT on relevant immune cell subsets was investigated and radical depletion of CD161highCD8 cells (proinflammatory T cells that produce IFNγ and IL-17, two of the cytokines that promote inflammatory processes in MS) was demonstrated (33). These cells were identified as mucosal-associated invariant T (MAIT) cells, a novel cell population which originates in the gut mucosa but circulates in blood, expresses the CNS-homing receptor CCR6 and infiltrates MS post-mortem brain lesion tissue strongly suggesting their implication in the inflammatory disease process (33).

Besides ascertaining the efficacy and safety, the StarMS trial provides one ideal opportunity to gain knowledge on the mechanism of action of aHSCT. We will test two main hypotheses.

Hypotheses for mechanistic studies

1. Post-therapy diversity of TCR and BCR repertoires is involved in mediating the response to the intervention (aHSCT, Alemtuzumab or Ocrelizumab) and will be greater in the aHSCT arm.

2. Post-therapy depletion of the CD8/MAIT pro-inflammatory subset of T cells is involved in mediating the response to the intervention (aHSCT, Alemtuzumab or Ocrelizumab) and will be greater in the aHSCT arm.

Objectives

To address the hypotheses, we will:

1. Analyse TCR and BCR repertoires pre- (baseline before mobilisation) and post-therapy (24 months) in highly purified peripheral blood T and B cell subsets, respectively

2. Interrogate the reconstitution in blood of candidate MS-associated B and T cell populations by immune profiling with multicolour flow-cytometry with reference to their pre-therapy profile. This will enable us to:
    a. Characterise immune reconstitution after aHSCT, Alemtuzumab or Ocrelizumab
    b. Examine the extent of depletion of the CD8/MAIT pro-inflammatory subset of T cells

c. Describe any immunological changes that precede disease recurrence post aHSCT, Alemtuzumab or Ocrelizumab

3.5.2 Neuropsychology study objectives

1. Assess the effect of aHSCT on cognitive recovery using the Cambridge Neuropsychological Test Automated Battery (CANTAB) (3), an automated battery of neuropsychological assessments (https://www.cambridgecognition.com/) and the Brief International Cognitive Assessment for MS (BICAMS) measured at 12 and 24 months (4).
2. To assess whether the two interventions differentially affect the degree of cognitive impairment after treatment using the CANTAB and BICAMs outcomes.

3.5.3 Optical Coherence Tomography (OCT) study objectives

1. To compare retinal nerve fibre layer thickness as a marker axonal damage between the two study arms
2. To compare ganglion-cell layer thickness as a marker of neuronal injury between the two study arms
3. To compare the microcystic macular oedema and associated thickening of the retinal inner nuclear layer as markers of active CNS inflammatory activity in the two treatment arms

3.5.4 Cost-effectiveness

Although cost-effectiveness will not be addressed definitively in this application, data will be collected for future economic analyses.

4. Trial Design

A multicentre parallel-group rater-blinded RCT that will randomize 198 eligible patients 1:1 to aHSCT (as per the MIST trial protocol: Cyclophosphamide 2g/m^2 mobilization and harvest followed by transplant using Cy/ATG conditioning regimen and unselected autologous graft) versus a highly effective disease modifying therapy (Alemtuzumab or Ocrelizumab) given and monitored as per licence. The trial will be conducted at 19 sites that have both tertiary referral MS clinics and are either JACIE accredited for allogeneic HSCT or accredited for autologous HSCT and have experience in aHSCT for autoimmune diseases (46). Patients with RRMS who fulfil the study criteria for highly active disease, with disease activity despite being on at least one previous DMT, will be recruited. The primary endpoint of treatment success, defined as NEDA rate, will be assessed at 2 years post-randomisation. All aHSCT participants will be entered onto the EBMT registry with yearly data collection by the MED-B form.

Mechanistic studies are integral to the clinical trial with assessment of the timeline of response to aHSCT and interrogation of the peripheral blood and CNS compartments. Serum, whole blood, peripheral blood mononuclear cells will be collected at various time points as per the study flow chart.

Recruitment to StarMS will take place over a period of 2 years and participants will be followed up for 2 years from randomisation.

At each follow up visit, participants will complete questionnaires on quality of life and information will be gathered on adverse events. Where participant recall is limited, the hospital medical notes will be used to identify information relating to adverse events and medication. Participants will give permission for the research team to access their medical notes as part of the consent process. Entry

into the trial will be documented in the medical notes, with copies of study documents for clinicians' reference. Consent will be reconfirmed at each study visit, and this will be documented in the medical notes.

4.1 Feasibility outcomes

Sheffield CTRU will aggregate study data on recruitment for a trial feasibility assessment based on review of the actual numbers of participants recruited during the internal pilot against the predicted number of recruits. The target recruitment during the internal pilot phase is 71 participants.

The criteria for continuing the trial will be viewed as guidelines rather than strict criteria in line with the CONSORT 2010 statement extension to randomised and feasibility trials (47). The emphasis will be on independent discussion of the feasibility of changes to the trial protocol to allow continuation of the trial. The following feasibility criteria will be reviewed by the Trial Steering Committee (TSC) after around 6 months of recruitment:

a. Red: Trial is not feasible – accrual of fewer than 18 participants in the pilot phase
b. Amber: Trial may be feasible if appropriate changes are made – accrual of between 18-49 participants in the pilot phase. This would trigger discussion with the TSC regarding changes possible to the trial protocol and procedures that could improve the recruitment to the trial.
c. Green: Trial is feasible – accrual of 50 or more participants in the pilot phase.

4.2 Primary outcome endpoint

Proportion of patients who have maintained NEDA status (defined as the absence of all three of the following: protocol defined clinical relapses; 6 months confirmed EDSS progression of at least 1 point with an absence of relapse at the time of assessment; any evidence of MRI disease activity as defined by T1 Gd-enhanced lesion or new and/or enlarging T2 lesion after month 6) in the 2-year post-randomisation follow up period.

4.2.1 Protocol defined clinical relapses

The protocol definition of relapse is below, note that **all** of the following criteria must be met:

1. Neurological symptoms, either newly appearing or re-appearing, provided these are
    a. Preceded by at least 30 days of clinical stability,

    and
    b. lasting for at least 24 hours
2. Absence of fever or known infection (fever with temperature (axillary, orally or intrauriculary) >37.5^{o}C)
3. Objective neurological impairment, correlating with the participants reported symptoms, defined as either
    a. Increase in at least two of the functional system (FS) scores of the EDSS
    or
    b. Increase of the total EDSS score of at least one point

Note that if the above criteria are met but there is another confirmed cause then this will not be considered a relapse. Details of the cause must be documented.

There will be a central adjudication of all relapses in the study. All suspected relapses will be reviewed by at least one member of the central neurology team in a blinded fashion. Sites will be required to provide sufficient information in order for the relapse to be reviewed by the central team. The site will be notified of the outcome of the central review and if there are any queries regarding the relapse, these will be discussed and the outcome documented. Only those relapses that have been confirmed

centrally will be used for the primary outcome measure. Please note that central confirmation of a relapse is also required prior to a participant switching treatments (see section 6.10 for further details).

4.2.2 EDSS progression

As per the MIST trial, true progression in terms of NEDA is defined as an increase of at least one point in the EDSS score compared to baseline, confirmed after 6 months from the time of worsening, with an absence of relapse at the time of assessment (19,48–50).

4.2.3 MRI disease activity

MRI scans will be taken at months 6, 12 and 24 post-randomisation to measure disease activity, defined by T1 Gd-enhanced lesion and/or enlarging T2 lesions. Research has shown persistence of some lesions within 3 months post-transplant and complete disappearance after this period (51). Therefore, MRI scans taken at month 6 will serve as a stable re-baseline, and future MRIs (at months 12 and 24) will be assessed against this.

4.3 Secondary outcomes

Safety

i) Serious adverse event (SAE) rate within the 2-year follow up period for each treatment arm
ii) Mortality rate (grade 5 SAEs) within the 2-year follow up period for each treatment arm
iii) Combined grade 4 and 5 SAE rates within the 2-year follow up period for each treatment arm
iv) Total number of adverse events (AEs) experienced by each patient in the 100 days post-randomisation
v) Total number of AEs within the 2-year follow up period for each treatment arm
vi) Long term safety events, including rates of significant infections, endocrine and reproductive dysfunction, secondary autoimmune diseases, incidence of late cardiovascular events, neoplasia and any other significant organ dysfunction within the 2-year follow up period (Ongoing data will be recorded for aHSCT participants via routine BSBMT/EBMT registry however follow up and analysis will be subject to additional funding and support). Please refer to section 8 for the suggested long term screening assessments for late effects of HSCT.

Clinical outcomes

i) Time to evidence of disease activity. Disease activity is defined as the presence of one of the following: protocol defined clinical relapses; confirmed EDSS progression of at least 1 point sustained for 6 months with an absence of relapse at the time of assessment; evidence of MRI disease activity defined as T1 Gd-enhanced lesion or new and/or enlarging T2 lesion after the re-baseline MRI at 6 months post-randomisation.
ii) EDSS scores at 3, 6, 9, 12, 18 and 24 months post-randomisation (52)
iii) MSFC scores at 3, 6, 9, 12, 18 and 24 months post-randomisation (53)
iv) Low contrast visual acuity scores at 3, 6, 9, 12, 18 and 24 months post-randomisation

Quality of Life/Health Economic Measures

i) EQ-5D-5L utility scores at 3, 6, 9, 12, 18 and 24 months post-randomisation (54)
ii) Eight RAND SF-36 dimension (Physical functioning, Role limitations due to physical health, Role limitations due to emotional problems, Energy/fatigue, Emotional well-being, Social

functioning, Pain, General Health) scores at 3, 6, 9, 12, 18 and 24 months post-randomisation (55)

iii) WHO QOL-Bref scores at 3, 6, 9, 12, 18 and 24 months post-randomisation (56)

iv) Global rating of change at 3, 6, 9, 12, 18 and 24 months post-randomisation (57)

4.4 Exploratory sub-study outcomes

Mechanistic study outcomes

i) Metrics of immune reconstitution and potential mechanisms
   a. Immune diversity indices of TCR and BCR repertoire at baseline and 24 months
   b. Depletion of circulating CD8+/MAIT cell subset expressed as percent variation of absolute counts (baseline to 12 months)
   c. Re-constitution of naïve- memory and effector T and B cell profiles, expressed as percent of CD4, CD8 T cells and CD19 B cells at baseline, 6 months, 12 months and 24 months

Neuropsychology study outcomes

i) Cambridge Neuropsychological Test Automated Battery (CANTAB) scores at 12 and 24 months post-randomisation

ii) Brief International Cognitive Assessment for MS (BICAMS) scores at 12 and 24 months post-randomisation

OCT study outcomes

i) Retinal nerve fibre, ganglion-cell layer and retinal inner nuclear layer thickness assessed by optical coherence tomography (OCT) imaging at 12 and 24 months post-randomisation

4.5 Blinding

In view of the nature of aHSCT, neither patients nor their treating physicians will be blinded to the treatment allocation. However, all neurological assessments (EDSS, MSFC and low contrast sensitivity) will be completed by an independent member of the study team who is blind to treatment allocation. These assessments form part of the NEDA assessment i.e. the primary endpoint. All participating centres will be required to identify at least one independent member of staff who can perform the assessments. Where possible, the same member of staff will complete all assessments for an individual participant. Participants will wear an appropriate head covering during these evaluations in order to maintain the blind due to the risk of hair loss in the aHSCT arm. Participants will be instructed not to tell the evaluating member of staff which type of treatment they have been allocated.

Likewise, the MRI component of NEDA will be assessed centrally by expert physicians at UCL (Prof O Ciccarelli and Prof F Barkhof, NMR Unit, UCL Institute of Neurology) who will be unaware of the treatment allocation and will perform MRI analysis using anonymised electronic copies of the appropriate images. Please refer to section 9.4 for further details.

5. Ancillary sub-studies

A number of sub-studies are running alongside the main study:

- Mechanistic studies
- Neuropsychology study
- Optical coherence tomography (OCT) study

As the assessments for these studies are integrated into the procedures for the main study, the details are included throughout the protocol and in study-specific guidance documents were necessary. A summary of the management of each study is provided below. Note that the data generated by each sub-study will be stored in the Prospect database at Sheffield CTRU (see sections 13 and 14 for details).

5.1 Mechanistic study

The mechanistic study is funded within the same award as the main trial i.e. UK NIHR Efficacy and Mechanism Evaluation (EME) Programme (project number 16/126/26) and it is led by Professor Paolo Muraro, Imperial College London. The samples will be analysed at Imperial College London and the derived data for use in the exploratory mechanistic studies will be entered into the Prospect database. Professor Muraro and his team will be responsible for the analysis of the data generated by the mechanistic studies with oversight by CTRU statisticians. At the end of the trial, samples will be stored for use in future research in a facility with an appropriate HTA licence.

5.2 Neuropsychology study

The neuropsychology study is funded by Sheffield Hospitals Charity (grant reference 171826) and it is led by Professor Annalena Venneri, Sheffield Teaching Hospitals. Study sites will be provided with a tablet computer in order for participants to complete the CANTAB assessments (see section 9.6). The results of the assessments will be entered into the Prospect database by site staff. CTRU statisticians will be responsible for the analysis of the data generated by the neuropsychology study with input from Professor Venneri and her team. As the neuropsychology study is not funded by the NIHR, it will not be included in the NIHR final report.

5.3 OCT study

The OCT study does not have any additional funding and this study is optional for sites as well as participants. The OCT study is led by Dr Simon Hickman and Professor Basil Sharrack, Sheffield Teaching Hospitals. OCT scans will be completed at participating sites using local equipment (see section 9.10). The results of the OCT scans will be entered into the Prospect database by site staff. CTRU statisticians will be responsible for the analysis of the data generated by the neuropsychology study with input from Dr Hickman and Professor Sharrack. As the OCT study is not funded by the NIHR, it will not be included in the NIHR final report.

6. Selection and withdrawal of participants

6.1 Patient identification

Site PIs will identify potential patients from the local population of patients with highly active relapsing remitting MS. A collaborative approach with neurologists and haematologists via the Trial Management Group (TMG) will support recruitment at all sites.

We aim to randomise 198 patients with highly active RRMS. We anticipate approximately 400 patients will need to be screened to achieve 198 eligible patients for randomisation to account for eligibility failure, participant decline rate and a small number of screen failures post-consent (i.e. assumes a 50% eligibility/decline rate).

6.2 Inclusion Criteria

1. Diagnosis of MS using the 2017 McDonald criteria (58).
2. Age 16-55 inclusive.

3. EDSS 0-6.0 inclusive*. If the EDSS score is 6.0 this must be due to confirmed relapse rather than progressive disease.
4. Severe inflammatory disease defined as RRMS course with 2 or more protocol defined relapses**, or 1 such relapse and evidence of MRI disease activity >3 months before or after its onset, in last 12 months despite being on a DMT*.
5. Clinical stability for >30 days following last relapse at the time of screening.
6. Satisfactory EBMT Autoimmune Disease Working Party (ADWP) recommended screening assessment prior to aHSCT (1)
7. Participants who have been reviewed by the central neurology team and confirmed as eligible.
8. Participants who, in the opinion of the local haematology lead or delegate, are fit enough to undergo treatment.
9. Able to undergo MRI examination

** Patients with EDSS scores of 0-1.5 or those who failed only first line treatments must also fulfil following criteria: short illness duration (<5 years), active disease clinically and radiologically (i.e. at least 2 relapses in the last 12 months and evidence of multiple Gad enhancing MRI lesion), high brain lesion load and brain or spinal cord atrophy* (2).

*** Relapse is defined section 4.2.1. Please note that when assessing eligibility an objective assessment of the relapse is preferred for inclusion in the trial (point 3 in section 4.2.1). However, if an objective assessment is not available, a detailed narrative of the relapse can be considered by the central team during the eligibility assessment.*

6.3 Exclusion criteria

1. Diagnosis of primary or secondary progressive MS.
2. Disease duration of >10 years from symptom onset (note: symptoms must be clearly attributable to MS).
3. Previous use of Alemtuzumab, Ocrelizumab or Cladribine.
4. Previous HSCT for any reason, or any previous experimental or commercial stem cell therapy.
5. JCV antibody Index of >1.5 in patients previously treated with natalizumab (unless they are CSF JCV PCR negative).
6. Prior diagnosis of Hepatitis B, Hepatitis C or HIV infection or current TB infection.
7. Pregnant or breast-feeding females.
8. Unwilling to use adequate contraception during the trial. Female participants of child-bearing potential must be willing to use adequate contraception for the duration of the trial (24 months), and for 12 months after discontinuation of Cyclophosphamide or Ocrelizumab, or 4 months after the last dose of Alemtuzumab. Male participants with female partners of child-bearing potential must be willing to use adequate contraception if they are randomised to the aHSCT arm during treatment and for at least six months following discontinuation (i.e. the last dose) of cyclophosphamide. See section 6.7 for more details.
9. Unable to comply with treatment protocol.
10. Contraindication to the use of Cyclophosphamide, G-CSF (Filgrastim or Lenograstim), or Rabbit ATG.
11. Participants with significant medical co-morbidity that precludes aHSCT as assessed by the local haematology team.
12. Significant language barriers, which are likely to affect the participant's understanding of the study, or ability to complete outcome questionnaires.
13. Concurrent participation in another interventional clinical trial.
14. AST and ALT >2.5 x upper limit of normal (ULN), bilirubin > 1.5 x ULN or direct bilirubin >ULN for participants with total bilirubin levels >1.5 x ULN

15. Current diagnosis of a clinically defined bleeding disorder (patients with platelet counts of $100x10^9$/l or above up to normal range are not excluded, as per section 18d. Persistently abnormal coagulation tests should be addressed to determine whether they constitute a defined bleeding disorder).
16. Current diagnosis of a clinically defined autoimmune disorder other than multiple sclerosis. (i.e. meeting full current international clinical and laboratory criteria for a specific autoimmune disorder).
17. Patients with history of myocardial infarction, angina pectoris, stroke or arterial dissection
18. Participants who are not considered medically fit for aHSCT defined by any of the following. Note that these criteria are not automatic exclusion criteria but if any of these criteria are met, and in the opinion of the PI the participant is medically fit enough to undergo aHSCT, the case may be put forward to the central team for discussion about eligibility:
    a. Renal: creatinine clearance <40ml/min (measured or estimated)
    b. Cardiac: clinical evidence of refractory congestive heart failure, left ventricular ejection fraction <45% by cardiac echo; uncontrolled ventricular arrhythmia; pericardial effusion with haemodynamic consequences as evaluated by an experienced echocardiographer
    c. Concurrent neoplasms or myelodysplasia
    d. Bone marrow insufficiency defined as neutropenia with an absolute neutrophil count $<1x10^9$/l, or thrombocytopenia with a platelet count $<100x10^9$/l, or anaemia with a haemoglobin <100g/l
    e. Diagnosis of hypertension, which is uncontrolled despite at least 2 anti-hypertensive agents
    f. Uncontrolled acute or chronic infection with any infection the investigator or central team consider a contraindication to participation (N.B. Baseline JC virus serology will be recorded, but positivity will not be an exclusion criterion).
    g. Other chronic disease causing significant organ failure, including established cirrhosis with evidence of impaired synthetic function on biochemical testing. This also includes known respiratory disease which, in the opinion of the local haematologist would represent a significant risk to the safe administration of aHSCT. Patients for whom there is concern about potential respiratory disease must undergo formal evaluation by a respiratory physician, including pulmonary function and blood gas measurement.

6.4 Informed Consent Process

Potential participants will receive an approved participant information sheet and be given the opportunity to ask questions from both the neurology and haematology specialist teams. Potentially eligible patients will be invited to provide their consent for the trial, including an eligibility review by the central team (see section 6.5). It will be made clear to potential participants that only those who have been approved for inclusion by the central team will be able to take part in the trial. Patients will have the opportunity to visit their local transplant centre, and also the opportunity to receive counselling from an independent clinician who is not a study investigator. Contact details for this independent clinician will be provided to the patient in the participant information sheet.

Patients will be given sufficient time to read and understand the information provided to them, and ask further questions as required. They will be advised that they are free to withdraw from the study at any time, without obligation, with no impact on subsequent clinical care. They will also be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for study purposes by authorised individuals other than the treating physicians. No study related procedures will occur before the approved consent form is signed, other than initial case note review by the referring clinician. As the study is a Clinical Trial of an Investigational Medicinal Product (CTIMP)

a medically qualified individual (site PI or other co-investigator who has been delegated this responsibility) will confirm eligibility and provide clinical oversight for the consent process. Consent will be taken by GCP accredited, appropriately trained and delegated medically qualified investigators. Patients who are unable to give informed consent will not be included in the study.

In addition, participants will be given the opportunity to consent for the following optional aspects of the trial:

- Blood sample collection for the mechanistic studies
- Blood sample collection and storage for future research
- Participation in the neuropsychology study
- Participation in the OCT studies.

Consent for all of these aspects of the study is optional and will not affect participation in the main study. (N.B. at a site level, participation in the OCT study is optional. Participation in all other sub-studies mentioned above is mandatory for all sites.)

In line with EBMT guidelines, participants will be asked to sign a local consent form confirming their understanding of the potential risks and benefits of aHSCT and agreeing to long-term safety and outcome data being collected in the EBMT registry (aHSCT participants only). The consultant haematologist undertaking aHSCT along with the study research nurse will supervise the latter process in line with Human Tissue Authority and JACIE requirements. The patient's GP will be informed as will their referring neurologist (if different from the PI). Patients are free to withdraw consent at any time with no impact on subsequent care. Wherever possible their reasons for withdrawing consent will be documented.

Participants will be informed that if they are allocated to the DMT arm, they may receive treatment with either Alemtuzumab or Ocrelizumab. This decision will be based on the participant's suitability for each drug based on current guidelines as well as clinician/participant preference.

For each participant, the original copies of the signed consent forms will be retained by the Investigator in the Site File but must be made available for inspection by relevant individuals in relation to the study. Patients will also receive a copy of the Participant Information Sheet and their signed consent form to keep, and a copy will be filed in their medical notes. Consent will be reconfirmed at each study visit and documented in the medical notes. A screening log will be maintained for each site, to document all potential participants screened, whether they were recruited, and any reasons for non-recruitment where this information is available.

6.5 Screening Procedures and Pre-randomisation Investigations

Consented patients will undergo screening and baseline assessments to ensure eligibility as per the Study Assessments Schedule in section 9.1. The potential participant should have the opportunity for a discussion with their local fertility team with regards to semen/oocyte/embryo cryopreservation, if appropriate.

Wash-out period

The required 'wash-out period' of current DMT must be confirmed. This will usually be a minimum of 6 weeks from the date of last administration (depending on local guidance)(59). This precaution aims to minimise a hypothetical risk of infectious complications (including that of PML) through sequential therapies. The central team can provide additional guidance on the requirements for washout as required. Unless indicated clinically, the wash-out will commence after the participant has consented to take part in the trial and been confirmed as eligible by the central team.

Note that steroids can be given throughout the wash-out period at the discretion of the treating clinician. Refer to Section 9.2 for further details on assessments and treatment for relapses.

Timing of screening and baseline assessments
Assessment of disease activity and screening blood tests should be completed within 8 weeks prior to randomisation. If the exact required screening tests have been taken for clinical reasons since the date of consent, these results can be used for the CRF. However, this must also take into account the window between assessment of disease activity and blood tests and randomisation as above.

Screening assessments will be completed prior to baseline assessments. When all screening assessments are completed, the participants' case details will be sent to the central neurology team for review. Baseline assessments will be completed only after eligibility has been confirmed by the central team.

Central review process
All potential participants will be reviewed centrally to determine suitability for the trial. This review will be completed by the lead neurologist or delegate (see **section** 6.5 for details) and the review will usually be completed via email correspondence. As part of the consent process, potential participants will be asked to agree for their non-identifiable clinical details to be shared with the central team for the purposes of eligibility review. The patient will also be informed that there is a possibility that they will not be able to take part in the study if the central team do not approve their eligibility.

All referrals of potentially eligible patients should include sufficient supporting clinical information. Further information may be requested if this is required to make the decision on eligibility. This may include anonymised clinic letters, hospital discharge summaries and MRI scan reports. All discussions around eligibility will be documented and these will be retained with the patient file. The review will take place after screening but prior to the baseline assessments being completed. The outcome of the central review of eligibility will be documented on the database and feedback will be provided to the site. If the potential participant is deemed ineligible after the central review, the site will inform the patient and the patient will be treated as per standard practice outside the trial.

In addition to the process above, it may be necessary for the central haematology team to review individual cases as per exclusion criterion 18 (section 6.3). If this review is required it will be completed by the lead haematologist or delegate and the review will usually be completed via email correspondence. The review will take place after screening but prior to the baseline assessments being completed. The outcome of this review will be documented on the database and feedback will be provided to the site.

Anonymised data on patients who are screened but not randomised will be collated, in line with the Consolidated Standard of Reporting Trials (CONSORT) guidelines.

6.6 Long term infertility
As expected of the normal standard of care, there should be a full discussion regarding the potential of the chemotherapy used in mobilisation and transplant leading to irreversible infertility and gonadal failure. Patients should be counselled and referred to local facilities for semen/oocyte/embryo cryopreservation if appropriate. Following transplantation, gonadal function should be assessed according to local SOPs and hormone replacement offered as appropriate.

6.7 Pregnancy & contraception
Patients are not eligible to take part in this trial if they are pregnant or breastfeeding at the time of screening. Pregnancy tests will also be performed within 7 days prior to mobilisation and within 7 days

prior to conditioning for those participants allocated the aHSCT intervention. Pregnancy tests will be performed within 7 days prior to treatment with Alemtuzumab and Ocrelizumab also. It is possible that if the treatment is given to a pregnant woman, it will harm the unborn child. Pregnant women must not therefore take part in this study; neither should women who plan to become pregnant during the study.

For the purposes of this trial, a woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. For the purpose of this document, a man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

Although the aHSCT regimen often results in infertility during this time, it is possible that women may become pregnant during the study follow-up period. All women who could become pregnant must use effective contraceptive measures during the course of this study, and for 12 months after discontinuation of Cyclophosphamide or Ocrelizumab, or 4 months after the last dose of Alemtuzumab. Recommended effective contraception is combined hormonal contraceptive (oral, intravaginal, transdermal) or progestogen-only hormonal contraceptive (oral, injectable, implantable) initiated at least one month prior to baseline, intrauterine device, intrauterine hormone-releasing system, vasectomised partner or bilateral tubal occlusion/ligation. This should be in addition to a barrier method, such as condom use. In the aHSCT arm, male participants with female partners of childbearing age, should practice true abstinence, or use a condom, along with their female partner using at least one of the measures described above during treatment and for at least six months following discontinuation (i.e. the last dose) of cyclophosphamide. Abstinence is acceptable only as true abstinence, when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception. The method(s) of contraception used must be stated in the patient medical notes.

Prior to entry into the trial, potential participants should be counselled about the importance of using adequate contraception for the duration of the study. If a female participant, or the female partner of a male participant becomes pregnant during the study they should inform their local research team immediately. See section 10.8 for details on the reporting procedure for pregnancy. Pregnant participants will continue to be followed up as per protocol. A specific information sheet and consent form will be used in order to gain consent to allow follow up until the end of the pregnancy for female participants and female partners of male participants.

6.8 Co-enrolment guidelines

Concurrent participation in any other interventional study is not allowed for the duration of the study (i.e. until the month 24 study visit). At the point of entry into the trial, patients should not already be taking part in an interventional trial.

6.9 Early stopping of protocol treatment

Given the patient population and the nature of the interventions (aHSCT, Alemtuzumab and Ocrelizumab), it is felt that withdrawal from either treatment group for medical reasons will be rare due to the clinical need for close monitoring and follow-up. As such there are no specific medical criteria for patient withdrawal. Any decision to withdraw a patient on medical grounds will be

discussed with the CI and lead neurologist or delegate(s) over email and/or teleconference. In the event that there are issues providing treatment as per the protocol this will not automatically require the participant to be withdrawn from trial treatment but should be discussed with the CI, lead neurologist or delegate(s). Details of discussions will be documented. However, patients may choose to withdraw from the trial at any time without prejudice to future clinical care; where possible the reasons for withdrawing will be recorded.

6.10 Switch to other treatment

Participants may be offered the opportunity to switch to the treatment given in the alternate arm to that which they were randomly allocated if they experience both a centrally verified protocol defined clinical relapse (see section 4.2.1) and at least one of the following 2 criteria: confirmed EDSS progression (see section 4.2.2) or evidence of MRI disease activity (defined as T1 Gd-enhanced lesion or new and/or enlarging T2 lesion) (see section 4.2.3).

In the DMT arm, switches to treatment will only be permitted after the 12 month follow up visit at which time patients would be expected to have received 2 courses of Alemtuzumab or 3 courses of Ocrelizumab. Potential participants must be made aware of this prior to consent. The new treatment must only be started following an appropriate washout period.

In the aHSCT arm, switches to treatment prior to the 12 month follow up visit must first be discussed with the central trial team. Switches to treatment after the 12 month follow up visit do not require the approval of the central team.

In the event that a participants switches treatment, all treatment will be documented in the patient notes and case report form. Participants will remain in the study for follow up as per the planned study schedule.

6.11 Early stopping of follow-up

Excessive participant withdrawal from follow-up has a negative impact on a study. Centres will explain the importance of remaining on study follow-up to participants, and that changes to planned treatment need not imply withdrawal from the study. Nevertheless, if participants do not wish to remain in the study their decision must be respected. If the participant explicitly states their wish not to contribute further data to the study, this will be recorded on a Study Completion/Discontinuation form. However, data up to the time of consent withdrawal will be included in the data reported for the study. This is made clear in the participant information sheet. Patients who have received a stem cell transplant as part of the trial, will be advised that they should continue with their clinical care in relation to this transplant, even if they no longer wish to contribute data to the study. Participants who stop study follow-up early will not be replaced.

7. Randomisation and enrolment

Prior to randomisation, all screening investigations will be reviewed by the local medically qualified investigator to confirm eligibility. This investigator will complete and sign the “Confirmation of Eligibility” form as documentation of this review.

Once eligibility has been confirmed and baseline data recorded, the participant will be randomly allocated to either the aHSCT arm with Cy/ATG conditioning (n=99) or the DMT arm (n=99). A member of the local study team will perform the randomisation by accessing a web-based randomisation system provided by the Sheffield CTRU (SCRAM). Patient details (ID, date of birth) will be entered and the treatment allocation will be returned. Randomisation will be completed using permuted blocks of

random size. This may be done using minimisation or stratified by centre, and baseline EDSS score (<=4.0 vs > 4.0). Full details will be contained in the statistical analysis plan.

Following randomisation, all patients must be given a patient contact card. Site on-call contact details for 24 hour medical care must be added to this card, and participants advised to carry this with them at all times whilst participating in the trial. 24 hour medical care will be provided via routine out of hours services i.e. trial-specific out of hours cover will not be required. It is likely that the out of hours contact details provided to sites will be different depending on the treatment allocation therefore care must be taken when completing the participant card to ensure the correct details are included. Participants must also be advised to contact site staff as soon as possible if they experience any symptoms of a relapse at any time during the study, including prior to treatment.

For participants randomised to the DMT arm, a decision will be made as to which DMT will be used, Alemtuzumab or Ocrelizumab. This decision will be based on the participant's suitability for each drug based on current guidelines as well as clinician/participant preference.

All participants will start trial treatment within 4 weeks of randomisation. The start of treatment in the aHSCT arm is the start of mobilisation and the start of treatment in the DMT arm is the first day of treatment with Alemtuzumab or Ocrelizumab. The timing of follow up visits will be calculated from the date of randomisation.

8. Trial treatment

In relation to COVID-19, sites must adhere to local Trust policies with regard to the operational management of patient treatment and follow up. Trial treatment will only be administered in line with current guidelines from the relevant agencies, including NICE, the Association of British Neurologists (ABN), the British Society of Blood and Marrow Transplantation and Cellular Therapy (BSBMTCT) and the European Society for Blood and Marrow Transplantation (EBMT).

8.1 IMP Details

The investigational medicinal products (IMPs) and non-investigational medicinal products (NIMPs) for this study will be sourced from local hospital stock within the participating centres. There are no requirements for trial-specific pharmacy involvement and local practices can be followed.

IMPs are the products in the study whose effects are being studied. NIMPs are products given to participants in the study to mitigate some of the effects of the IMPs. The drugs classified as NIMPs are standard supportive therapies but all trial patients must be treated according to the following schedule in order to isolate the effects of the IMP. The products used in the StarMS study, and their classification is stated in Table 2.

Table 1: Categorisation of each product in the StarMS trial.

Product	**Category**
Cyclophosphamide	IMP
G-CSF (Filgrastim*)	IMP
G-CSF (Lenograstim)	IMP
Rabbit ATG	IMP
Alemtuzumab	IMP
Ocrelizumab	IMP
Mesna	NIMP

Product	Category
Methylprednisolone	NIMP
Prednisolone	NIMP
Chlorpheniramine	NIMP
Paracetamol	NIMP
Pneumococcal conjugate vaccine	NIMP
Conjugate HIB (haemophilus influenza Type B) vaccine	NIMP
DTP (diphtheria, pertussis & tetanus) vaccine	NIMP
Inactivated polio vaccine	NIMP
Pneumococcal polysaccharide vaccine	NIMP

**Note: the use of Filgrastim biosimilars is acceptable however the protocol will only refer to Filgrastim throughout for consistency.*

8.2 Patients randomised to aHSCT

The aHSCT group will receive mobilization and conditioning regimens as used in the MIST trial, along with enhanced supportive care with appropriate prophylactic and therapeutic anti-microbial cover and intensive care support as required. Immunosuppressive therapy, including steroids, will be discontinued prior to mobilization. Venous access will obtained as per local routine practice, as appropriate.

Participants will be admitted to hospital during the conditioning phase, although depending on usual local practices, some sites may have facilities to carry out mobilisation as a day case, if hospital accommodation is available. Individual decisions will be made by the local investigators dependent on clinical and geographical factors.

Doses should be calculated using actual body weight, and actual m^2, unless otherwise indicated in this section. See section 8.2.2 for consideration if actual weight is larger than ideal weight for Cyclophosphamide in the conditioning regimen.

A pregnancy test will be carried out for all female participants of childbearing potential (see section 6.7 for definition), both prior to mobilisation, and prior to conditioning.

8.2.1 Mobilisation

Cyclophosphamide (IMP)

All participants in the aHSCT arm will undergo peripheral blood stem cell mobilisation. Participants will receive an infusion of Cyclophosphamide 2g/ m^2 from baseline date of mobilisation, to be given in line with local Trust procedures.

Mesna (NIMP)

Mesna will be given during the mobilisation phase with hydration, to prevent haemorrhagic cystitis caused by the chemotherapy. Dose and administration will be in line with local Trust procedures.

G-CSF (Filgrastim or Lenograstim) (IMP)

This is followed by G-CSF. Filgrastim or Lenograstim can be used depending on local practice. The guidance for each is provided below.

Filgrastim: 5-10µg/kg, rounded according to local practice to the nearest syringe or vial size, given subcutaneously and commencing on day +5 until the day of stem cell harvest.

Lenograstim: 5-10µg/kg/day given subcutaneously and commencing on day 5 until the day of stem cell harvest.

Stem cell harvest

Monitoring of full blood count and peripheral blood CD34+ counts will be carried out according to local standard practice, during the mobilisation phase. Participants will undergo stem cell harvest once peripheral blood CD34+ levels exceed $10x10^6$/L. This is expected to occur onwards from day 10 following Cyclophosphamide (and after 5 days Filgrastim or Lenograstim). Once achieved, apheresis will continue until a peripheral blood stem cell (PBSC) containing a minimum CD34+ count of 2.5 $x10^6$/kg has been obtained with a maximum of three apheresis procedures. In line with current guidelines, centres should aim for a target of 5 $x10^6$/kg. PBSC will undergo standard cryopreservation in accredited facilities and the final product will have a minimum CD34+ count of 2.0 $x10^6$/kg after processing. CD34+ selection will not be undertaken. Centres should allow for 10% wastage through quality assessment in this calculation.

The decision to admit the patient for the mobilisation and give the patient prophylactic antibiotics and other supportive care measures rests with the local supervising physician.

Requirements for mobilisation

Reharvesting may be permitted in instances of mobilisation failure, microbiological contamination of harvests and other issues influencing the scheduling of transplant, and will be documented on the CRF and in the patient's medical notes. Decisions will be made on an individual basis by the site Haematologist, in discussion with clinical coordinators. The central team should also be informed, as additional mobilising Cyclophosphamide and/or G-CSF may impact on outcomes. The use of lower dose or no Cyclophosphamide may be considered for patients in whom a second mobilisation regimen is attempted.

Summary of mobilisation regimen

The table below details the timing of doses of each product during the mobilisation phase.

Table 2: Timing of administration of IMP during mobilisation phase

Day	0	1	2	3	4	5	6	7	8	9	10	11
Cyclophosphamide $2g/m^2$	✓											
Filgrastim 5-10µg/kg or Lenograstim 5-10µg/kg						✓	✓	✓	✓	✓	✓	✓
Mesna (dose as per local practice)	✓											
PB CD34 count								✓**	✓	✓	✓	✓
Stem cell harvest								✓*	✓*	✓*	✓*	✓*

*Stem cell harvest is approximate, the day of this will depend on adequate Peripheral Blood (PB) CD34+ counts, as described in **8.2.1.** G-CSF will continue until apheresis is discontinued.

** Monitoring of PB CD34 counts is approximate, this will be carried out according to local standard practice

8.2.2 Conditioning

In order to avoid a theoretical risk of cumulative cardiac and other toxicities from Cyclophosphamide and to allow reporting of microbiological cultures prior to infusion of the stem cells, a minimum of three weeks must separate the administration of Cyclophosphamide for mobilisation and commencement of transplant conditioning. To benefit from the potential stabilising effect of the mobilisation Cyclophosphamide on MS activity the commencement of transplant conditioning should aim to occur within around 6 weeks of the date of administration of Cyclophosphamide for mobilisation, unless there are clinical reasons (such as infections) that should be discussed with the central team on an individual basis and treatment planned accordingly.

Participants will be required to go into en-suite isolation rooms (ideally with clean air facilities) during the conditioning and transplant procedure. This is made clear in the patient information sheet, and patients are reassured that visitors are still permitted, whilst in isolation.

Cyclophosphamide (IMP)
Cyclophosphamide 50mg/kg/day IV over 1 hour will be given in 500ml of normal saline on days -5 to -2. If actual weight is < ideal weight, Cyclophosphamide dose will be calculated based on actual weight. If actual weight > ideal weight, Cyclophosphamide dose will be calculated using adjusted weight. Please see Appendix A for an ideal weight table.

Ideal body weight (kg) (19)

Men: 50 + 0.91 x (height in cm - 152);
Women: 45 + 0.91 x (height in cm – 152)

Adjusted body weight

Ideal weight + 25% x (actual weight minus ideal weight).

The dose of Cyclophosphamide will be capped at 4g/day (or nearest dose banded equivalent). In cases where this is an issue due to dose banding, the dose will be agreed with the central study team (CI or delegate).

Mesna (NIMP)
Mesna will be given IV throughout the administration of Cyclophosphamide to prevent haemorrhagic cystitis. Dose and administration will be in line with local Trust procedures.

Supportive care
Standard hydration will be given throughout the administration of Cyclophosphamide, and diuretics will be used and fluids decreased as necessary to maintain baseline weight. Fluid balance must be monitored closely, with twice daily monitoring of weight and potentially electrolytes. Weight gain should not exceed 2kg above baseline. Sites should aim for electrolytes, especially sodium, potassium and magnesium, to be maintained well within the normal ranges. Any other medication usually given as part of normal supportive care during stem cell transplant will be prescribed and administered in line with local Trust practices.

Rabbit ATG (IMP)
Rabbit ATG (Thymoglobulin; Genzyme) doses will be given IV 0.5mg/kg on day -5, 1.0mg/kg on day -4 and 1.5mg/kg on day -3, day -2 and day -1. ATG will be given over a minimum of 10 hours. Administration will be as per local Trust practices and a test dose of ATG is permitted if this is standard

local practice. Please note that dose is given based on actual body weight. There is no adjustment for ideal body weight for Rabbit ATG.

Methylprednisolone (NIMP) (1g IV), Chlorpheniramine (NIMP), Paracetamol (NIMP)
Methylprednisolone 1g IV, Paracetamol PO or IV, standard dose as per local protocol, and Chlorpheniramine IV or oral, standard dose as per local protocol, given 30 minutes before infusion of Rabbit ATG. Ongoing cover with Paracetamol and Chlorpheniramine as needed.

Methylprednisolone will be given intravenously at 1g per day for five days to cover the five doses of ATG. After the fifth day, Methylprednisolone will be tapered as per local practice to cover febrile or other reactions due to ATG. A suggested tapering schedule is provided with table 4 below.

Foley catheter Guideline
Since neurogenic bladder with delayed emptying is common, a bladder scan will be completed prior to conditioning. A Foley catheter will be considered in patients with history of urinary retention or if indicated based on the bladder scan. The Foley catheter can be removed at the discretion of the clinician after completion of Cyclophosphamide

Stem cell reinfusion
Stem cells will be re-infused at day 0 according to local practice. In cases where it is necessary to re-infuse over a period of more than one day, this will be discussed and agreed with the central study team (CI or delegate).

Infection prophylaxis and treatment guidelines
Prophylactic broad spectrum antibiotics and tapering steroids, along with Paracetamol, will be given until neutrophil recovery to minimize fever (infective or ATG related), which has been previously associated with the Uhthoff phenomenon in MS (60). It is recommended that the antibiotics are administered IV from day 1 and continued for the duration of the period when neutrophil count is less than 0.5×10^9/L. Otherwise supportive care will follow institutional protocols.

G-CSF (Filgrastim or Lenograstim) (IMP)
Filgrastim or Lenograstim can be used depending on local practice. The guidance for each is provided below.

Filgrastim: 5-10µg/kg, rounded according to local practice to the nearest syringe or vial size, given subcutaneously and commencing on day 5 until absolute neutrophil count is $>1.0 \times 10^9$/L for 2 days.

Lenograstim: 5-10µg/kg/day given subcutaneously and commencing on day 5 until absolute neutrophil count is $>1.0 \times 10^9$/L for 2 days

Summary of conditioning regimen

Table 3: Timing of administration of IMP during conditioning phase

Day	**-6**	**-5**	**-4**	**-3**	**-2**	**-1**	**0**	**1**	**2**	**3**	**4**	**5**
Cyclophosphamide 50mg/kg/day*		✓	✓	✓	✓							
Mesna (dose as per local practice)		✓	✓	✓	✓							
Standard hydration (as per local practice)	✓	✓	✓	✓	✓	✓						
Rabbit ATG (Thymoglobulin; Genzyme) mg/kg/day		0.5	1	1.5	1.5	1.5						
Methylprednisolone (1g/day)		✓	✓	✓	✓	✓						
Paracetamol, Chlorpheniramine		✓	✓	✓	✓	✓						
Oral Prednisolone (mg/day) or IV Methylprednisolone (mg/day)**							60	60	60	40	40	20**
Stem cell reinfusion							✓					
G-CSF (Filgrastim or Lenograstim) (5-10µg/kg/day)												✓ (continued until absolute neutrophil count >1.0x10^9/L for 2 days)

* The dose of Cyclophosphamide will be capped at 4g/day as per the details in the text above.

**Prednisolone Guideline (this can be modified as necessary based on the opinion of the treating clinician): Prednisolone to prevent rATG fever is 60 mg/day for three days (day 0, 1, 2), 40mg/day for two days (day 3, 4), then 20 mg/day until engraftment, then 10 mg/day for two days, then stop or resume pre-transplant dose in patients where a prolonged taper is appropriate. Please see section 8.2.3 for further fever guidance. Dosing and administration of steroids is at the discretion of the treating physician and dependent on the individual patient's condition, but the doses should be documented on the participant's case report form to reflect their medication charts and medical records.

8.2.3 Fever guidance

If fever occurs despite Prednisolone, blood cultures will be drawn and broad spectrum antibiotics will be escalated according to local practice. Any fever >38C associated with ATG administration should be aggressively managed, additional pulses of intravenous Methylprednisolone (e.g. 250mg) with additional Paracetamol and Chlorpheniramine (IV or oral) may be given for ATG related fever according to the discretion of the treating physician. In addition, standard of care management for potential infection should be provided as appropriate.

8.2.4 Supportive care

Patients will receive standard supportive care measures according to EBMT and other current post-transplant guidelines, including late effects screening to 24 months (1,23,24,26,61,62). Supportive care should follow local standard operating procedures and is at the discretion of the transplant physician, but it is recommended that this should include prophylactic broad spectrum antibiotics (as detailed in 'Infection prophylaxis' section above), transfusion of platelets to maintain a platelet count of >20 $x10^9$/L, and transfusion of red cells to maintain a haemoglobin concentration of >80g/L.

Antifungal prophylaxis (according to site preference), and antiviral prophylaxis (e.g. aciclovir) (dose in line with local practice) should aim to continue from the start of conditioning for at least 3 and 12 months post-transplant respectively but may be modified as necessary at the discretion of the treating clinician. After stable engraftment, pneumocystis prophylaxis should commence and continue for at least 12 months, as per local policy (e.g. co-trimoxazole, nebulised pentamidine or atovaquone). All patients positive for anti-toxoplasma antibodies at pre-transplant workup should receive oral cotrimoxazole daily until day-1. Then after engraftment and reconstitution of blood counts they should receive the standard 3 times weekly cotrimoxazole prophylaxis, as tolerated, as per the pneumocystis prophylaxis schedule for 12 months. Other prophylactic antibiotics can be administered according to local policy (e.g. penicillin V).

CMV- and EBV-related disease are recognised, potentially fatal, but preventable, complications following autologous transplantation in patients with MS and active surveillance is mandatory.

For CMV reactivation, CMV Ab-positive participants should undergo CMV PCR screening for the first 100 days post-transplant, according to local standard operating procedures (SOPs) for allogeneic transplantation. As a minimum this should be weekly until day +60 and, if consistently negative, may be reduced to 2-weekly until day +100 post-transplant. Rising EBV PCR levels should be initially investigated according to clinician discretion and local protocols, usually with LDH levels and clinically appropriate imaging (e.g. CT scan, PET-CT scan, immunoglobulin, serum protein electrophoresis). Cases considered at risk of EBV-driven post-transplant lymphoproliferative disorder (EBV-PTLD) or other complications should be discussed with the TMG and/or clinical coordinators, irrespective of the EBV PCR level before administration of rituximab or other directed therapy, although treatment for symptom control may be administered in line with local clinical practice.

8.2.5 Vaccination

As routine standard of care based on EBMT and IDSA protocols (63) patients will receive pneumococcal conjugate vaccine at 3, 4 and 5 months, followed by conjugate HIB, DTP and inactivated polio vaccine at 6, 7 and 8 months and pneumococcal polysaccharide vaccine at one year. Table 5 summarises these standard vaccinations. A window of + 2 weeks will be permitted for vaccinations to occur.

Table 4: Standard vaccinations following stem cell transplant.

Vaccination	Months after stem cell transplant											
	1	2	3	4	5	6	7	8	9	10	11	12
Pneumococcal conjugate			✓	✓	✓							
Conjugate HIB (Haemophilus influenza type b)						✓	✓	✓				
DTP (diphtheria, pertussis & tetanus)						✓	✓	✓				
Inactivated polio						✓	✓	✓				
Pneumococcal polysaccharide												✓

All patients who are not on immunosuppressive therapy will have serology for measles and varicella tested at 24 months (as per routine policy). All those who are negative will be immunised with 2 doses of MMR and varicella vaccine at least 4 weeks apart as per routine practice. Patients will have an annual Influenza vaccine.

Vaccinations will be carried out according to local practice at each site, which is likely to be by primary care teams. However, it is important that the vaccinations occur at the timings specified in this study protocol ("due" date + 2 weeks), and that these are recorded for the immune reconstitution analysis.

Participants will be provided with a vaccination proforma which they should take to their GP or Nurse to record the dates and batch number of each vaccination. Participants will be asked to bring this proforma with them to the next study visit after these vaccinations, and the Research Nurse will transfer the information to the study database.

Participants will also be provided with information regarding the need for other vaccines as part of recommendations for general population and occupational health needs (e.g. hepatitis B vaccine), as well as vaccination for other members of their household. Their treating Haematologist will provide full information as to which vaccinations may be required, and the timing for these.

(As indicated below, serum samples will be taken and frozen for the planned Mechanistic Immune Reconstitution at baseline and 3, 6, 9, 12, and 24 months).

8.2.6 Long Term Screening following aHSCT

See table 5 for suggested long term screening for late effects of HSCT.

Table 5: Suggested long term screening for late effects of HSCT, assessed as part of standard care following a stem cell transplant (timing for follow-up is from randomisation)

Recommended timing of assessment	**Baseline**	**3 months**	**6 months**	**1 year**	**2 years**
General					
Weight*	1	1	1	1	1
Blood pressure*	1	1	1	1	1
Performance status (Karnofsky/Lansky)	1	1	1	1	1
Haematology					
FBC*	1	1	1	1	1
Renal					
Renal function*	1	1	1	1	1
Urine protein (dipstick)*	1	1	1	1	1
Liver					
Liver function*	1	1	1	1	1
Haematinics (iron, B12, folate)	1		1	1	1
Endocrine					
Thyroid function TSH, Free T4	1	1	1	1	1

Recommended timing of assessment	Baseline	3 months	6 months	1 year	2 years
Gonadal function FSH, LH, oestradiol, Progesterone, menstrual history (last menstrual period and typical cycle documented as length of period over 28 days) (not applicable to post-menopausal women) FSH, LH, Testosterone (men)	1	1	1	1	1
Bone					
Bone profile	1	1	1	1	1
Respiratory					
Clinical assessment	1	1	1	1	1
Pulmonary function testing*	1			1	1
Chest x-ray*	1		**	**	**
Vascular					
Echocardiogram*	1			1	1
HbA1c*	1		1	1	1
Lipid profile *	1		1	1	1
Immune System					
CD3/4/8/19/56 subsets	1	1	1	1	1
Immunoglobulin levels and serum protein electrophoresis.	1*	1	1	1	1
Infection assessment based on inpatient admission for infection.*	1	1	1	1	1
Ocular					
Cataracts assessment (clinical/opticians)	1			1	1
New cancers					
New cancers				1	1
Second autoimmune diseases					
Second autoimmune diseases				1	1

* = to be completed as part of the trial procedures. Refer to the study assessments schedule for full details

1 = recommended for all transplant patients

** = reassessment recommended if previously abnormal

8.3 Patients randomized to comparator DMT arm (control group)

After randomisation to the DMT arm, a decision will be made to treat the participant with Alemtuzumab or Ocrelizumab. This decision will be based on the participant's suitability for each drug based on current guidelines as well as clinician/participant preference.

8.3.1 Alemtuzumab

Alemtuzumab administered by IV infusion over 2 treatment courses:

1. 12 mg/day on 5 consecutive days
2. 12 mg/day on 3 consecutive days, 12 months later (administered & monitored as per license).

Standard supportive care will follow institutional protocols.

A pregnancy test will be carried out for all female participants of childbearing potential (see section 6.7), within 7 days prior to the start of both treatment courses of Alemtuzumab.

Liver function tests must be performed before initial treatment with Alemtuzumab and at monthly intervals until at least 48 months after the last infusion of Alemtuzumab. Between study visits, liver function tests can be completed as per usual local arrangements e.g. via the GP. In this case, study teams must ensure there is a mechanism by which they can check that tests have been completed and review the results. The review must be documented in the participant notes.

Blood tests to check the platelet count must be conducted immediately after the infusion of Alemtuzumab on Days 3 and 5 of the first infusion course, as well as immediately after infusion on Day 3 of any subsequent course of Alemtuzumab.

Administration and monitoring for Alemtuzumab will be in accordance with latest available guidelines. Refer to the latest guidance from EMA and GOV UK for details.

8.3.2 Ocrelizumab

Ocrelizumab administered and monitored as per license by IV infusion as follows:

- Initial dose – 600mg administered as two separate intravenous infusions; first as a 300mg infusion, followed 2 weeks later by a second 300mg infusion
- Subsequent doses – a single 600mg infusion every six months. The first subsequent dose should be administered six months after the first infusion of the initial dose. A minimum of 5 months should be maintained between each dose.

Standard supportive care will follow institutional protocol.

A pregnancy test will be carried out for all female participants of childbearing potential (see section 6.7, within 7 days prior to each dose of Ocrelizumab.

8.4 Dispensing

With the exception of ATG, Alemtuzumab and Ocrelizumab this study does not mandate the use of a specific brand of each IMP. Due to the small numbers of participants overall at each site, all IMPs and NIMPs will be taken from local hospital stock. Note that the vaccinations (NIMPs) may be provided by primary care teams in line with local site practice. However, please note that IMPs must be sourced from the EU. In the event that the UK leaves the EU, it is acceptable for IMPs to be sourced from the UK or the EU. Labels for IMPs will not be required as all IMPs:

- Have a marketing authorisation in the UK, and
- Are dispensed to a trial participant in accordance with a prescription given by an authorised healthcare professional, and
- Are labelled in accordance with the requirements of Schedule 5 of the Medicines for Human Use (SI1994/3194) Regulations that apply in relation to dispensed relevant medicinal products, and
- Are being used within the terms of their marketing authorisation, or are used in routine practice as supported by published evidence (19,64).

Dispensing will therefore be done in accordance with local procedures and there is no requirement for trial-specific prescriptions or labelling.

In this study, SmPCs replace the Investigator's Brochure (IB) and IMP dossier, and this is reviewed annually and updated as required. The specific SmPCs used for the IMPs in this study are as follows:

- Cyclophosphamide 1000 mg Powder for Solution for Injection or Infusion
- Neupogen 30 MU (0.3 mg/ml) solution for injection (Filgrastim)
- Granocyte 13 million IU/mL, powder and solvent for solution for injection/infusion (Lenograstim)
- Thymoglobuline 25 mg powder for solution for infusion (Rabbit ATG, Genzyme)
- Lemtrada 12 mg concentrate for solution for infusion (Alemtuzumab, Genzyme)
- Ocrevus 300mg concentrate for solution for infusion (Ocrelizumab, Roche)

8.5 Accountability

Specific trial accountability recording for IMPs and NIMPs is not required although a record of administration will be kept. All IMPs in StarMS are being used within the terms of their marketing authorisation, or are used in routine practice as supported by published evidence (19,59). Local prescribing practices and general site pharmacy stock will be used.

8.6 IMP and NIMP storage and destruction/disposal

All IMPs and NIMPs will be obtained from local stock therefore there is no requirement for segregated storage. There are no specific requirements for temperature monitoring within the trial therefore this will be completed as per the local standard practice at each site.

There are no specific requirements for IMP and NIMP destruction/disposal as part of the StarMS trial. Sites will follow local standard practice.

8.7 Adherence

As the trial treatment is administered by clinical staff, there is no opportunity in this trial for patient-related non-adherence. Records will be maintained in the CRF and in the patient's medical notes to document that doses and regimens are correctly administered.

8.8 Dose Modifications and Interruptions

Except for dose adjustment and capping of Cyclophosphamide (see section 8.2.2) no formal dose capping will be used as there is reportedly insufficient pharmacokinetic data to suggest that a full weight-based dosing schedule for chemotherapy agents in obese patients should not be used (65). Dose banding is permissible according to local pharmacy policy.

All other dose modifications or interruptions require approval from the lead Haematologist (or deputy), and this must be documented on the CRF and in the patient's medical notes.

Although considered unlikely, participants experiencing adverse events relating to an IMP or NIMP used in the study, which are not tolerable, will have this medication discontinued. This may result in a participant being unable to receive the planned intervention, depending on the reaction, and which product this relates to. Any decision to discontinue the study medication would be made by the local investigator and documented.

8.9 Overdose of Study Treatment

An overdose of study treatment is considered unlikely in this study, as participants will be in hospital at the time of receiving medication. In the unlikely event of an error in the dose calculation or administration of the study products, this will be reported to the CTRU and the Sponsor as a protocol

non-compliance, as soon as it is identified. This is likely to be assessed as major non-compliance, and the Sponsor will advise on the appropriate action to be taken. The incident will also be reported through normal local Trust reporting procedures.

All medications taken by the participant will be recorded in the CRF, including dosage information, where specified, or overdose.

8.10 Concomitant Medications

All patients must washout of their current DMT prior to starting trial treatment, as per section 6.5.
Participants should not have received live vaccines for at least 6 weeks prior to starting treatment with Alemtuzumab or Ocrelizumab. Live vaccines should not be administered during the study in participants treated with Alemtuzumab. Live vaccines should not be administered to participants treated with Ocrelizumab until B-cell repletion occurs.

Anti-platelet or anti-coagulant therapy is prohibited other than when given:

a) As routine standard-of-care thromboprophylaxis e.g., during inpatient admission and/or bed rest, to cover an in-situ central venous catheter or other device for vascular access, or required for surgical or other procedures, as per organisational protocols
b) In the clinically indicated treatment of a venous thromboembolic event or other indication for therapeutic anti-coagulant or anti-platelet therapy arising during the trial.

Such events will be appropriately reported and patients assessed on an individualised basis, and would not automatically exclude patients from continuing on the trial protocol treatment and follow up. The nature, dose and duration of anti-platelet and/or anti-coagulant therapy will be documented, along with any details of effect on trial drug administration and/or follow up. The latest version of the Alemtuzumab SmPC will be followed.

In order to protect against temporary liver function test abnormalities, azoles used for antifungal prophylaxis should be withheld until Cyclophosphamide conditioning has been completed.

Participants are permitted to continue on any other medications they may be taking for conditions other than MS, for the duration of the trial. Participants will be monitored for fluid and electrolyte balance during the aHSCT regimen, as they would in standard care.

Any changes to concomitant medications will be documented on the CRF at each study visit.

9. Assessments and procedures

Figure 1: Study flow chart – Screening, Randomisation and Treatment

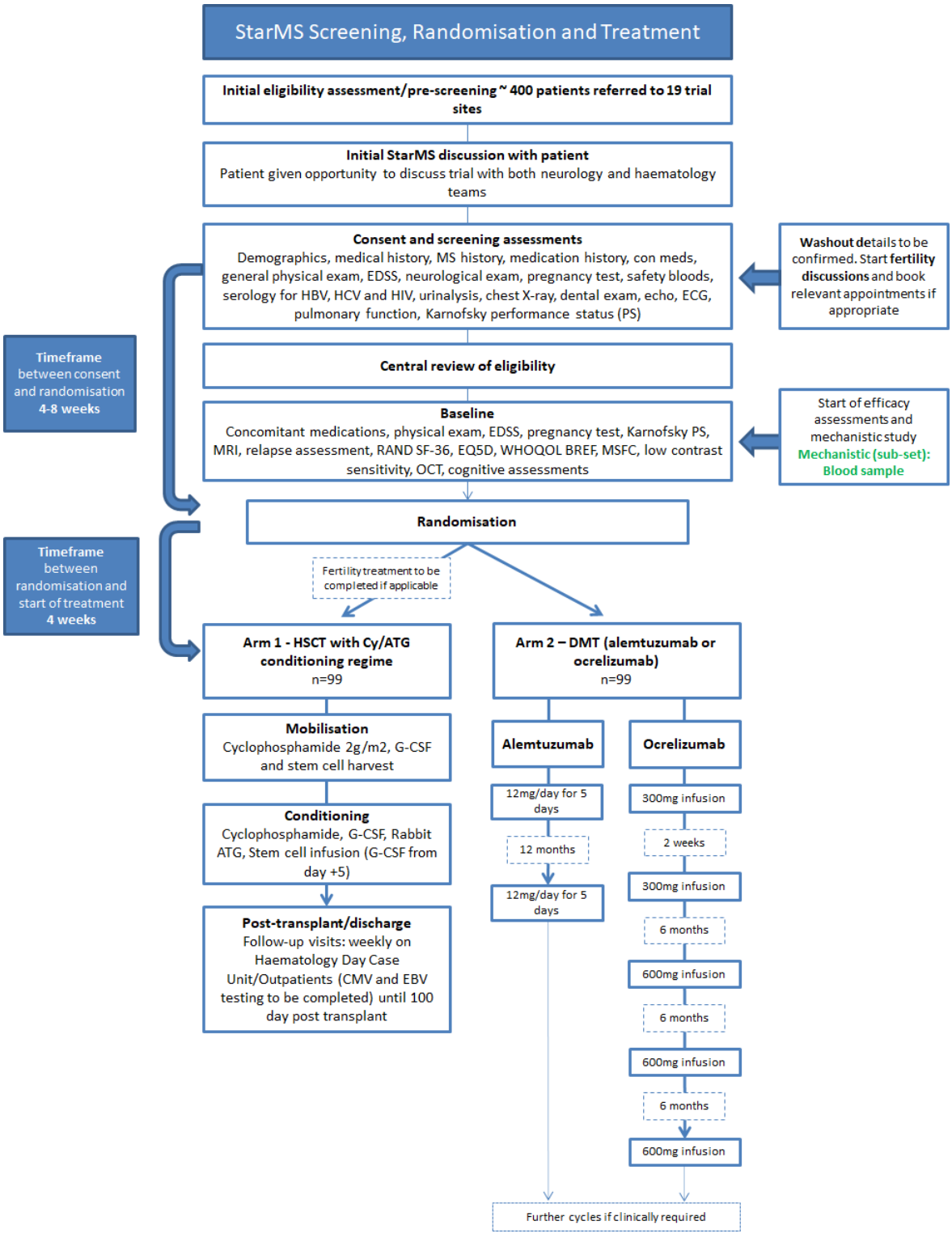
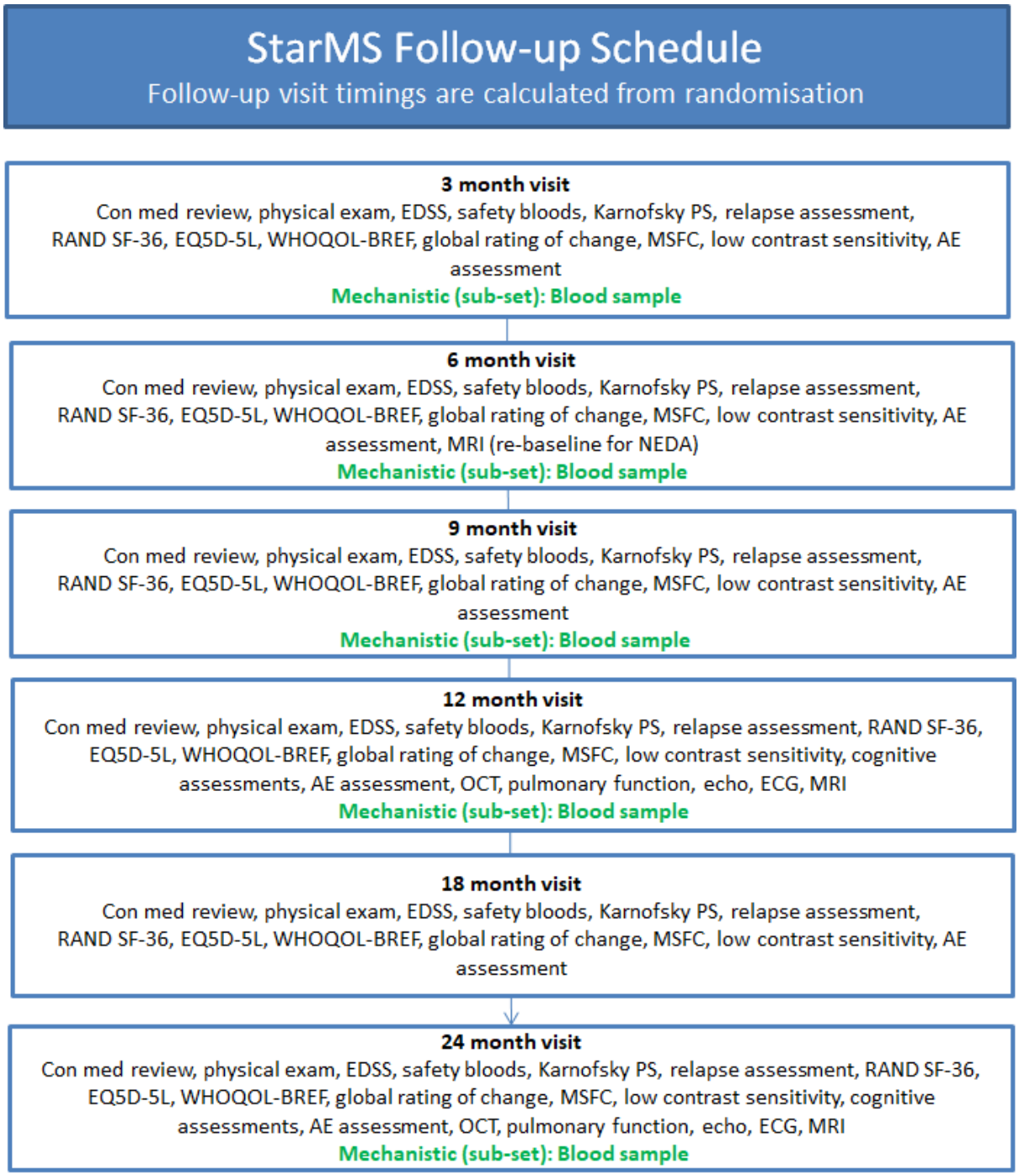


Figure 2: Study flow chart – Follow up



9.1 Study Assessment Schedule

The study assessment schedule below details the assessments required during the course of the study. All participants will undergo these assessments regardless of which treatment arm they are randomised to, unless otherwise indicated. Follow up visit timings will be calculated from the date of randomisation. A window of +/- 2 weeks is permitted for each study visit to take place. Where it is impossible to schedule the visit within this window, e.g. due to patient availability, the site will contact CTRU for advice.

Following stem cell transplant, patients will be required to attend hospital between the study visits below. These additional visits will be as per routine practice following stem cell transplants, and will allow ongoing safety monitoring following the procedure.

Table 6: Study assessments table

Assessments	Screening[1]	Baseline[2]	aHSCT procedure or Alemtuzumab or Ocrelizumab	Month 3	Month 6	Month 9	Month 12	Month 18	Month 24	Relapse visit[3]
Consent	✓									
Eligibility assessment	✓	✓								
Demographics	✓									
General Medical History	✓									
Smoking History	✓									
MS History	✓									
Medication history	✓									
Concomitant medications	✓	✓		✓	✓	✓	✓	✓	✓	✓
General Physical Examination	✓	✓		✓	✓	✓	✓	✓	✓	✓
Expanded Disability Status Scale (EDSS)[3]	✓	✓		✓	✓	✓	✓	✓	✓	✓
Neurological examination	✓									
Washout	✓									
Fertility discussions[4]	✓									
Pregnancy test[5]	✓	✓								
Safety bloods[6]	✓			✓	✓	✓	✓	✓	✓	✓
Viral and other serology screen[7]	✓									
Clotting screen	✓									
Blood TB test[8]	✓									
Immunoglobulin and serum protein electrophoresis	✓									
Urinalysis	✓									
Chest x-ray	✓									
Dental exam	✓									
Echocardiogram	✓						✓		✓	
ECG	✓						✓		✓	
Pulmonary function[9]	✓						✓		✓	

Assessments	Screening[1]	Baseline[2]		Month 3	Month 6	Month 9	Month 12	Month 18	Month 24	Relapse visit[3]
Performance status (Karnofsky)	✓	✓		✓	✓	✓	✓	✓	✓	
Central eligibility review[10]	✓									
MRI		✓[11]			✓		✓		✓	✓[12]
Relapse assessment[3]		✓		✓	✓	✓	✓	✓	✓	✓
RAND SF-36		✓		✓	✓	✓	✓	✓	✓	
EQ5D		✓		✓	✓	✓	✓	✓	✓	
WHOQOL- BREF		✓		✓	✓	✓	✓	✓	✓	
Global Rating of Change				✓	✓	✓	✓	✓	✓	
Multiple Sclerosis Functional Composite (MSFC)[3]		✓		✓	✓	✓	✓	✓	✓	
Low contrast sensitivity[3]		✓		✓	✓	✓	✓	✓	✓	
Randomisation		✓								
Adverse events	✓	✓		✓	✓	✓	✓	✓	✓	✓
Optional sub-studies:										
Cambridge Neuropsychological Test Automated Battery (CANTAB)		✓					✓		✓	
Brief International Cognitive Assessment for MS (BICAMS)		✓					✓		✓	
Optical Coherence Tomography		✓					✓		✓	
Serum sample – mechanistic studies[13]		✓		✓	✓	✓	✓		✓	✓
Anticoagulated whole blood sample for mechanistic studies		✓		✓	✓		✓		✓	✓
For participants in aHSCT arm only:										
Adherence to re-vaccination policy					✓	✓	✓	✓	✓	

1. Screening assessments will be completed to ensure the patient is eligible for the study, prior to the baseline assessments being performed.
2. Baseline assessments will be completed as close to randomisation as possible after completing the screening assessments and before completing the randomisation process.

3. To be completed by a blinded member of staff. Where possible, the same member of staff will complete all blinded assessments for an individual participant throughout their time in the study. Participants will wear an appropriate head covering during these evaluations. Participants will be instructed not to tell the evaluating member of staff which type of treatment they have been allocated.
4. Fertility discussions and appointments must be booked as soon as possible after consent. For participants allocated to aHSCT, who wish to undergo fertility treatment, this will be completed within the 4 week window from randomisation to starting treatment.
5. For women of childbearing potential a pregnancy test will be repeated prior to conditioning and mobilisation in the aHSCT arm, and prior to each dose of treatment for patients receiving Alemtuzumab or Ocrelizumab.
6. FBC, biochemistry – to include a thyroid function test, non-fasting glucose test and lipid profile. HbA1c (to be included if done as standard). Note: participants allocated to receive Alemtuzumab must have liver function tests before initial treatment and at monthly intervals until at least 48 months after the last infusion of Alemtuzumab. Participants allocated to receive Alemtuzumab must also have blood tests to check the platelet count immediately after the infusion of Alemtuzumab on days 3 and 5 of the first infusion course, as well as immediately after infusion on day 3 of any subsequent course of Alemtuzumab.
7. To include HBV, HCV, HIV, EBV, CMV, HSV 1 and 2, VZV, HTLV 1 and 2, anti-toxoplasma and JC virus as per standard local protocols.
8. Screening blood test to include blood TB test
9. To include FEV1 (forced expiratory volume in 1 second), DLCO (carbon monoxide diffusion in the lung), FVC (forced vital capacity) and o_2 saturation.
10. The central neurology review and central haematology review (if applicable) should take place as soon as possible after screening, and prior to baseline assessments, to allow further evaluation as required. Randomisation must not take place until all screening and baseline assessments have been completed and the central team have confirmed that the participant is eligible for the study.
11. The maximum time permitted between the scan at baseline and randomisation is 8 weeks. If there are any delays then the scan should be repeated if at all possible. It is also recommended that there is a low threshold for repeating the scan if there are any clinical concerns.
12. If a relapse is suspected, an MRI should be completed as per the protocol requirements if possible.
13. As samples will be shipped via Royal Mail, please consider shipping times when scheduling appointments requiring samples for the mechanistic studies. Where possible, avoid scheduling these appointments on Thursday afternoons and Fridays.

Assessments post 24 months: aHSCT patients are routinely followed for clinical and MRI disease activity, disability progression and late adverse events annually. Data will be collected on site using the MED B and stored on the BSBMT/EBMT PROMISE database (and/or its successor registry system). Although this will be completed through routine data collection and reporting, additional funding and support will be sought to ensure completeness and analyse the dataset.

9.2 Relapse visits

All relapses must be reported to the research teams immediately. Relapses occurring during the trial must be confirmed by an independent member of staff who is blind to treatment allocation, ideally within 3 days from the onset of symptoms and a maximum of 5 days from onset. This may be completed at a scheduled study visit if the relapse occurs within a few days before the visit or at an unscheduled visit where a full clinical neurological examination will be performed with EDSS scoring followed by MRI if feasible.

Treatment for relapses will be according to local routine practice. It is recommended that participants are treated with IV Prednisolone 1g per day for 3 days or oral Methylprednisolone 500mg per day for 5 days, without oral tapers.

9.3 Unscheduled visits

Participants' local care team may also be part of the research team for StarMS. Therefore, participants may be seen at additional visits outside those scheduled for the study, but these visits would be part of usual care. Any adverse events identified at additional usual care visits will be documented in the CRF.

9.4 Procedures for Assessing Efficacy

NEDA status is defined as the absence of all three of the following: 1) protocol defined relapses (see section 4.2.1); 2) 6 months confirmed EDSS progression of at least 1 point (see section 4.2.2); 3) any evidence of MRI disease activity as defined by T1 Gd-enhanced lesion and/or enlarging T2 lesion after month 6 (see section 4.2.3). In order to assess NEDA status, clinical and radiological examinations will be performed at relevant study visits as per table 6.

All neurological assessments during follow up must be completed by an independent member of staff who is blind to treatment allocation.

Expanded Disability Status Scale (EDSS)

Disability progression will be assessed using EDSS as per the study assessments schedule in section 9.1. EDSS must be completed by a delegated member of staff with neurostatus certification.

MRI

MRI scans will be undertaken according to standard clinical protocols, using at a minimum, a 1.5T scanner using a single dose gadolinium contrast. MRIs will be undertaken at baseline and at months 6, 12 and 24 for all participants. These scans will be assessed centrally by expert physicians at UCL who will be unaware of the treatment allocation and will perform MRI analysis using anonymised electronic copies of appropriate images. Further details, including information on transfer of scan images to UCL, will be provided in a study-specific guidance document.

Optimal MRI acquisition protocol:

- Whole brain coverage
- Pre gadolinium 3D volumetric T2 weighted FLAIR
- Pre gadolinium 3D volumetric T1 weighted
- Post gadolinium 2D T1 weighted spin echo, contiguous 3mm slices

Local site arrangements and procedures may not allow for the optimal protocol to be acquired. In those cases, the local protocol must include at least:

- Whole brain coverage
- 2D T2 weighted FLAIR or T2 weighted fast/turbo spin echo
- 2D post gadolinium T1 weighted spin echo

Relapse assessment

Participants will be assessed at each visit for any evidence of a new relapse. If a relapse is suspected, further assessments will be completed as per the 'relapse visit' on the study assessments table. The number of relapses will be documented.

9.5 Procedures for Assessing Disability

Multiple Sclerosis Functional Composite (MSFC)

Three variables are recommended for as primary measures in a MSFC:

1. Timed 25-foot walk (a quantitative measure of lower extremity function)
2. 9-Hole Peg Test (9-HPT) (a quantitative measure of upper extremity (arm and hand) function)
3. Paced Auditory Serial Addition Test (PASAT) (a measure or cognitive function that specifically assesses auditory information processing speed and flexibility, as well as calculation ability).

The various components of the MSFC should be administered by one member of the study team during a single study visit. The full procedure for the MSFC is detailed in a study-specific guidance document.

Low contrast sensitivity

Binocular vision will be assessed using the low contrast Sloan letter chart (66) as per the study assessment schedule. The full procedure for testing low contrast sensitivity will be detailed in a study-specific guidance document.

9.6 Procedures for Assessing Safety

Safety assessments will be performed as detailed in the study assessment schedule in section 9.1.

Following an EMA restriction placed on Alemtuzumab in May 2019, the drug is now subject to restrictions when prescribing for new patients, and new monitoring requirements have been published. Please refer to the latest guidance from EMA and GOV UK to ensure that the monitoring requirements are adhered to as necessary.

Adverse events and long term safety evaluation

All adverse events will be recorded in the medical notes and the case report form. Refer to section 10.1 for the definition of an adverse event and details on how these are to be reported. Adverse events will be recorded throughout the mobilisation and conditioning period and at every visit after that time until the participant's involvement in the trial ends. Long term safety evaluations will include significant infections, endocrine and reproductive dysfunction, secondary autoimmune diseases, incidence of late cardiovascular events, neoplasia and any other significant organ dysfunction, up to 24 months for all patients.

If there are any clinical concerns about a participant, identified through any of the research procedures or assessments, these will be referred to the appropriate clinical team for further investigation. This includes abnormal blood results, responses to questionnaires that cause concern about the participant's wellbeing, and any other concerns aside from the expected course of MS.

It is anticipated that a treatment-related death would result in immediate convening of the DMEC and review of safety data. This will be discussed and agreed with the DMEC at the study outset and documented in the DMEC charter.

General physical examination
A full physical examination will be performed by the investigator including assessment of skin, lymph nodes, blood pressure, heart rate, temperature, height (screening only), weight, oral inspection, lung/heart/abdominal examination.

Safety bloods
Safety bloods will be taken as per the study assessment schedule and processed locally by the participating site. Blood tests will include the following: FBC, biochemistry, thyroid function test, lipid profile, (HbA1c if done as standard)

ECG
To be completed locally and reported with details of any abnormalities.

Echocardiogram
To be completed locally. The assessment will include left ventricular ejection fraction and details of any abnormalities.

Pulmonary function
Pulmonary function assessment will include will include FEV1 (forced expiratory volume in 1 second), DLCO (carbon monoxide diffusion in the lung), FVC (forced vital capacity) and o_2 saturation.

9.7 Procedures for Assessing Quality of Life

The following questionnaires will be completed as per the study assessment schedule to assess quality of life:

- RAND SF-36 (55)
- EQ-5D-5L (54)
- WHOQOL-BREF (56)
- Global rating of change (57)

Analysis of this data in relation to cost effectiveness is not currently part of this study protocol.

Questionnaires will be provided in print to the participant for self-completion. Data from the paper questionnaires will be entered onto the study database by the local research team. At the time of completion, questions may be clarified for the participant if the question is not understood, but the researcher will not provide any bias towards any of the answer options.

9.8 Procedures for Assessing Cognitive Function

Cognitive function will be assessed via the Cambridge Neuropsychological Test Automated Battery (CANTAB) and the Brief International Cognitive Assessment for MS (BICAMS) for participants who have provided consent for this optional sub-study. The CANTAB will be administered using a tablet computer which will be provided to participating sites for this purpose. Specific training on the use of the CANTAB will be provided. The results from the CANTAB will be entered in the case report form by site staff. The BICAMS includes three cognitive assessments which participants will be asked to complete on paper. The results from the BICAMS assessments will be entered in the case report form by site staff. Specific training on the use of the BICAMS will be provided.

9.9 Procedures for Mechanistic studies

Samples for mechanistic studies will be collected from participants who have provided consent for this optional sub-study. Sites will collect the samples according to a sample collection manual and the samples will be shipped to the Imperial College London, Wolfson Neuroscience Laboratories for analysis. Whole blood will be collected in TransFix/EDTA Vacuum Blood Collection Tubes and shipped by Royal Mail Safebox at ambient temperature.

9.10 Procedures for OCT study

OCT scans will be performed as per the study assessments schedule. These scans will only be performed at sites that have signed up for this sub-study and for patients who have provided optional consent. Full details on the procedures required for the scans will be provided in a detailed study-specific guidance document.

9.11 Additional Procedures for aHSCT arm

All aHSCT participants will be entered onto the EBMT registry with yearly data collection by the MED-B form. This form will collect annual follow up of efficacy (NEDA) and late adverse events.

9.12 Participant Withdrawals

Participants may wish to withdraw from study treatment, or there may be a clinical need to withdraw the participant (see section 6.9). Participants withdrawing from the aHSCT arm prior to stem cell re-infusion and participants withdrawing from Alemtuzumab or Ocrelizumab treatment will be followed up at subsequent time points as per the protocol, unless they withdraw from the trial (see below). Participants will be considered as having received aHSCT if they receive the stem cell transplant on Day 0 and they are informed in the participant information sheet that they must continue with the clinical care required following this treatment.

Participants may withdraw their consent for the study at any time, without providing a reason for this. If this occurs, this will be documented on a study completion/discontinuation form and the patient notes, and no further data will be collected for this participant for the study. If a participant does volunteer a reason for their withdrawal of consent, this will be documented on the form. Any data collected up to the point of the participant's withdrawal will be retained, and used in the final analysis, and this is made clear to the patient at the time of consent.

9.13 Loss to Follow-up

Participants will be defined as lost to follow up if they do not attend or contribute data at the month 24 visit. If a participant is lost to follow up, this will be recorded in the CRF using the study completion/discontinuation form.

9.14 Site and study closure procedures

The end of the trial is defined as the end of the grant funding period, assuming that this is after last patient last visit (LPLV), to allow for ongoing study sample analysis. Where LPLV occurs after the end of the grant funding period the end of trial will be defined as LPLV. Sites will be closed once data cleaning is completed, after LPLV.

10. Safety Reporting

ICH-GCP requires that both investigators and sponsors follow specific procedures when reporting adverse events/reactions in clinical studies. These procedures are described in this section.

For this study, the products have been categorised as either Investigational Medicinal Product (IMP), or Non-Investigational Medicinal Product (NIMP) (see section 8.1). NIMPs are medicinal products which are not the object of investigation, but which are specified in the protocol. These include any specified medicinal product given to participants to mitigate the effects of an IMP, or support/rescue medication.

10.1 Definitions

The definitions of the EU Directive 2001/20/EC Article 2 based on the Principles of ICH-GCP apply to this protocol. These definitions are given in Table 7 below.

Table 7: Definitions of Adverse Events and Reactions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical study patient to whom a medicinal product has been administered irrespective of relationship
Adverse Reaction (AR)	Any AE that is judged, in the opinion of the PI, to be related to an investigational medicinal product or is the result of an interaction between an investigational medicinal product and a non-investigational medicinal product.
Unexpected Adverse Reaction (UAR)	An adverse reaction, the nature or severity of which is not consistent with the information about the medicinal product in question set out in the Summary of Product Characteristics (SmPC).
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR)	Respectively any adverse event, adverse reaction or unexpected adverse reaction that: • Results in death • Is life-threatening* • Requires hospitalisation or prolongation of existing hospitalisation** • Results in persistent or significant disability or incapacity • Congenital anomaly/birth defect • Is another important medical event***

*The term life-threatening in the definition of a serious event refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event that hypothetically might cause death if it were more severe, for example, a silent myocardial infarction.

**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, that has not worsened or for an elective procedure do not constitute an SAE.

***Other important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event/experience when, based upon appropriate medical judgement, they may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

10.2 Recording and reporting

All AEs and ARs will be recorded on the adverse event report form, within the participant CRF, including those that fulfil the criteria for being serious (see section 10.1). Sites are asked to enter all available information onto the StarMS study database as soon as possible after the site becomes aware of the event. Investigators must record all AEs occurring for each participant from the time of consent until the participant has completed the trial (i.e. 24 month follow-up period).

SAEs, SARs and SUSARs will require more detailed information to be recorded. In such cases, the event must also be reported to the Sheffield CTRU within 24 hours of the site becoming aware of the event. The CTRU will notify the Sponsor of each of these events in accordance with the Agreement between Sheffield Teaching Hospitals and University of Sheffield. There are some events which do not require immediate reporting (see section 10.5).

10.3 Study Centre/Investigator Responsibilities

All AEs and ARs, whether expected or not, will be recorded in the participant's medical notes and recorded on an adverse event form within the CRF. SAEs and SARs will be notified to the CTRU within 24 hours of the investigator becoming aware of the event, unless these are any of the expected SARs defined in section 10.5.

For this study, the NIMPs are Mesna, Methylprednisolone, Prednisolone, Chlorpheniramine, Paracetamol, and the following vaccines: pneumococcal conjugate, conjugate HIB (haemophilus influenza Type B), DTP (diphtheria, tetanus and pertussis), inactivated polio, and pneumococcal polysaccharide.

Where a SAR is a result of a possible interaction between a NIMP and an IMP, the MHRA require these to be reported as SUSARs. There are no known interactions between any of the IMPs and NIMPs used in this study, however, if an investigator suspects an interaction resulting in a SAR has occurred between the two types of products, Sheffield CTRU should be contacted within 24 hours of becoming aware of the event.

If an adverse reaction associated with a NIMP is likely to affect the safety of the trial participants, the site must inform the CTRU, within 24 hours of becoming aware of the event. The decision as to whether the reaction is likely to affect the safety of the trial participants will be the joint responsibility of the chief investigator and lead neurologist, or delegated deputies in their absence.

Assessment of severity (intensity)

The severity of all AEs will be assessed using the NCI CTCAE criteria version 4.03. According to the NCI-CTCAE, adverse reactions are reported by grade (level of severity) on a scale of 1 to 5. Toxicity is graded as mild (Grade 1), moderate (Grade 2), severe (Grade 3), or life-threatening (Grade 4), or Death (Grade 5).

Assessment of relatedness

The relatedness of all AEs will be assessed and recorded on the AE form. The investigator should make an assessment of relatedness prior to sending the SAE form to the CTRU.

10.4 SAE Notification Procedure

CTRU will be notified of all SAEs, within 24 hours of the investigator becoming aware of the event (except for expected SARs, see 10.5). Investigators must notify CTRU of all SAEs occurring for each participant from the time of consent until the participant has completed the trial (i.e. 24 month follow-up period).

The SAE form must be completed by the investigator (a clinician named on the delegation log who is responsible for the participant's care). In the absence of the investigator the form will be completed by a member of the study team and faxed/emailed as appropriate. The responsible investigator will subsequently check the SAE form, make changes as appropriate, sign and re-send the form to CTRU as soon as possible.

All SAE forms must be sent by fax to 0114 222 0870 or email to ctru-saes-group@sheffield.ac.uk. Receipt of the initial report should be confirmed within one working day. The site research team should contact the study team at CTRU if confirmation of receipt is not received within one working day.

Concomitant medications are recorded throughout the study and will not be collected on AE/SAE forms as standard. However for any event classified as a SAR or SUSAR CTRU may request additional information on concomitant treatments to facilitate onward reporting.

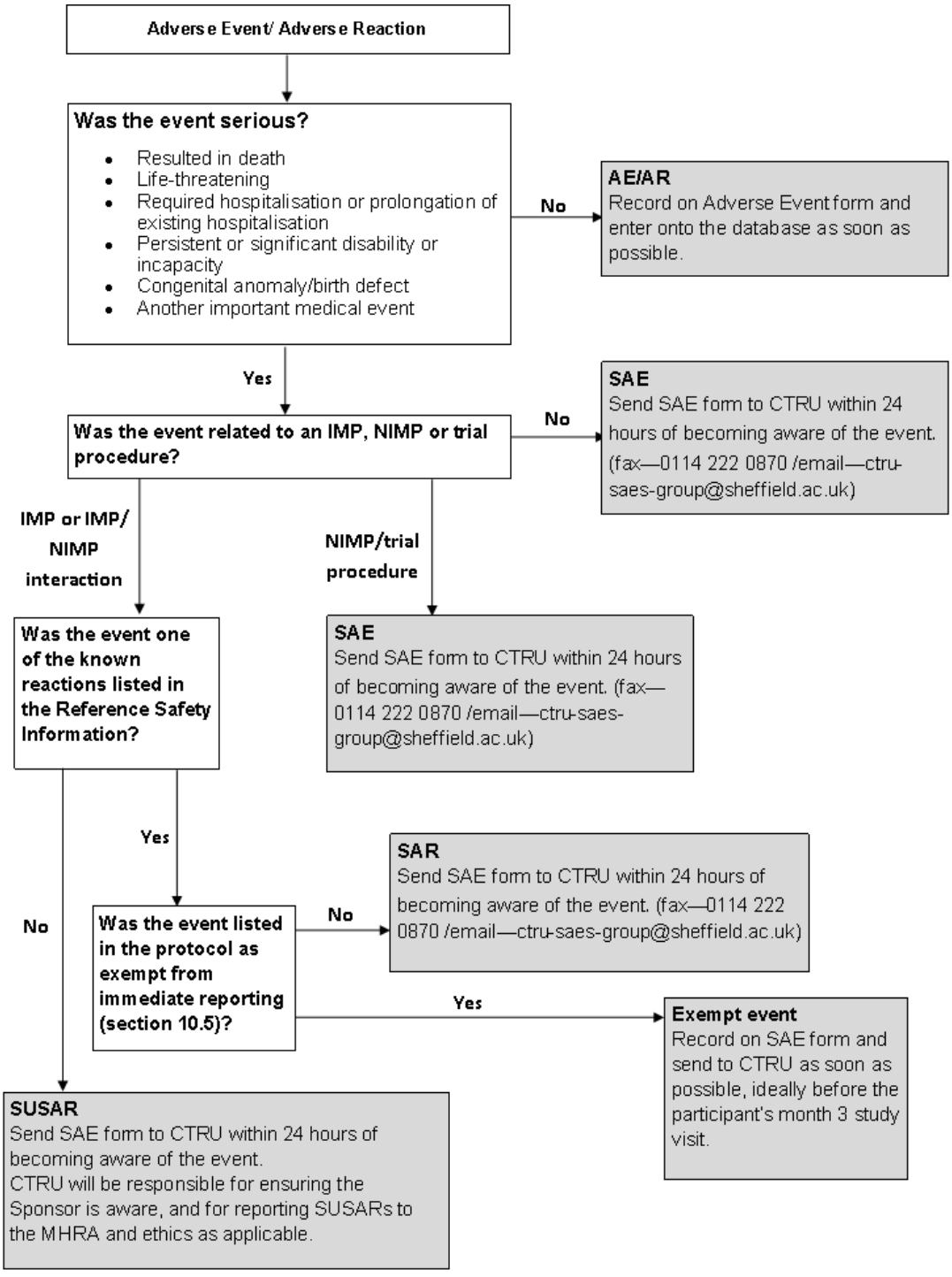
Follow up

Initial SAE reports must be followed by detailed reports when further information becomes available.

Participants must be followed up until clinical recovery is complete and laboratory results have returned to normal or baseline, or until the event has stabilised. Follow up information will be provided on an SAE report marked as such.

Further clarification on the reporting process can be seen in Figure 3

Figure 3: Procedure for AE/SAE reporting



10.5 Events that do not require immediate reporting

Patients receiving chemotherapy may require admission to hospital for appropriate medical intervention following development of some of the more severe known side effects of treatment. Where these events are confirmed as reactions to IMPs or NIMPs in the aHSCT arm (see section 10.3 for assessment of relatedness) these do not require immediate reporting by site.

The following SARs are exempt from immediate reporting, for the purpose of this study:

- Admissions to control symptoms of vomiting and diarrhoea, unless the condition requires admission to a high dependency or intensive care facility, or is life threatening or proves fatal (i.e. grade 4 or above, according to NCI CTCAE criteria)
- Admissions for supportive treatment during an episode of febrile neutropenia, unless this proves fatal or requires admission to a high dependency or intensive care facility (i.e. grade 4 or above, according to NCI CTCAE criteria)
- Admissions relating to myelosuppression unless the condition requires admission to a high dependency or intensive care facility, or is life threatening or proves fatal (i.e. grade 4 or above, according to NCI CTCAE criteria)

The following events related to NIMPs are exempt from immediate reporting, for the purpose of this study:

- Admissions relating to skin reactions and abnormal liver function tests caused by supportive care medications, unless the condition requires admission to a high dependency or intensive care facility, or is life threatening or proves fatal (i.e. grade 4 or above, according to NCI CTCAE criteria)

Timelines for reporting expected SARs

The expected SARs defined in section 10.5 should be reported on an SAE form. SAE forms should be completed and returned to Sheffield CTRU via fax or email as soon as possible, ideally before the follow up visit at month 3.

10.6 CTRU Responsibilities

The Chief Investigator or delegate will be responsible for the assessment of expectedness to confirm agreement with the site investigator. An unexpected adverse reaction is one not defined in the protocol as expected (section 10.5), not previously reported in the Reference Safety Information (RSI) used in the study, or one that is more frequent or more severe than reported in the RSI. If a SAR is assessed as 'unexpected', it is classified as a SUSAR.

The RSI to be used in the study will be section 4.8 of the SmPCs in the version which has been submitted to and approved by the MHRA for this trial.

The Sponsor has delegated CTRU responsibility for the reporting of SUSARs and other SARs to the regulatory authorities and the research ethics committee as appropriate. CTRU will also keep all investigators informed of any safety issues that arise during the course of the study. CTRU will report all SAEs to the Sponsor as documented in the delegation of duties agreement.

If an adverse reaction associated with a NIMP is likely to affect the safety of the trial participants, the CTRU may be required to report this to the MHRA and REC as an urgent safety measure, a substantial amendment or via a notification to terminate the trial early, as applicable. The decision as to whether the reaction is likely to affect the safety of the trial participants will be made by the chief investigator or a delegated deputy in the CI's absence.

The DMEC and TSC will also receive information on all AEs and SAEs, at a frequency agreed with each committee and documented in the appropriate charter/terms of reference.

10.7 SUSARs

All SUSARs should be recorded on an SAE form, and faxed or emailed to the CTRU within 24 hours of discovery. The CTRU will be responsible for reporting SUSARs to the MHRA and REC. Each site will be informed of SUSARs occurring across the study.

10.8 Reporting pregnancies during the trial

Female participants, and male participants with female partners, will be advised to use an adequate form of contraception during the course of the study; however, it is possible that women could become pregnant during the follow-up phase of the study. If this occurs, this will be recorded using the Pregnancy Report form within the CRF, and also (for participants in the aHSCT arm) notified to the EBMT. Note that pregnancies in female partners of male participants only need to be reported if they occur during treatment with aHSCT or within 6 months after discontinuation (i.e. last dose) of cyclophosphamide. The Chief Investigator and the TMG will be informed, so that a discussion can take place regarding the participant's continuation in the study. Any such discussions will be documented, and recommendations for continuation or discontinuation in the study will be made according to clinical judgement.

Any participant who becomes pregnant during the course of the study will be asked to consent to follow up of the pregnancy, irrespective of any treatment withdrawal or changes. In addition, any female partner of a male participant in the aHSCT arm who becomes pregnant between the participant starting treatment and up to 6 months after discontinuation (i.e. last dose) of cyclophosphamide will be asked to consent to follow up of the pregnancy.

The DMEC and TSC will be advised at each meeting, of any pregnancies reported since their previous meeting.

11. Statistics

Sample Size

The primary binary outcome is the proportion of patients who have maintained NEDA at 2 years from randomisation. Assuming 40% NEDA in the control arm, and that an absolute increase of 25% to 65% NEDA is of clinical importance [see changes from first stage for justification], to have 90% power to detect this difference, using a continuity corrected chi-squared test at the 5% (two-sided) level 90 patients per group are required (180 in total). Adjusting for a predicted drop-out rate of 10%, the project aims to recruit and randomise 198 patients over 24 months at 19 centres, a rate of around 1.25 patients/month at anchor sites or 0.5 patients/month at other sites.

The NEDA proportions selected for the control & treatment arms are supported by the best available literature. Four recent large RCTs have reported a NEDA proportion at 2 years for Alemtuzumab and Ocrelizumab of between 32 & 48% (9), with the CARE-MS trials reporting NEDA rates for Alemtuzumab of 32 & 39% (10,20,36). NEDA rates at 2 years in the literature for the investigative treatment arm range from 78% to 83% (9,12). It should be noted that the populations included in aHSCT studies thus far are individuals with less active disease than would be included in our proposed study. Therefore, our proposed 40% NEDA proportion for the control Alemtuzumab arm is perhaps higher than seen in trials to date, & our proposed 65% NEDA rate for the treatment aHSCT arm is at the lower end than that seen in clinical studies, we have selected a conservative absolute difference in treatment effect.

Statistical analysis

As the trial is a parallel group RCT, data will be reported and presented according to the revised CONSORT statement (67,68). The primary effectiveness statistical analyses will be performed on an intention-to-treat (ITT) basis. Every effort will be made to follow up all participants in both arms for research assessments. There is no planned interim analysis, beyond checking the recruitment rate at the end of the pilot phase. All statistical exploratory tests will be two-tailed with $\alpha = 0.05$. Baseline demographic, physical and clinical characteristics and health-related quality of life data will be described and summarised overall and for both treatment groups.

The primary aim is to estimate and compare the effectiveness of aHSCT with Cy/ATG conditioning regime vs DMT (Alemtuzumab or Ocrelizumab) in highly active RRMS. The primary binary outcome is whether the participant has "No evidence of disease activity" or NEDA during the 2 years post-randomisation follow-up period.

The primary effectiveness analysis, on the ITT sample, will compare the NEDA rate, at 2 years post-randomisation, between the two randomised groups (aHSCT with Cy/ATG conditioning regimen vs DMT (Alemtuzumab or Ocrelizumab) using a multiple logistic regression model with centre and baseline stratification variables (e.g. EDSS score) as co-variates; the 95% confidence interval for treatment group parameter, the odds ratio, will be reported. We shall also calculate the absolute difference in the estimated NEDA rate between the two randomised groups and its associated confidence interval.

For the primary analysis, we will undertake a conservative analysis and any patient whose NEDA status at 2 years is missing or unknown (excluding those that died before 24 month follow up) will assumed to be not disease free; and will not contribute any information to the numerator for the NEDA rate at 2 years but will be in the denominator. However, we anticipate the amount of missing primary outcome data will be relatively small as trial participants will be intensively followed up and regularly monitored throughout the 2-year post-randomisation follow-up period.

As the criteria for switching treatments after 12 months is that the patient has some evidence of disease activity; participants who switch treatments will be regarded as a treatment failure and will not contribute information to the numerator in the primary outcome, but will be included in the denominator for the calculation of the NEDA rate.

Missing primary outcome data

For the primary outcome, NEDA at 24 months follow-up, missing data will be imputed through a variety of methods, with the default (primary) analysis being a worst case scenario (patients with missing data are assumed to be not disease free) and a best case scenario (patients with missing NEDA data are assumed disease free) alongside multiple imputation using chained equations (MICE). Missing outcome data for participants who have died before the end of the 24-month follow-up will not be imputed. The estimates of the treatment effect and its associated confidence interval, from the various imputation methods, will be graphically displayed alongside the results for the observed data.

Sensitivity Analyses for the Primary outcome

We will complement the ITT analysis of the primary outcome with a complier average causal effects analysis (CACE) as a secondary analysis to estimate the efficacy of the aHSCT with Cy/ATG conditioning regimen vs DMT (Alemtuzumab or Ocrelizumab) in highly active RRMS. A complier will be defined as a participant who complies with the protocol i.e. receives the mobilisation and conditioning regimens and the autologous graft or has received the two cycles of Alemtuzumab (12mg/day on 5 consecutive

days and 12mg/day on 3 consecutive days, 12 months later) or two cycles of Ocrelizumab (the initial dose – 600mg administered as two separate intravenous infusions; first as a 300mg infusion, followed 2 weeks later by a second 300mg infusion and a single 600mg infusion six-monthly thereafter).

Safety outcomes and adverse events

To standardize the reporting of adverse reactions in clinical trials, the National Cancer Institute (NCI) has developed Common Terminology Criteria for Adverse Events (NCI-CTCAE) to describe the severity of organ toxicity for patients receiving therapy. According to the NCI-CTCAE, adverse reactions are reported by grade (level of severity) on a scale of 1 to 5. Toxicity is graded as mild (Grade 1), moderate (Grade 2), severe (Grade 3), or life-threatening (Grade 4), or Death (Grade 5).

The primary safety outcome is the serious adverse event rate (SAE), defined as (see Table 7) any adverse event, adverse reaction or unexpected adverse reaction that:

- Results in death (Grade 5)
- Is life-threatening* (Grade 4)
- Requires hospitalisation or prolongation of existing hospitalisation**
- Results in persistent or significant disability or incapacity
- Congenital anomaly/birth defect
- Is another important medical event

within the 2-year post-randomisation follow-up.

The SAE rate will be compared between the two randomised groups using a Chi-squared test; a 95% confidence interval for the difference in the estimated SAE rate between the two randomised groups will also be calculated. Secondary outcomes such as the mortality rate (grade 5) and combined (grade 4 and 5) SAE rates, which we assume will be rarer, will be compared between the two randomised groups using Fisher's Exact test; a 95% confidence interval for the difference in the estimated SAE rate between the two randomised groups will also be calculated.

Since patients may experience more than one adverse event; we will also count the total number of AE experienced, by each patient, in the 100 days post-randomisation and compare the total count of the number of AE between the two groups with a Poisson generalised linear model (GLM) and report the relative risk ratio and its associated 95% confidence interval from this model.

Secondary outcomes

Clinical outcomes

For the time to event outcome (time to evidence of disease activity) will be summarised with Kaplan Meier estimates of the time to evidence of disease activity and compared between the randomised groups using the log-rank test. A Hazard ratio and its associated 95% confidence interval will also be estimated using a Cox-proportional hazards regression model. Patients with no evidence of disease activity will be censored at their last known date of post-randomisation follow-up.

The repeated continuous secondary outcomes e.g. EDSS, MSFC and Low contrast visual acuity scores measured at 3, 6, 9, 12, 18 & 24 months post-randomisation will be compared between the randomised groups using a longitudinal multi-level mixed effects linear regression model with fixed effects for group and time and baseline score and random intercepts for subject and a random slope for time. A 95% CI for the mean difference in this parameter between the treatment groups will also be calculated.

Quality of Life/Health Economic measures

The repeated continuous secondary outcomes RAND SF-36 (and its eight dimensions) EQ-5D-5L, and WHO QOL-Bref measured at 3, 6, 9, 12, 18 & 24 months post-randomisation will be compared between the randomised groups using a series of longitudinal multi-level mixed effects linear regression models with adjustment for baseline covariates (65) and a random intercept for subject and random slope for time. A 95% CI for the mean difference in this parameter between the treatment groups will also be calculated.

The repeated continuous secondary outcomes neuropsychology (CANTAB and BICAMS) measured at 12 & 24 months post-randomisation will be compared between the randomised groups using a longitudinal multi-level mixed effects linear regression model with adjustment for baseline covariates (69). A 95% CI for the mean difference in this parameter between the treatment groups will also be calculated.

Subgroup Analyses

A series of exploratory sub group analyses, using multiple logistic regression, with the primary outcome NEDA status at 24-month post-randomisation as the response will be carried out. We will use an interaction statistical test between the randomised intervention group and subgroup to directly examine the strength of evidence for the treatment difference between the treatment groups varying between subgroups. Age and disability levels (based on the baseline EDSS score) will be the only a priori defined sub groups to be considered for interaction test. Sub group analysis will be performed regardless of the statistical significance on the overall intervention effect. A graphical plot of the mean profile/outcome (Y-axis) by subgroups (X-axis) for intervention and control groups will be used to display the interaction.

For the primary outcome we shall estimate the NEDA rate over 2 years in the DMT arm separately for those treated with Alemtuzumab and Ocrelizumab and calculate the difference in NEDA rates (and their associated 95% CI) between 1) aHSCT and Ocrelizumab treated patients; 2) aHSCT and Alemtuzumab; 3) Alemtuzumab and Ocrelizumab. It should be noted that these are exploratory (and non-randomised) comparisons and not subject to the benefits of randomisation; as the characteristics of the drug sub-groups may not be balanced when compared to aHSCT.

Mediation analyses

A secondary mediation analysis will investigate putative mediational factors using modern causal inference methods. This involves using parametric regression models to test for mediation of aHSCT on treatment success through the biomarkers. Analyses will adjust for baseline measures of the marker, and possible measured confounders. We will test for possible biomarkers to select patients by testing interactions between baseline markers and treatment on treatment response and safety outcomes.

Registry based long-term data reporting will continue for all patients receiving aHSCT as per routine standards for BSBMT/EBMT members (all participating centres). Annual assessment of disease activity, incidence of adverse events, will be collected for aHSCT participants and collated on the EBMT database. Analysis of this data will be subject to securing additional funding and support**.**

12. Study supervision

The StarMS trial will be led by the Chief investigator working in co-ordination with the co-applicants and Sheffield CTRU. The sponsor will be Sheffield Teaching Hospitals NHS Foundation Trust. Sheffield CTRU will take responsibility for project management and already have a scope of practice for governance and safety reporting with the sponsor, although specific details will be agreed and documented in a contract. There will be a dedicated trial manager who will be supervised by the CI

and by a senior member of staff at CTRU (CTRU study lead), meeting at regular intervals, and will liaise with the whole study team. The CTRU study lead will provide oversight for delivery of all CTRU support including trial management, data management, QA, randomization, statistics, health economics, analysis reporting and dissemination. Health Research Authority (HRA) approval will be sought prior to commencement of the trial at participating centres.

Three committees will be established to govern study conduct, deliver the trial, monitor its performance and ensure its safety: Trial Steering Committee (TSC), Data Monitoring and Ethics Committee (DMEC) and Trial Management Group (TMG). The committees will function in accordance with Sheffield CTRU standard operating procedures.

12.1 Trial Steering Committee (TSC)

The TSC will consist of an independent chair, neurologist and haematologist, statistician and patient representatives. The role of the TSC is to provide supervision of the protocol and statistical analysis plan, to provide advice on and monitor progress of the study, to review information from other sources and consider recommendations from the DMEC. The TSC meet at regular intervals, as defined in the TSC terms of reference.

The Trial Steering Committee (TSC) will regularly review the clinical opinion and use of new DMTs available and advise the trial team on the modification of the comparator arm if required.

12.2 Data Monitoring and Ethics Committee (DMEC)

The DMEC will consist of an independent statistician, neurologist and haematologist with clinical trial expertise. The DMEC will review reports provided by the CTRU to assess the progress of the study, the safety data and the critical endpoint data as required. The DMEC will be able to recommend study termination to the TSC / funder on safety grounds. There are no pre-planned interim analyses. In the event of a treatment-related death, we would expect an immediate DMEC meeting to be convened. This will be agreed with the DMEC at the study start and documented in the DMEC charter.

The DMEC will meet at regular intervals, as defined in the DMEC charter. The usual format for DMEC meetings will include an open session to which members of the study team may attend, followed by a closed session with independent members only and to which unblinded data will be available. The DMEC may recommend the trial is stopped or modified on the basis of the data, in writing, to the chair of the TSC.

12.3 Trial Management Group (TMG)

The TMG consists of the CI and co-CI, collaborators and staff from CTRU. The CI will chair regular meetings to discuss the day-to-day running of the study, including any implementation issues.

13. Data handling and record keeping

Participant confidentiality will be respected at all times and the principles of the General Data Protection Regulation (GDPR) will be followed. The investigator will ensure that identifiable data is kept securely and protected from unauthorised parties.

Data management will be provided by the University of Sheffield Clinical Trials Research Unit (CTRU) who adhere to their own Standard Operating Procedures (SOPs) relating to all aspects of data management, including data protection and archiving. A separate data management plan (DMP) will detail data management activities for the study in accordance with SOP (Shef/CTRU/DM009).

The investigator or delegate at each site will maintain comprehensive and accurate source documents to record all relevant study information regarding each participant. The CTRU will provide worksheets (shadow CRFs) to allow the site staff to check what is required for a visit. The worksheets do not need to be completed if alternative source documentation is provided. However, they must be completed for data points where source documentation is not collected elsewhere and where completed, worksheets must accurately reflect the database as they form part of the source data.

If a participant consents to being sent information about the study, such as being informed of the results once the study is complete, their name and email address and/or postal address will be collected in the consent CRF. All other CRFs will only identify the participant by their study ID number. All participants will be assigned a unique study ID number at screening that will link all of the clinical information collected for them on the study database. It will also be used in all correspondence between CTRU and participating centres.

Study records, including source data, will be stored for 25 years after the completion of the study by participating sites, before being destroyed. Each investigator is responsible for ensuring records are retained and securely archived during the retention period and information supplied to the Chief Investigator and Sponsor. Where trial related information is documented in the medical records, those records will be retained for at least 25 years after completion of the study. Access will be restricted to authorised individuals.

Data held by the CTRU will be stored in accordance with the archiving Standard Operating Procedure (CTRU SOP PM012) for 25 years following completion. Archived documents will be logged on a register which will also record items retrieved, by named individuals, from the archive. Electronic data will be stored in an 'archive' area of the secure CTRU server for a minimum of 25 years to ensure that access is future-proofed against changes in technology. Electronic data may also be stored (e.g. on a compact disc or USB flash drive) with the paper files.

Laboratory specimens to be preserved or stored will be labelled without the use of patient identifiable information. Labels will contain study ID, type of sample, and the date the sample was taken, and will be cryo-labels to withstand freezing of the sample.

14. Data access and quality assurance

The study will use the CTRU's in-house data management system (Prospect) for the capture and storage of study specific participant data. Access to Prospect is controlled by usernames and encrypted passwords, and a comprehensive access management feature will be used to ensure that users have access to only the minimum amount of data required to complete tasks relevant to their study role. This feature can also be used to restrict access to personal identifiable data.

The study team at each site will enter data from source documents into the study specific Prospect database when available. After data have been entered, electronic validation rules are applied to the database on a regular basis; discrepancies are tracked and resolved through the Prospect database. All entries and corrections are logged with the person, date and time captured within the electronic audit trail.

Participant confidentiality will be respected at all times. All research data will be anonymised, and will only be identifiable by the participant's study ID number. No patient identifiable data will be transferred from the database to the statistician.

Participating investigators shall agree to allow study-related monitoring, including audits, ethics committee review and regulatory inspections by providing direct access to source data and documents as required. Participants' consent for this will be obtained as part of the consent process.

14.1 Site Assessment

Throughout this protocol, the trial 'site' refers to the hospital at which trial-related activities are conducted. Participating sites must be able to comply with:

- Trial treatments, imaging, clinical care, follow up schedules and all requirements of the trial protocol
- Requirements of the UK Policy Framework for Health and Social Care Research and the Medicines for Human Use (clinical trials) Act (SI 2004/1031 and all amendments)
- Data collection requirements

aHSCT procedures must be undertaken at a transplant centre accredited by JACIE for allogeneic transplants in adults, or for autologous transplants in adults if they have previous experience of autologous HSCT for autoimmune diseases. All participating sites must have an appropriate Principal Investigator (PI) i.e. a health care professional authorised by the site, ethics committee and regulatory authority to lead and coordinate the work of the trial on behalf of the site. Other investigators at site wishing to participate in the trial must be trained and approved by the PI, and this must be documented on the site delegation log. All investigators must be medical doctors and have experience in either autologous stem cell transplants, or working with patients with MS.

All site staff, including research staff, must be appropriately qualified by education, training and experience to perform the trial related duties allocated to them, which must be recorded on the site delegation log. CVs for all staff must be kept up to date, and copies held in the Investigator Site File (ISF), and the Trial Master File (TMF). Staff should also have completed GCP training and copies of the GCP certificate are held within the ISF and TMF.

Before each site is activated, capability to conduct the trial will be assessed and documented using a site assessment form. The CTRU will arrange a site initiation visit with each site, site staff will be trained in the day-to-day management of the trial and essential documentation required for the trial will be checked. Once all the required documentation is in order, and site staff have been trained, CTRU will formally activate the site to start recruitment. Sites should not open to recruitment until CTRU have provided this confirmation of activation.

14.2 Risk Assessment

A risk assessment has been performed by the Sponsor and CTRU, in accordance with Sheffield CTRU Standard Operating Procedures. The study has been categorised as Type B = somewhat higher than the risk of standard medical care. The level of risk has been agreed with the Sponsor.

Central and on-site monitoring will be undertaken at a level appropriate to the detailed risk assessment, and will be documented in the Site Monitoring Plan (SMP). This will include (at a minimum):

1. Source Data Verification (SDV)
2. SAEs/SUSARs – reported to the Sponsor and followed up to resolution
3. Resolution of data queries
4. Investigator site file maintenance
5. Training records for site staff (trial specific and GCP) and appropriate delegation of duties
6. Patient consent procedures
7. Reporting of protocol non-compliances

14.3 On-site Monitoring

On-site monitoring will be performed according to the StarMS monitoring plan and in line with the Sheffield CTRU Site Monitoring SOP.

A site initiation visit will be performed at each participating site before each site recruits their first participant. During this visit, the Monitor will review with site staff the protocol, study requirements and their responsibilities to satisfy regulatory, ethical and Sponsor requirements.

Regular site monitoring visits will occur throughout the study and additional visits will be undertaken where required. At these visits, the Monitor will review activity to verify that the:

1. Data are authentic, accurate and complete.
2. Safety and rights of the patient are being protected and
3. Study is conducted in accordance with the approved protocol and study agreements, GCP and all applicable regulatory requirements.

Accurate and reliable data collection will be assured by verification and cross-check of the eCRF against Investigator's records by the Study Monitor (source document verification) (see section 13 for further details on data collection). Study Monitor will contact and visit sites regularly to inspect CRFs throughout the study, to verify adherence to the protocol and completeness, consistency and accuracy of the data being entered on the CRFs.

A close-out visit will be performed after the last patient last visit at each site. Further close-out activities may be carried out remotely after this time, up to database freeze.

14.4 Central Monitoring at CTRU

CTRU staff will review entered data for possible errors and missing data points. A central review of consent forms will also be completed, and sites will be requested to post consent forms to CTRU on an ongoing basis. This will be made clear to the participant prior to their consent to the trial.

14.5 Regulatory information

As a CTIMP, the trial will be conducted in accordance with ICH GCP and the Clinical Trials and Medicine for Human Use (Clinical Trials) Regulations 2004. A site agreement between the Sponsor and the participating sites outlines responsibilities of all parties and is to be signed prior to commencement of recruitment at sites. All clinicians responsible for recruiting patients to the trial will be required to complete training in International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceutical/s for Human Use (ICH) Good Clinical Practice (GCP).

Although StarMS involves autologous HSCT, all HSCT procedures will be undertaken at sites accredited in accordance with the international quality standards for clinical and laboratory practice in Haematopoietic Cell Therapy of the Joint Accreditation Committee for ISCT and EBMT (JACIE), either for allogeneic HSCT or for autologous HSCT if there is previous experience in autologous HSCT for autoimmune diseases.

15. Publication

Results of the study will be disseminated through peer reviewed scientific journals and at clinical and academic conferences, as well as submission of a final report to the funder, which will be made available online.

Details of the study will also be made available on the Sheffield CTRU website. Summaries of the research will be updated periodically to inform readers of ongoing progress.

Information throughout the course of the study may be disseminated at conferences and other events, providing this does not relate to any endpoint, but these must be with the approval of the Chief Investigator, and the funder must be informed with sufficient notice.

The study will also be added to the EudraCT trial repository.

The results will be published on a freely accessible database within one year of completion of the trial. Anonymised datasets will be made available after publication of the main trial results.

Full details, including guidance on authorship are documented in the StarMS Publication and Dissemination Plan.

16. Finance

StarMS is funded by the UK NIHR Efficacy and Mechanism Evaluation (EME) Programme (project number 16/126/26) and full details are included in a separate agreement. Payments for research activity at participating centres including participant travel costs will be detailed in the site agreements.

The neuropsychology study is funded by Sheffield Hospitals Charity (grant reference 171826).

17. Ethics approval

Before initiation of the study at participating sites, the protocol, informed consent forms, and information materials to be given to the participants will be submitted to an NHS Research Ethics Committee for approval. Any further amendments will be submitted and approved by the ethics committee.

In addition, the study will be submitted for HRA review and approval. Recruitment of study participants will not commence until the letter of approval has been received from the HRA.

18. Regulatory approval

The study will be conducted in accordance with the UK Clinical Trials Regulations 2004 and as such will be submitted to the Medicines and Healthcare Regulatory Agency (MHRA) for review. The study will not commence recruitment until a Clinical Trial Authorisation (CTA) has been granted by the MHRA.

19. Indemnity / Compensation / Insurance

The University of Sheffield has in place clinical trials insurance against liabilities for which it may be legally liable, and this cover includes any such liabilities arising out of this clinical study.

Standard NHS indemnity operates in respect of the clinical treatment which is provided.

20. References

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21. APPENDIX

21.1 Appendix A

Ideal body weight (IBW) table for Cyclophosphamide dose calculation; adapted from equations used in the MIST trial (19)

	IBW	
Height (cm)	Male	Female
145	43.63	38.63
146		39.54
147	45.45	40.45
148	46.36	41.36
149	47.27	42.27
150	48.18	43.18
151	49.09	44.09
152	50	45
153	50.91	45.91
154	51.82	46.82
155	52.73	47.73
156	53.64	48.64
157	54.55	49.55
158	55.46	50.46
159	56.37	51.37
160	57.28	52.28
161	58.19	53.19
162	59.1	54.1
163	60.01	55.01
164	60.92	55.92
165	61.83	56.83
166	62.74	57.74
167	63.65	58.65
168	64.56	59.56
169	65.47	60.47
170	66.38	61.38
171	67.29	62.29
172	68.2	63.2
173	69.11	64.11

	IBW	
Height (cm)	Male	Female
174	70.02	65.02
175	70.93	65.93
176	71.84	66.84
177	72.75	67.75
178	73.66	68.66
179	74.57	69.57
180	75.48	70.48
181	76.39	71.39
182	77.3	72.3
183	78.21	73.21
184	79.12	74.12
185	80.03	75.03
186	80.94	75.94
187	81.85	76.85
188	82.76	77.76
189	83.67	78.67
190	84.58	79.58
191	85.49	80.49
192	86.4	81.4
193	87.31	82.31
194	88.22	83.22
195	89.13	84.13
196	90.04	85.04
197	90.95	85.95
198	91.86	86.86
199	92.77	87.77
200	93.68	88.68
201	94.59	89.59
202	95.5	90.5
203	96.41	91.41
204	97.32	92.32
205	98.23	93.23
206	99.14	94.14
207	100.05	95.05
208	100.96	95.96
209	101.87	96.87
210	102.78	97.78