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# Efficacy and safety of autologous haematopoietic stem cell transplantation versus alemtuzumab, ocrelizumab, ofatumumab or cladribine in relapsing remitting multiple sclerosis (StarMS): protocol for a randomised controlled trial

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## ABSTRACT

**Introduction** Autologous haematopoietic stem cell transplantation (aHSCT) is increasingly used as treatment for patients with active multiple sclerosis (MS), typically after failure of disease-modifying therapies (DMTs). A recent phase III trial, 'Multiple Sclerosis International Stem Cell Transplant, MIST', showed that aHSCT resulted in prolonged time to disability progression compared with DMTs in patients with relapsing remitting MS (RRMS). However, the MIST trial did not include many of the current high-efficacy DMTs (alemtuzumab, ocrelizumab, ofatumumab or cladribine) in use in the UK within the control arm, which are now offered to patients with rapidly evolving severe MS (RES-MS) who are treatment naïve. There remain, therefore, unanswered questions about the relative efficacy and safety of aHSCT over these high-efficacy DMTs in these patient groups. The StarMS trial (Autologous Stem Cell Transplantation versus Alemtuzumab, Ocrelizumab, Ofatumumab or Cladribine in Relapsing Remitting Multiple Sclerosis) will assess the efficacy, safety and long-term impact of aHSCT compared with high-efficacy DMTs in patients with highly active RRMS despite the use of standard DMTs or in patients with treatment naïve RES-MS.

**Methods and analysis** StarMS is a multicentre parallel-group rater-blinded randomised controlled trial with two arms. A total of 198 participants will be recruited from 19 regional neurology secondary care centres in the UK. Participants will be randomly allocated to the aHSCT arm or DMT arm in a 1:1 ratio. Participants will remain in the study for 2 years with follow-up visits at 3, 6, 9, 12, 18 and 24 months postrandomisation. The primary outcome is the proportion of patients who achieve 'no evidence of disease activity' during the 2-year postrandomisation follow-up period in an intention to treat analysis. Secondary outcomes include efficacy, safety, cost-effectiveness and immune reconstitution of aHSCT and the four high-efficacy DMTs.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is a multicentre randomised controlled trial comparing autologous haematopoietic stem cell transplantation (aHSCT) against the current most effective disease-modifying therapies for highly active relapsing remitting multiple sclerosis, including treatment naïve patients with rapidly evolving severe multiple sclerosis.
⇒ The primary outcome, 'no evidence of disease activity', will be assessed with blinded Expanded Disability Status Scale assessments and central review of relapses and MRI scans.
⇒ Several secondary outcome measures will further the knowledge of the safety, efficacy and mechanism of aHSCT, including immunological, neuropsychology, optical coherence tomography and cost-effectiveness studies.
⇒ The trial is aligned with other similar trials underway in Europe and North America providing an opportunity to replicate the results and provide robust safety and efficacy evidence of aHSCT.
⇒ The relatively short, 2-year, follow-up is a study limitation, although following the trial, patients will be followed up as part of an observational registry.

**Ethics and dissemination** The study was approved by the Yorkshire and Humber—Leeds West Research Ethics Committee (20/YH/0061). Participants will provide written informed consent prior to any study specific procedures. The study results will be submitted to a peer-reviewed journal and abstracts will be submitted to relevant national and international conferences.

**Trial registration number** ISRCTN88667898.

## INTRODUCTION

Autologous haematopoietic stem cell transplantation (aHSCT) suppresses or attenuates the course of autoimmune diseases, possibly via an immune 'resetting' mechanism.[1] AHSCT is being used increasingly as treatment for patients with highly active relapsing remitting multiple sclerosis (RRMS), usually after failure of one or more disease-modifying therapies (DMT).[2] Observational and clinical trial data suggest that aHSCT reduces relapse rate, improves disability and quality of life (QoL) in excess of those observed with DMT and is potentially more cost-effective.[3–14]

The largest trial to date, the Multiple Sclerosis International Stem Cell Transplant (MIST), a phase III randomised controlled trial with 5 years of follow-up (mean 2.8), showed that aHSCT resulted in prolonged time to disability progression compared with the concurrent FDA-approved disease-modifying therapies (DMTs).[6] In the aHSCT group versus controls, gains were evidenced in the following: mean Expanded Disability Status Scale (EDSS) score improvement, where higher numbers denote worse impairment or disability, 3.38 to 2.36 versus 3.31 to 3.98, respectively; reduction in relapse rate, 1 versus 39; and reduced disability progression evidenced by an increase in EDSS of 1.0 confirmed after 6 months after 1 year of treatment, 6% versus 60%, respectively. There were no significant side effects or treatment-related mortality in the aHSCT arm. There were 72 grade 3 toxicities, mainly electrolyte abnormalities, culture negative febrile neutropenia and infections in the aHSCT group, although post-treatment infections were similar in both groups. There were no Common Toxicity Criteria grade 4 non-haematopoietic toxicities.

While these results suggest that aHSCT is safe and has superior efficacy compared with many currently available DMTs, the majority of high-efficacy DMTs (alemtuzumab, ocrelizumab, ofatumumab and cladribine) were not used in the MIST control arm. Standard practice has since evolved and patients are now routinely offered such therapies early in the disease course as either their initial therapy or after their first relapse while on first line.[15] The use of aHSCT in treatment naïve patients (patients who have not previously been treated with a DMT) with rapidly evolving severe MS (RES-MS) is now considered as a treatment option.[2 9] The StarMS trial (Autologous Stem Cell Transplantation versus Alemtuzumab, Ocrelizumab, Ofatumumab or Cladribine in Relapsing Remitting Multiple Sclerosis) will, therefore, assess the safety, efficacy and long-term impact of aHSCT using the non-myeloablative 'Cy/ATG' conditioning regimen compared with high-efficacy DMTs (alemtuzumab, ocrelizumab, ofatumumab or cladribine). These DMTs are the evidence-based UK standard of care in patients who have highly active RRMS despite first-line DMTs or in treatment naïve patients with RES-MS. The Cy/ATG conditioning regimen was effective in the MIST trial and historical data suggest there may be significantly less short-term toxicity than more intensive regimens.[10 16]

A mechanistic study has been embedded in the trial design to assess baseline immune profiles and post-transplant immune reconstitution with a view to identifying biomarkers associated with, and potentially predictive of, clinical response. Whole blood, serum and cerebrospinal fluid (CSF) samples will be collected from consented patients and stored for future research, such as vaccination and neurofilament light chain and other biomarker studies. Additional substudies involving optical coherence tomography (OCT) and neuropsychology assessments are available to all patients to take part in, where the trial site is taking part in these substudies.

### Trial objectives and hypotheses

The primary objective is to assess the clinical efficacy, as measured by 'No Evidence of Disease Activity' (NEDA-3) rate at 2 years postrandomisation of aHSCT compared with DMTs (alemtuzumab, ocrelizumab, ofatumumab or cladribine) in patients who have highly active RRMS despite first-line DMTs or treatment naïve patients with RES-MS.

Secondary objectives are to determine whether the relative safety and toxicity profile of aHSCT compared with a DMT is acceptable. Furthermore, to assess the impact of aHSCT compared with DMTs on cost-effectiveness, QoL, neuropsychological performance, OCT, and other clinical outcomes.

#### Mechanistic sub-study objectives

To advance understanding of aHSCT mechanisms of efficacy by:

1. Analysing T cell receptors (TCR) and B cell receptors (BCR) repertoires pretherapy and post-therapy.
2. Interrogating the reconstitution in blood of B and T cell populations by immune profiling with multicolour flow cytometry with reference to their pretherapy profile. This will enable us to:
   a. Characterise immune reconstitution after aHSCT or DMT.
   b. Examine the extent of depletion of the pro-inflammatory lymphocyte populations of special interest in aHSCT, such as the mucosal-associated invariant T (MAIT) cells.
   c. Identify immunological changes post-aHSCT that are associated with long-term MS stabilisation or remission.
   d. Describe any immunological changes that precede disease recurrence in the first 2 years after aHSCT or initiation of high-efficacy DMT.

### Optical coherence tomography sub-study objectives

Between study arms, compare:

1. Retinal nerve fibre layer thickness as a marker of axonal damage.
2. Ganglion-cell layer thickness as a marker of neuronal injury.
3. The microcystic macular oedema and associated thickening of the retinal inner nuclear layer as markers of active CNS inflammatory activity.

### Neuropsychology sub-study objectives

1. Assess the effect of aHSCT on cognitive recovery using the Cambridge Neuropsychological Test Automated Battery (CANTAB) and the Brief International Cognitive Assessment for MS (BICAMS).
2. Assess whether the two interventions differentially affect the degree of cognitive impairment after treatment using the CANTAB and BICAMs outcomes.

## METHODS AND ANALYSIS

The trial is registered at http://www.isrctn.com/ISRCTNISRCTN88667898.

### Trial design

The study is a multicentre, parallel-group, rater-blinded, randomised controlled trial with two arms (aHSCT group and DMT group).

### Setting and participants

Recruitment will take place at up to 19 UK sites that have both tertiary referral MS clinics and are either Joint Accreditation Committee of ISCT and European Society for Blood and Marrow Transplantation (EBMT) accredited for allogeneic HSCT, or accredited for aHSCT and have experience in aHSCT for autoimmune diseases.[17]

Written informed consent will be obtained by Good Clinical Practice accredited, appropriately trained and delegated medically qualified investigators. A medically qualified individual, usually the site principal investigator or other coinvestigator, will confirm eligibility and provide clinical oversight for the consent process.

Participation in the mechanistic, OCT and neuropsychology substudies is optional and will not affect participation in the main trial.

### Eligibility criteria

Table 1 details the eligibility criteria.

### Screening assessments

Potential participants will undergo screening procedures (online supplemental appendix 1) to confirm eligibility. Results will be reviewed by the local medically qualified investigator, and the Lead Trial Neurologist, or delegate, and Lead Trial Haematologist, where appropriate.

### Randomisation

Participants will be randomly allocated to the aHSCT arm or DMT arm in a 1:1 ratio. The local study team will randomise participants via a web-based randomisation system provided by Sheffield Clinical Trials Research Unit. Randomisation will be done using minimisation by centre and baseline EDSS score (≤4.0 vs > 4.0).

### Interventions

Trial treatment will be administered in line with current guidelines from the relevant agencies, including, the Association of British Neurologists, the British Society of Blood and Marrow Transplantation and Cellular Therapy and the EBMT.

All investigational medicinal products (IMPs) are being used within the terms of their marketing authorisation or as used in routine practice.

### Autologous haematopoietic stem cell transplantation

Tables 2 and 3 summarise the treatment regimen for aHSCT delivery.

#### *Standard supportive care*

1. According to EBMT and other current post-transplant guidelines, screen for late effects screening up to at least 24 months.[18–23]
2. Consideration, at the discretion of the transplant physician, for:
   - Prophylactic broad spectrum antibiotics.
   - Transfusion of platelets to maintain a platelet count of $>20\times10^9$/L.
   - Transfusion of red cells to maintain a haemoglobin concentration of >80 g/L.
3. Antifungal (fluconazole) and antiviral prophylaxis (aciclovir) should aim to continue from the start of conditioning for at least 3 and 12 months post-transplant respectively, at the discretion of the treating clinician.
4. After stable engraftment, pneumocystis prophylaxis with cotrimoxazole for at least 12 months, as per local policy.
5. Where pretransplant antitoxoplasma antibodies are positive oral cotrimoxazole should be given daily until day-1. After engraftment and reconstitution cotrimoxazole should be given three times weekly, as per the pneumocystis prophylaxis schedule for 12 months.
6. CMV surveillance and EBV surveillance with treatment where indicated.

#### *Vaccination*

As routine standard of care, participants will receive vaccinations following aHSCT (table 4), usually via their general practitioner.

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 two doses of MMR and varicella vaccine at least 4 weeks apart as per routine practice. Patients will have an annual Influenza non-live vaccine.

### Disease-modifying therapies

Selection of DMT will be based on the participant's suitability and clinician/participant preference. Standard supportive care will follow institutional protocols.

**Table 1** Inclusion and exclusion criteria

| | |
|---|---|
| Inclusion criteria | |
| 1 | Diagnosis of MS using the 2017 McDonald criteria[38] |
| 2 | Age 16–55 inclusive |
| 3 | EDSS 0–6.0 inclusive* |
| 4 | Severe inflammatory disease defined as RRMS course with 1 or more protocol defined relapses† or evidence of MRI disease activity‡ in the last 12 months (at time of screening) despite being on a DMT, or rapidly evolving severe MS§ in treatment naïve patients¶ |
| 5 | Clinical stability for >30 days following last relapse at time of screening |
| 6 | Confirmation of eligibility from the central neurology team following review |
| 7 | Fitness to undergo aHSCT, in the opinion of the local haematology lead or delegate |
| 8 | Ability to undergo MRI examination |
| Exclusion criteria | |
| 1 | Diagnosis of primary or secondary progressive MS |
| 2 | Disease duration of >10 years from symptom onset (symptoms must be clearly attributable to MS) |
| 3 | Previous use of alemtuzumab, ocrelizumab, ofatumumab or cladribine |
| 4 | Previous HSCT for any reason, or previous experimental or commercial stem cell therapy |
| 5 | JCV antibody index of >1.5 in patients previously treated with natalizumab (unless CSF JCV PCR negative) |
| 6 | Prior diagnosis of Hepatitis B, Hepatitis C or HIV infection or current TB infection |
| 7 | Pregnant or breastfeeding females |
| 8 | Unwilling to use adequate contraception during the trial |
| 9 | Unable to comply with treatment protocol |
| 10 | Contraindication to 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 $100\times10^9$/l or above up are not excluded) |
| 16 | Current diagnosis of a clinically defined autoimmune disorder other than MS |
| 17 | History of myocardial infarction, angina pectoris, stroke or arterial dissection |
| 18 | Participants not considered medically fit for aHSCT defined by any of a-g below. These criteria are not automatic exclusion criteria. If any are met, but the PI believes the participant is medically fit to undergo aHSCT, the case may be put forward to the central team for discussion:<br>a. Renal: creatinine clearance<40 mL/min<br>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<br>c. Concurrent neoplasms or myelodysplasia<br>d. Bone marrow insufficiency (neutropenia with an absolute neutrophil count<$1\times10^9$/l, or thrombocytopenia with a platelet count<$100\times10^9$/l, or anaemia with a haemoglobin<100 g/L)<br>e. Diagnosis of hypertension, which is uncontrolled despite at least two anti-hypertensive agents<br>f. Uncontrolled acute or chronic infection with any infection considered to contraindicate participation (baseline JC virus serology will be recorded, but positivity will not be an exclusion criterion)<br>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 that would represent a significant risk to the safe administration of aHSCT. Potential respiratory disease must be formally evaluated by a respiratory physician via pulmonary function and blood gas measurement |

*Patients with EDSS scores of 0–1.5 must also fulfil the following criteria: short illness duration (<5 years), active disease clinically and radiologically (ie, at least two relapses in the last 12 months and evidence of multiple Gad enhancing MRI lesion), high brain lesion load and brain or spinal cord atrophy.[39]
†See 'Outcomes' section.
‡Two or more new/newly enlarging lesions on a T2 weighted MRI scan.
§Defined as patients with two or more disabling relapses in 1 year, and with one or more gadolinium-enhancing lesions or a significant increase in lesion load on T2 weighted brain MRI compared with a previous MRI.[40]
¶When patients present with RES-MS, and when first-line DMTs are failing to control their disease before a full course of treatment has been completed or other interventions (such as repeated courses of steroids and plasma exchange) have been used but failed to control their illness, they are often referred to as 'treatment naïve'.[2]
aHSCT, autologous haematopoietic stem cell transplantation; CSF, cerebrospinal fluid; DMTs, disease-modifying therapies; EDSS, Expanded Disability Status Scale; G-CSF, granulocyte colony stimulating factor; JCV, John Cunningham virus; PCR, Polymerase Chain Reaction; RES-MS, rapidly evolving severe multiple sclerosis.

### *Alemtuzumab*

Administered by IV infusion over two treatment courses:

- 12 mg/day on 5 consecutive days.
- 12 mg/day on 3 consecutive days, 12 months later.

Liver function will be tested before initial treatment and at monthly intervals until at least 48 months after the last infusion. Platelet count must be checked after the infusion on days 3 and 5 of the first infusion course as

**Table 2** Summary of mobilisation regimen

| Day | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cyclophosphamide 2g/m$^2$ | ✓ | | | | | | | | | | | |
| G-CSF (filgrastim 5–10 µg/kg/day or lenograstim 5–10 µg/kg/day) | | | | | | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Mesna (dose as per local practice) | ✓ | | | | | | | | | | | |
| Monitoring of PB CD34+ count | | | | | | | | ✓* | ✓ | ✓ | ✓ | ✓ |
| Stem cell harvest | | | | | | | | ✓† | ✓† | ✓† | ✓† | ✓† |

*Monitoring of peripheral blood (PB) CD34 counts is approximate and will be carried out according to local practice.
†Stem cell harvest is approximate, this will take place once PB CD34+ levels exceed 10×10$^6$/L.
G-CSF, granulocyte colony stimulating factor.

well as immediately after infusion on day 3 of any subsequent course.

Administration and monitoring will be in accordance with latest available guidelines.

### *Ocrelizumab*

Administered and monitored as per license by intravenous infusion as follows:

- Initial dose—600 mg administered as two separate 300 mg intravenous infusions separated by 2 weeks.
- Subsequent doses—a single 600 mg infusion every 6 months, with a minimum of 5 months. The first subsequent dose should be administered 6 months after the first infusion of the initial dose.

### *Cladribine*

Cladribine administered and monitored as per licence over 2 years (treatment courses) as follows:

- 1.75 mg/kg per year given over two treatment weeks, one at the beginning of the first month and one at the beginning of the second month of the respective treatment year.
- Each treatment week consists of 4 or 5 days on which a patient receives 10 mg or 20 mg (one or two tablets) as a single daily dose, depending on body weight (see online supplemental appendices 2 and 3).

Lymphocyte counts must be:

- Normal before initiating cladribine in year 1.
- At least 800 cells/mm$^3$ before initiating cladribine in year 2.

If necessary, the treatment course in year 2 can be delayed for up to 6 months to allow for recovery of lymphocytes. If this recovery takes more than 6 months, the participant should receive no further cladribine.

**Table 3** Summary of conditioning regimen (after stem cell harvest)

| Day | –6 | –5 | –4 | –3 | –2 | –1 | 0 | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cyclophosphamide 50 mg/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 (1 g/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) (5–10 µg/kg/day) | | | | | | | | | | | | ✓ (continued until absolute neutrophil count>1.0×10$^9$/L for 2 days) |

*Capped at 4 g/day.
†Fever guidance: the prednisolone schedule may be modified based on the opinion of the treating clinician. If fever occurs despite prednisolone, blood cultures will be taken and broad-spectrum antibiotics initiated. Any fever>38C associated with ATG administration may be managed with additional administration of IV methylprednisolone, paracetamol and chlorpheniramine, at the discretion of the treating physician.
G-CSF, granulocyte colony stimulating factor.

Table 4 Standard vaccinations following stem cell transplantation

| Vaccination | Months after stem cell transplant | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
| COVID-19 (SARS-CoV-2) | | * | | | | | | | | | | |
| Pneumococcal conjugate | | | ✓ | ✓ | ✓ | | | | | | | |
| Conjugate HIB (haemophilus influenza type b) | | | | | | ✓ | ✓ | ✓ | | | | |
| DTP (diphtheria, pertussis and tetanus) | | | | | | ✓ | ✓ | ✓ | | | | |
| Inactivated polio | | | | | | ✓ | ✓ | ✓ | | | | |
| Pneumococcal polysaccharide | | | | | | | | | | | | ✓ |

*Revaccination should take place from 2 months onwards based on clinical practice and guidance at the time.

Lymphocyte counts should be monitored at 2 and 6 months after the start of treatment in each treatment year. If the lymphocyte count is below 500 cells/mm$^3$, it should be actively monitored until values increase again.

### *Ofatumumab*

Ofatumumab administered as 20 mg by subcutaneous injection with:

- Initial dosing at weeks 0, 1 and 2, followed by.
- Subsequent monthly dosing starting at week 4.

If an injection is missed, it should be administered as soon as possible without waiting until the next scheduled dose. Subsequent doses should be administered at the recommended intervals.

Administration and supportive care will follow institutional protocols.

## Pregnancy

Patients are not eligible to take part in this trial if they are pregnant or breast feeding at the time of screening. Pregnancy tests will also be performed for patients with childbearing potential 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 alemtuzumab, ocrelizumab and cladribine treatment cycle. Regular pregnancy testing during ofatumumab treatment is not required in standard practice as the treatment is given every 4 weeks. Instead, a pregnancy test will be completed prior to initiation of treatment only.

## Concomitant medications

Participants must wash out any current DMT prior to starting trial treatment. This will usually be a minimum of 6 weeks from the date of last administration to the start of trial treatment (depending on local guidance). This precaution aims to minimise a hypothetical risk of infectious complications (including that of progressive multifocal leukoencephalopathy) through sequential therapies. Steroids may be given throughout the wash-out period at the discretion of the treating clinician.

Live vaccines should not be administered during the study in participants treated with alemtuzumab and should not be administered to participants treated with ocrelizumab or ofatumumab until B-cell repletion occurs. In participants treated with cladribine, live or attenuated live vaccines should be avoided during and after cladribine treatment if the participant's white blood cell counts are not within normal limits.

Antiplatelet or anticoagulant therapy is prohibited except when given:

1. As routine standard-of-care thromboprophylaxis.
2. In the clinically indicated treatment of a venous thromboembolic event or other indication for therapeutic anticoagulant or anti-platelet therapy arising during the trial.

Such events will be appropriately reported and patients assessed on an individualised basis. The events would not automatically exclude patients from continuing the trial protocol treatment and follow-up. Full details of antiplatelet and/or anticoagulant therapy will be documented. The latest version of the alemtuzumab SmPC will be followed.

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 any other medications they may be taking for conditions other than MS, for the duration of the trial.

## Treatment switching

Participants may be offered the opportunity to switch to the treatment given in the alternate arm to that they were randomly allocated if they experience a centrally verified protocol-defined clinical relapse and at least one of the following two criteria: confirmed EDSS progression (defined as an increase of at least one point in the EDSS score compared with baseline, confirmed after 6 months from the time of worsening) or evidence of MRI disease activity (defined as T1W Gd-enhanced lesion or new and/or enlarging T2W lesion).

Switches from DMT to aHSCT will only be permitted after the 12-month follow-up visit and following an appropriate wash out period.

Switches from aHSCT to DMT prior to the 12-month follow-up visit must be discussed with the central trial team.

Participants who switch treatments will remain in the study for follow-up as per the study assessments schedule.

## Outcomes

### Primary outcome

The proportion of patients who have achieved and 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 one full point with an absence of relapse at the time of assessment; any evidence of MRI disease activity as defined by T1W Gd-enhanced lesion or new and/or enlarging T2W lesion after month 6) in the 2-year postrandomisation follow-up period.

#### *Protocol-defined clinical relapses*

All of the criteria must be met to constitute a protocol-defined relapse:

1. Neurological symptoms, either newly appearing or re-appearing, provided these are
   1. Preceded by at least 30 days of clinical stability.
   2. Lasting for at least 24 hours.
2. Absence of fever or known infection (temperature>37.5°C)
3. Objective neurological impairment, correlating with the participant's reported symptoms, defined as either
   1. Increase in at least two of the functional system scores of the EDSS.
   2. Increase in the total EDSS step score of at least one full point

If the above criteria are met, but there is another confirmed cause that explains the symptoms, this will not be considered a relapse. All suspected relapses will be centrally adjudicated in a blinded fashion by at least one member of the central neurology team.

#### *EDSS progression*

True progression in terms of NEDA is defined as an increase in at least one full point in the EDSS score compared with baseline, confirmed after 6 months from the time of worsening, with an absence of relapse at the time of assessment.[6 24–26]

#### *MRI disease activity*

MRI scans (sequences in online supplemental appendix 4) taken at months 6, 12 and 24 postrandomisation will measure disease activity, defined by T1W Gd-enhanced lesion and/or enlarging T2W lesions. Scans taken at month 6 will serve as a stable rebaseline, and future MRIs (at months 12 and 24) will be assessed against this criterion.

### Secondary outcomes

#### *Safety*

The following, occurring in the 2-year follow-up period:

- Rate of adverse events and serious adverse events.
- Mortality rate.
- Long-term safety events, including significant infections, endocrine and reproductive dysfunction, secondary autoimmune diseases, incidence of late cardiovascular events, neoplasia and any other significant organ dysfunction.

#### *Clinical outcomes*

- Time to evidence of disease activity.
- Scores on the following at 3, 6, 9, 12, 18 and 24-month postrandomisation.
  - EDSS*.
  - Multiple sclerosis functional composite*.
  - Low contrast visual acuity*.
  - Symbol digit modality test.

*Assessments to be completed by a blinded member of staff.

#### *QoL/health economic measures*

Scores on the following at 3, 6, 9, 12, 18 and 24-month postrandomisation

- EuroQol 5 dimension 5 level.[27]
- Short form 36.[28]
- Global rating of change.[29]
- Multiple Sclerosis Quality of Life-54.[30]
- Neurological Fatigue Index Multiple Sclerosis.[31]
- Hospital Anxiety and Depression Scale.[32]

### Exploratory outcomes

#### *Mechanistic study outcomes*

1. Metrics of immune reconstitution and potential mechanisms
   1. Immune diversity indices of TCR and BCR repertoire at baseline and 24 months.
   2. Depletion of circulating CD8+/MAIT cell subset expressed as percent variation of absolute counts (baseline to 12 months).
   3. Reconstitution of naïve-T and B cell profiles and 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*

Scores on the following at 12 and 24 months postrandomisation:

1. CANTAB.
2. BICAMS.

#### *OCT study outcomes*

Retinal nerve fibre, ganglion-cell layer and retinal inner nuclear layer thickness are assessed by OCT imaging at 12 and 24-month postrandomisation.

### Power calculation

The primary binary outcome is the proportion of patients who have maintained NEDA at 2 years from randomisation. The original study design was a head to head trial of alemtuzumab versus aHSCT. Based on this design, the sample size was calculated by assuming 40% NEDA in the control arm,[33 34] and that an absolute increase of 25%–65% NEDA is of clinical importance. To achieve 90% power, using a continuity corrected $\chi^2$ test at the 5%

(two-sided) level, detecting this difference requires 90 patients per group (ie, 180 in total). Adjusting for a 10% attrition rate will require a total of 198 patients.

Following the addition of ocrelizumab, ofatumumab and cladribine, and the results of the MIST trial, the sample size was reviewed. The MIST trial estimated the NEDA rate at 24 months follow-up as 95% in 53 patients with RRMS who received aHSCT.[6] This new NEDA estimate is higher than the 78%–85% reported previously. Based on the best available literature,[33–35] we assume 50% NEDA in the control arm and conservatively assume an NEDA rate of 75% in the aHSCT arm: that is, an absolute increase in 25% gives a sample size of 85 per group (170 in total). With 10% attrition rate, the sample size increases to 95 per group (N=2×95=190), almost the same as the original sample size calculation of N=198.

### Study assessments and follow-up

Assessments and follow-up visits will take place as per the study assessments table (online supplemental appendix 1).

## Statistical analysis

Data will be reported and presented according to the revised Consolidated Standards of Reporting Trials statement.[36 37] All statistical exploratory tests will be two tailed with $\alpha$=0.05. 95% CIs will be calculated and reported for each test as appropriate.

### Primary outcome

Primary effectiveness analyses will be performed on an intention-to-treat (ITT) basis. Participants with missing outcome data for any reason will be considered as treatment failures and excluded from the numerator of the NEDA rate but included in the denominator.

The primary effectiveness analysis will compare the NEDA rate, at 2 years postrandomisation, between the two arms (aHSCT vs DMT). A multiple logistic regression will be modelled with the centre as a random covariate and baseline EDSS score as a fixed covariate; the 95% CI for treatment group parameter and the OR will be reported. The absolute difference in the estimated NEDA rate between the two randomised groups and its associated CI will also be calculated. Participants who switch treatments will be regarded as a treatment failure.

#### *Sensitivity analyses*

Sensitivity to missing data assumptions in the ITT will be explored using a best-case scenario (patients with missing NEDA data apart from deaths assumed to be disease free) alongside multiple imputation using chained equations (MICE).

### Safety outcomes and adverse events

A $\chi^2$ test will compare the SAE rate between the two arms. Secondary outcomes such as mortality and SAE rates will be compared using Fisher's exact test. The total number of adverse events (AEs) experienced by each patient in the 100 days postrandomisation, in each arm will be compared with a Poisson generalised linear model. The relative risk will be reported.

### Secondary outcomes

Time to evidence of disease activity will be summarised with Kaplan-Meier estimates and compared between the arms using the log-rank test. A HR will be estimated using a Cox-proportional HR model. Patients with NEDA will be censored at their last known date of postrandomisation follow-up.

For all continuous secondary outcomes, treatment effect at each time point will be estimated using a three-level mixed effect linear model with arm, time point, arm by time point interactions, baseline score and EDSS groups as fixed covariates and with sites, participants and repeated measures as random effects. The statistical analysis plan contains full details.

### Subgroup analyses

Exploratory subgroup analyses, using multiple logistic regression, with the primary outcome NEDA status at 24-month postrandomisation as the response will be carried out. An interaction statistical test between the randomised intervention group and subgroup will directly examine the strength of evidence for the treatment difference between the treatment groups varying between subgroups. Age and disability levels (based on baseline EDSS score) will be the only a priori defined subgroups to be considered for an interaction test. Subgroup analysis will be performed regardless of the statistical significance on the overall intervention effect.

The primary outcome, NEDA-3 rate at 24 months, will be calculated separately in the DMT arm for those treated with alemtuzumab, ocrelizumab, ofatumumab and cladribine. We will conduct exploratory comparisons of individual treatments and calculate the difference in NEDA rates for all pairwise comparisons of aHSCT, ocrelizumab, cladribine, alemtuzumab and ofatumumab-treated patients. Note that these are exploratory (and non-randomised) comparisons and not subjected to the benefits of randomisation, as the characteristics of the drug sub-groups may not be balanced when compared with aHSCT.

## Patient and public involvement

A patient and public involvement (PPI) panel reviewed the project prior to the funding application to provide input on the design, methodology and overall patient experience of the project proposal. A participant from the MIST trial has been included as a coapplicant for the grant helping shape the project and, along with a PPI forum consisting of MS patients who have previously undergone aHSCT, reviewed all patient-facing documents.

The trial has PPI representatives as part of the Trial Steering Committee (TSC) in order to ensure ongoing PPI involvement in the management of the trial. In addition, there will be PPI representation on the Trial Management Group (TMG) to ensure that the study team

does not lose sight of what is important to patients when making key decisions. PPI representatives will be involved in advance of disseminating the findings of the research.

### Study status

The StarMS trial began recruitment in September 2021. Recruitment is expected to continue until January 2024 with follow-up completed in January 2026. The current protocol is V.6.1, 05 July 2022.

## ETHICS AND DISSEMINATION

The study was approved by the Yorkshire and Humber—Leeds West Research Ethics Committee (ref: 20/YH/0061). Any amendments will be submitted and approved by the ethics committee. A Clinical Trial Authorisation (CTA) was granted by the Medicines and Healthcare products Regulatory Agency (MHRA) (CTA 21304/0273/001–0001). Participants will provide written informed consent (see online supplemental file 2) prior to any study-specific procedures. The study results will be submitted to a peer-reviewed journal and abstracts will be submitted to relevant national and international conferences.

All AEs will be recorded from consent until the participant has completed the trial, and assessed for severity and relatedness to the trial IMPs and Non Investigational Medicinal Products (NIMPs). Suspected unexpected serious adverse reactions will be reported to the appropriate regulatory and ethics bodies by the Clinical Trials Research Unit (CTRU). COVID-19 infections will be recorded as an adverse event of special interest.

Three committees will govern study conduct, deliver the trial, monitor its performance and ensure its safety: a TSC, Data Monitoring and Ethics Committee and TMG.

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**Contributors** GB and JP jointly wrote the first manuscript and are involved in the study implementation. KEMD, RG, KH, ER edited the manuscript and are involved in study implementation. DPap, CC were involved in the design of the trial and will be involved in oversight of study implementation. CB contributed to study design as a patient representative. MB contributed to the detail of the statistical analysis plan and reviewed the document. OC, AJC, GG, IG, MK, CK, RN, DPal, AP, NS, ES, TdS, AV, CY contributed to study design. TdS designed and leads the vaccination sub-study. AV designed and leads the neuropsychology sub-study. SJW was involved with the design of the trial in general and designed the Statistical analysis in particular. JAS, BS and PAM jointly led the study conception, design, funding application and co-chair the study, contributing to study management and central eligibility review; and PAM leads the immunological mechanistic sub-study. All authors read and approved the final manuscript.

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terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.



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