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Autologous stem cell transplantation versus alemtuzumab, ocrelizumab, ofatumumab or cladribine in relapsing-remitting multiple sclerosis

Submission date
07/09/2020

Recruitment status
No longer recruiting

Registration date
09/09/2020

Overall study status
Ongoing

Last Edited
07/10/2024

Condition category
Nervous System Diseases

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Background and study aims
Multiple sclerosis is a chronic autoimmune inflammatory disease of the central nervous system which leads to impairment in strength, sensation, balance, vision, cognition and sphincter function. Relapsing-remitting multiple sclerosis (RRMS) is a type of multiple sclerosis with flare-ups and periods of remission in between. For patients with highly active relapsing-remitting multiple sclerosis (RRMS), disease-modifying therapies are available but there is growing evidence that autologous haematopoietic stem cell transplantation (aHSCT) may be more effective in reducing relapse rates and improving disability and quality of life. The aim of this study is to compare aHSCT against the four most effective disease-modifying therapies currently available in the UK, alemtuzumab, ocrelizumab, ofatumumab and cladribine.

Who can participate?
Patients aged between 16 and 55 with highly active RRMS

What does the study involve?
Patients will be randomly allocated to receive either aHSCT or a disease-modifying therapy (alemtuzumab, ocrelizumab, ofatumumab or cladribine). For patients who receive aHSCT, some of their stem cells will be removed (harvested) from their peripheral blood and stored. Patients will then undergo a process to eliminate their immune cells. Then the stem cells that were harvested earlier are transplanted (re-infused) back into the patients' blood. The re-infused stem cells give rise to a new generation of immune cells, replacing cells of the original ‘sick’ immune system. Patients who are allocated to receive a DMT will receive either alemtuzumab, ocrelizumab, ofatumumab or cladribine. The local treating clinician will decide which treatment each patient should receive based on standard clinical criteria and will involve patients in this decision. In patients who receive alemtuzumab, the drug will be given as an intravenous (IV) infusion (into a vein) on two occasions 12 months apart. In patients who receive ocrelizumab, the drug is given as an IV infusion at 6-monthly intervals. In patients who receive ofatumumab, the drug is given by subcutaneous (under the skin) injection at monthly intervals. In patients who

receive cladribine, the drug is given as an oral tablet taken over two treatment courses (over 2 years). Participants will be followed up within the trial for 2 years to compare the effectiveness of aHSCT against these four DMTs. The safety profile of both treatment options will also be compared along with effects on cognitive function and quality of life.

What are the possible benefits and risks of participating?
It is not known which treatment is more effective at treating RRMS and this is the reason for carrying out this study. The results of this study will inform the treatment of future patients with highly active RRMS. The study will also be looking at the way in which stem cell transplant works in the body. By taking part in the study, participants will be directly helping to do this.
Participants will be contacted regularly by the study nurse during the study, so will receive more follow-up care than normal. They will also be given a phone number for the study team in case they have any questions or concerns.
The study treatments can all cause side effects, some of which can be serious. Full details will be provided before patients decide whether or not to take part. They are also given the opportunity to discuss this in detail with the study doctor.
Taking part in this study will mean additional appointments at the hospital. Although this means extra travel, participants will be reimbursed for travel costs in attending these hospital appointments if required.

Where is the study run from?
University of Sheffield (UK)

When is the study starting and how long is it expected to run for?
March 2019 to September 2026

Who is funding the study?
National Institute for Health Research Efficacy and Mechanism Evaluation (EME) Programme (UK)

Who is the main contact?
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Contact information

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Additional identifiers

Clinical Trials Information System (CTIS)
2019-001549-42

Integrated Research Application System (IRAS)
265127

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
CPMS 44920, IRAS 265127

Study information

Scientific Title
A multicentre, randomised controlled trial to evaluate the efficacy of autologous haematopoietic stem cell transplantation versus alemtuzumab, ocrelizumab, ofatumumab or cladribine in relapsing-remitting multiple sclerosis

Acronym
StarMS

Study objectives
Current study hypothesis as of 07/10/2022:
aHSCT is more efficacious at achieving 'No Evidence of Disease Activity' (NEDA) than treatment with a highly effective disease-modifying therapy (alemtuzumab, ocrelizumab, ofatumumab or cladribine) and has an acceptable safety profile in patients with highly active RRMS.

Previous study hypothesis:
aHSCT is more efficacious at achieving 'No Evidence of Disease Activity' (NEDA) than treatment

with a highly effective disease-modifying therapy (alemtuzumab or ocrelizumab) and has an acceptable safety profile in patients with highly active RRMS.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 19/03/2020, Yorkshire and the Humber - Leeds West (NHSBT Newcastle Blood Donor Centre, Holland Drive, Newcastle upon Tyne, NE2 4NQ, UK; +44 (0)207 1048 007; leedswest.rec@hra.nhs.uk), REC ref: 20/YH/0061

Study design
Randomized; Interventional; Design type: Treatment, Drug, Other

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Relapsing-remitting multiple sclerosis

Interventions
Current interventions as of 07/10/2022:
The StarMS study will run in multiple hospitals throughout the UK. It will compare treatment with autologous haematopoietic stem cell transplantation (aHSCT) with the most effective disease-modifying therapy (DMT) for highly active relapsing-remitting multiple sclerosis (RRMS).

Recruitment and screening
Approximately 19 hospital sites across the UK will participate in the StarMS trial. Patients with highly active RRMS will be identified by their local clinician and invited to take part. If their local clinician is not part of a site which is participating in StarMS, patients will be referred to their closest StarMS centre via a clinical referral for discussion about their ongoing treatment which may include the StarMS trial if the neurologist thinks this is appropriate. All potential participants will speak with a representative from the haematology and neurology teams at their local participating centre to discuss the trial and procedures. If they wish to take part, informed consent will be obtained and the participant will proceed to have full screening procedures carried out. Participants will be instructed on the requirement and process for washing out their current treatment if applicable.

There are a number of optional tests which participants can take part in if they wish. These will be discussed with the patient and it will be made clear to them that they can still take part in the main trial, even if they do not wish to undergo the additional assessments. The optional aspects are: blood sample collection for mechanistic studies, cognitive function tests, optical coherence tomography (OCT), blood sample storage for future research and cerebrospinal fluid (CSF) collection for future research. As part of the screening procedures, participants will undergo a physical and neurological examination. A disability assessment will also be performed and information will be collected regarding medical history including MS and medication history. If the patient appears to be eligible, further screening assessments will be completed. These will include blood tests, urinalysis, a dental examination, chest x-ray, cardiac assessments (ECG and

echocardiogram) and a pulmonary function test. Patients will also be given the opportunity to discuss fertility treatment options if applicable.

Baseline and randomisation
If the participant meets the eligibility criteria based on the results of the screening assessments, the case will be referred to the central neurology team who will review key details for all patients to confirm eligibility. No personal data will be shared with the central team and the participants will be informed of this requirement prior to consent. If the central team confirms the patient is suitable, a number of baseline assessments will be completed. These include a number of quality of life questionnaires, a neurology assessment to check for any evidence of disease activity, MRI, a disability assessment, a visual examination, cognitive function tests, blood tests for laboratory analyses and OCT scan.

Patients will then be randomly allocated to receive either stem cell transplant or DMT. Participants allocated to the DMT arm will be treated with alemtuzumab, ocrelizumab, ofatumumab or cladribine. This decision will be made locally and will be based on the participants' suitability for the drugs as well as clinician/participant preference. Trial treatment will start within 4 weeks of randomisation. The start of treatment for stem cell transplantation is defined as the date of the first administration of cyclophosphamide for mobilisation.

aHSCT group
Mobilisation: participants will first undergo the process of mobilisation. This involves infusion of cyclophosphamide (2 g/m^2) which is a strong immune-suppressing chemotherapy drug. Participants will then receive daily injections of G-CSF (growth factor), starting 5 days after the infusion of cyclophosphamide. As a result, stem cells will migrate from the bone marrow to the blood. Enough cells can usually be counted after approximately 5 days of treatment with G-CSF but this varies between patients. Daily CD34+ counts will commence from around day 7 following cyclophosphamide in order to monitor levels. During the mobilisation phase, Mesna will be given in line with local practice to prevent haemorrhagic cystitis.

Leukapheresis: once there are sufficient stem cells in the bloodstream, they will be harvested (a process called leukapheresis). This procedure requires inserting two needles into two veins, one in each arm (or rarely the neck). One needle is used to transport blood via a tube to the centrifuge, the machine that separates the stem cells from the blood itself; whereas the other needle and tube are used to re-infuse the reminder of the blood back into the participant. The whole procedure takes about 3–5 hours. The amount of blood in the infusion system is always less than ½ litre of blood. The collected cells will be cryopreserved (frozen) until later use at transplantation (see below). A small number of participants may experience a failure of blood stem cells collection. In this case, the Haematologist may decide either to repeat the procedure or to exclude the participant from the trial.

Conditioning: the conditioning regimen includes infusions of cyclophosphamide (50 mg/kg/day) given on 4 days. Antithymocyte globulin (‘ATG’) is also given for 5 days starting the same day as cyclophosphamide at increasing doses. ATG is a protein derived from rabbits that is commonly used to effectively deplete immune cells in recipients of stem cell transplantation. Again, Mesna will be given in line with local practice. Methylprednisolone (1 g/day), paracetamol and chlorpheniramine are given alongside ATG, to mitigate some of the effects of the chemotherapy.

Stem cell reinfusion: On the day after the last infusion of ATG, harvested blood stem cells will be reinfused into the patient (‘autologous stem cell transplantation’). Five days after the reintroduction of the stem cells, participants are given G-CSF (Filgrastim or Lenograstim; 5-10 mcg/kg/day) to stimulate further development of new immune cells from the infused stem cells.

Participants may be in hospital for several weeks to carry out these steps and will be monitored closely for any unwanted consequences that may occur as a result of the therapy. Antibiotic treatment and transfusions of red blood cells or platelets are usually necessary in the period immediately following the transplantation, and will be administered as per local usual clinical practice. Follow up tests and visits that are routine following HSCT will be carried out according to local policies, and may be in addition to defined study visits.

After being discharged from hospital, participants will have weekly follow up visits up to 100 days after the stem cell reinfusion. Viral (CMV and EBV) screening will be completed at these visits. Participants and their GPs will be provided with guidance regarding re-vaccination and details will be captured for the trial.

DMT group
Participants allocated to the DMT group will receive either alemtuzumab, ocrelizumab, ofatumumab or cladribine at the discretion of the local treating clinician. Alemtuzumab is administered over two treatment courses: initially 12 mg/day for five days then 12 months later this is followed by 12 mg/day for 3 days. Ocrelizumab is given at 6-monthly intervals. The initial dose is 600 mg administered by two separate infusions 2 weeks apart. Future doses are given as a single 600 mg infusion. Ofatumumab is administered as 20mg by subcutaneous injection with initial dosing at weeks 0, 1 and 2 followed by subsequent monthly dosing at week 4. Cladribine is administered over two years 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. Follow up visits will be completed as per the details below. The timing of follow up visits will be calculated from randomisation.

3-month visit: concomitant medication review, physical examination, disability assessments, blood tests, performance status, relapse assessment, visual test, questionnaires, adverse event assessment, blood samples taken for research and symbol digit modalities test.

6-month visit: concomitant medication review, MRI, physical examination, disability assessments, blood tests, performance status, relapse assessment, visual test, questionnaires, adverse event assessment, blood samples taken for research and symbol digit modalities test.

9-month visit: concomitant medication review, physical examination, disability assessments, blood tests, performance status, relapse assessment, visual test, questionnaires, adverse event assessment, blood samples taken for research and symbol digit modalities test.

12-month visit: concomitant medication review, MRI, cardiac function tests (ECG and echocardiogram), pulmonary function tests, physical examination, disability assessments, blood tests, performance status, relapse assessment, visual test, questionnaires, cognitive function test, adverse event assessment, OCT scan, blood samples taken for research and symbol digit modalities test.

18-month visit: concomitant medication review, physical examination, disability assessments, blood tests, performance status, relapse assessment, visual test, questionnaires, adverse event assessment, blood samples taken for research and symbol digit modalities test.

24-month visit (primary endpoint): concomitant medication review, MRI, cardiac function tests (ECG and echocardiogram), pulmonary function tests, physical examination, disability assessments, blood tests, performance status, relapse assessment, visual test, questionnaires, cognitive function test, adverse event assessment, OCT scan, blood samples taken for research and symbol digit modalities test.

Optional CSF collection.
In the event that a participant experiences a relapse during the study, they will be asked to attend for an appointment as soon as possible in order that a full assessment of the relapse can be completed.

Participants may be offered the opportunity to switch to the treatment given in the alternate arm to that which they were randomly allocated if their disease remains active. Ongoing care: Ongoing care after the trial is at the discretion of the investigator and treating physician. For participants allocated to the DMT arm, this could include aHSCT if permitted by NHS England (NHSE) specialist commissioning at that time.

Previous interventions from 08/02/2022 to 07/10/2022:
The StarMS study will run in multiple hospitals throughout the UK. It will compare treatment with autologous haematopoietic stem cell transplantation (aHSCT) with the most effective disease-modifying therapy (DMT) for highly active relapsing-remitting multiple sclerosis (RRMS).

Recruitment and screening
Approximately 19 hospital sites across the UK will participate in the StarMS trial. Patients with highly active RRMS will be identified by their local clinician and invited to take part. If their local clinician is not part of a site which is participating in StarMS, patients will be referred to their closest StarMS centre via a clinical referral for discussion about their ongoing treatment which may include the StarMS trial if the neurologist thinks this is appropriate. All potential participants will speak with a representative from the haematology and neurology teams at their local participating centre to discuss the trial and procedures. If they wish to take part, informed consent will be obtained and the participant will proceed to have full screening procedures carried out. Participants will be instructed on the requirement and process for washing out their current treatment if applicable.

There are a number of optional tests which participants can take part in if they wish. These will be discussed with the patient and it will be made clear to them that they can still take part in the main trial, even if they do not wish to undergo the additional assessments. The optional aspects are: blood sample collection for mechanistic studies, cognitive function tests, optical coherence tomography (OCT), blood sample storage for future research and cerebrospinal fluid (CSF) collection for future research. As part of the screening procedures, participants will undergo a physical and neurological examination. A disability assessment will also be performed and information will be collected regarding medical history including MS and medication history. If the patient appears to be eligible, further screening assessments will be completed. These will include blood tests, urinalysis, a dental examination, chest x-ray, cardiac assessments (ECG and echocardiogram) and a pulmonary function test. Patients will also be given the opportunity to discuss fertility treatment options if applicable.

Baseline and randomisation
If the participant meets the eligibility criteria based on the results of the screening assessments, the case will be referred to the central neurology team who will review key details for all patients to confirm eligibility. No personal data will be shared with the central team and the participants will be informed of this requirement prior to consent. If the central team confirms the patient is suitable, a number of baseline assessments will be completed. These include a number of quality of life questionnaires, a neurology assessment to check for any evidence of disease activity, MRI, a disability assessment, a visual examination, cognitive function tests, blood tests for laboratory analyses and OCT scan.

Patients will then be randomly allocated to receive either stem cell transplant or DMT. Participants allocated to the DMT arm will be treated with alemtuzumab, ocrelizumab or cladribine. This decision will be made locally and will be based on the participants' suitability for the drugs as well as clinician/participant preference. Trial treatment will start within 4 weeks of randomisation. The start of treatment for stem cell transplantation is defined as the date of the first administration of cyclophosphamide for mobilisation.

aHSCT group
Mobilisation: participants will first undergo the process of mobilisation. This involves infusion of cyclophosphamide (2 g/m²) which is a strong immune-suppressing chemotherapy drug. Participants will then receive daily injections of G-CSF (growth factor), starting 5 days after the infusion of cyclophosphamide. As a result, stem cells will migrate from the bone marrow to the blood. Enough cells can usually be counted after approximately 5 days of treatment with G-CSF but this varies between patients. Daily CD34+ counts will commence from around day 7 following cyclophosphamide in order to monitor levels. During the mobilisation phase, Mesna will be given in line with local practice to prevent haemorrhagic cystitis.

Leukapheresis: once there are sufficient stem cells in the bloodstream, they will be harvested (a process called leukapheresis). This procedure requires inserting two needles into two veins, one in each arm (or rarely the neck). One needle is used to transport blood via a tube to the centrifuge, the machine that separates the stem cells from the blood itself; whereas the other needle and tube are used to re-infuse the reminder of the blood back into the participant. The whole procedure takes about 3–5 hours. The amount of blood in the infusion system is always less than ½ litre of blood. The collected cells will be cryopreserved (frozen) until later use at transplantation (see below). A small number of participants may experience a failure of blood stem cells collection. In this case, the Haematologist may decide either to repeat the procedure or to exclude the participant from the trial.

Conditioning: the conditioning regimen includes infusions of cyclophosphamide (50 mg/kg/day) given on 4 days. Antithymocyte globulin (‘ATG’) is also given for 5 days starting the same day as cyclophosphamide at increasing doses. ATG is a protein derived from rabbits that is commonly used to effectively deplete immune cells in recipients of stem cell transplantation. Again, Mesna will be given in line with local practice. Methylprednisolone (1 g/day), paracetamol and chlorpheniramine are given alongside ATG, to mitigate some of the effects of the chemotherapy.

Stem cell reinfusion: On the day after the last infusion of ATG, harvested blood stem cells will be reinfused into the patient (‘autologous stem cell transplantation’). Five days after the reintroduction of the stem cells, participants are given G-CSF (Filgrastim or Lenograstim; 5-10 mcg/kg/day) to stimulate further development of new immune cells from the infused stem cells. Participants may be in hospital for several weeks to carry out these steps and will be monitored closely for any unwanted consequences that may occur as a result of the therapy. Antibiotic treatment and transfusions of red blood cells or platelets are usually necessary in the period immediately following the transplantation, and will be administered as per local usual clinical practice. Follow up tests and visits that are routine following HSCT will be carried out according to local policies, and may be in addition to defined study visits.

After being discharged from hospital, participants will have weekly follow up visits up to 100 days after the stem cell reinfusion. Viral (CMV and EBV) screening will be completed at these visits. Participants and their GPs will be provided with guidance regarding re-vaccination and details will be captured for the trial.

DMT group
Participants allocated to the DMT group will receive either alemtuzumab, ocrelizumab or cladribine at the discretion of the local treating clinician. Alemtuzumab is administered over two treatment courses: initially 12 mg/day for five days then 12 months later this is followed by 12 mg/day for 3 days. Ocrelizumab is given at 6-monthly intervals. The initial dose is 600 mg administered by two separate infusions 2 weeks apart. Future doses are given as a single 600 mg infusion. Cladribine is administered over two years as follows: 1.75mg/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. Follow up visits will be completed as per the details below. The timing of follow up visits will be calculated from randomisation.

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6-month visit: concomitant medication review, MRI, physical examination, disability assessments, blood tests, performance status, relapse assessment, visual test, questionnaires, adverse event assessment, blood samples taken for research and symbol digit modalities test.

9-month visit: concomitant medication review, physical examination, disability assessments, blood tests, performance status, relapse assessment, visual test, questionnaires, adverse event assessment, blood samples taken for research and symbol digit modalities test.

12-month visit: concomitant medication review, MRI, cardiac function tests (ECG and echocardiogram), pulmonary function tests, physical examination, disability assessments, blood tests, performance status, relapse assessment, visual test, questionnaires, cognitive function test, adverse event assessment, OCT scan, blood samples taken for research and symbol digit modalities test.

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Optional CSF collection.
In the event that a participant experiences a relapse during the study, they will be asked to attend for an appointment as soon as possible in order that a full assessment of the relapse can be completed.

Participants may be offered the opportunity to switch to the treatment given in the alternate arm to that which they were randomly allocated if their disease remains active. Ongoing care: Ongoing care after the trial is at the discretion of the investigator and treating physician. For participants allocated to the DMT arm, this could include aHSCT if permitted by NHS England (NHSE) specialist commissioning at that time.

Previous interventions from 26/01/2021 to 08/02/2022:
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with autologous haematopoietic stem cell transplantation (aHSCT) with the most effective disease-modifying therapy (DMT) for highly active relapsing-remitting multiple sclerosis (RRMS).

Recruitment and screening
Approximately 19 hospital sites across the UK will participate in the StarMS trial. Patients with highly active RRMS will be identified by their local clinician and invited to take part. If their local clinician is not part of a site which is participating in StarMS, patients will be referred to their closest StarMS centre via a clinical referral for discussion about their ongoing treatment which may include the StarMS trial if the neurologist thinks this is appropriate. All potential participants will speak with a representative from the haematology and neurology teams at their local participating centre to discuss the trial and procedures. If they wish to take part, informed consent will be obtained and the participant will proceed to have full screening procedures carried out. Participants will be instructed on the requirement and process for washing out their current treatment if applicable.

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DMT group
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9-month visit: concomitant medication review, physical examination, disability assessments, blood tests, performance status, relapse assessment, visual test, questionnaires, adverse event assessment, blood samples taken for research and symbol digit modalities test.

12-month visit: concomitant medication review, MRI, cardiac function tests (ECG and echocardiogram), pulmonary function tests, physical examination, disability assessments, blood tests, performance status, relapse assessment, visual test, questionnaires, cognitive function test, adverse event assessment, OCT scan, blood samples taken for research and symbol digit modalities test.

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In the event that a participant experiences a relapse during the study, they will be asked to attend for an appointment as soon as possible in order that a full assessment of the relapse can be completed.

Participants may be offered the opportunity to switch to the treatment given in the alternate arm to that which they were randomly allocated if their disease remains active. Ongoing care: Ongoing care after the trial is at the discretion of the investigator and treating physician. For participants allocated to the DMT arm, this could include aHSCT if permitted by NHS England (NHSE) specialist commissioning at that time.

Original interventions:
The StarMS study will run in multiple hospitals throughout the UK. It will compare treatment with autologous haematopoietic stem cell transplantation (aHSCT) with the most effective disease-modifying therapy (DMT) for highly active relapsing-remitting multiple sclerosis (RRMS).

Recruitment and screening
Approximately 19 hospital sites across the UK will participate in the StarMS trial. Patients with highly active RRMS will be identified by their local clinician and invited to take part. If their local clinician is not part of a site which is participating in StarMS, patients will be referred to their closest StarMS centre via a clinical referral for discussion about their ongoing treatment which may include the StarMS trial if the neurologist thinks this is appropriate. All potential participants will speak with a representative from the haematology and neurology teams at their local participating centre to discuss the trial and procedures. If they wish to take part, informed consent will be obtained and the participant will proceed to have full screening procedures carried out. Participants will be instructed on the requirement and process for washing out their current treatment if applicable.

There are a number of optional tests which participants can take part in if they wish. These will be discussed with the patient and it will be made clear to them that they can still take part in the main trial, even if they do not wish to undergo the additional assessments. The optional aspects are: blood sample collection for mechanistic studies, cognitive function tests, optical coherence tomography (OCT) and blood sample storage for future research. As part of the screening procedures, participants will undergo a physical and neurological examination. A disability assessment will also be performed and information will be collected regarding medical history including MS and medication history. If the patient appears to be eligible, further screening assessments will be completed. These will include blood tests, urinalysis, a dental examination, chest x-ray, cardiac assessments (ECG and echocardiogram) and a pulmonary function test.

Patients will also be given the opportunity to discuss fertility treatment options if applicable.

Baseline and randomisation
If the participant meets the eligibility criteria based on the results of the screening assessments, the case will be referred to the central neurology team who will review key details for all patients to confirm eligibility. No personal data will be shared with the central team and the participants will be informed of this requirement prior to consent. If the central team confirms the patient is suitable, a number of baseline assessments will be completed. These include a number of quality of life questionnaires, a neurology assessment to check for any evidence of disease activity, MRI, a disability assessment, a visual examination, cognitive function tests, blood tests for laboratory analyses and OCT scan.

Patients will then be randomly allocated to receive either stem cell transplant or DMT. Participants allocated to the DMT arm will be treated with alemtuzumab or ocrelizumab. This decision will be made locally and will be based on the participants suitability for the drugs as well as clinician/participant preference.

Trial treatment will start within 4 weeks of randomisation. The start of treatment for stem cell transplantation is defined as the date of the first administration of cyclophosphamide for mobilisation.

aHSCT group
Mobilisation: participants will first undergo the process of mobilisation. This involves infusion of cyclophosphamide (2 g/m^2) which is a strong immune-suppressing chemotherapy drug. Participants will then receive daily injections of G-CSF (growth factor), starting 5 days after the infusion of cyclophosphamide. As a result, stem cells will migrate from the bone marrow to the blood. Enough cells can usually be counted after approximately 5 days of treatment with G-CSF but this varies between patients. Daily CD34+ counts will commence from around day 7 following cyclophosphamide in order to monitor levels. During the mobilisation phase, Mesna will be given in line with local practice to prevent haemorrhagic cystitis.

Leukapheresis: once there are sufficient stem cells in the bloodstream, they will be harvested (a process called leukapheresis). This procedure requires inserting two needles into two veins, one in each arm (or rarely the neck). One needle is used to transport blood via a tube to the centrifuge, the machine that separates the stem cells from the blood itself; whereas the other needle and tube are used to re-infuse the reminder of the blood back into the participant. The whole procedure takes about 3–5 hours. The amount of blood in the infusion system is always less than ½ litre of blood. The collected cells will be cryopreserved (frozen) until later use at transplantation (see below). A small number of participants may experience a failure of blood stem cells collection. In this case, the Haematologist may decide either to repeat the procedure or to exclude the participant from the trial.

Conditioning: the conditioning regimen includes infusions of cyclophosphamide (50 mg/kg/day) given on 4 days. Antithymocyte globulin ('ATG') is also given for 5 days starting the same day as cyclophosphamide at increasing doses. ATG is a protein derived from rabbits that is commonly used to effectively deplete immune cells in recipients of stem cell transplantation. Again, Mesna will be given in line with local practice. Methylprednisolone (1 g/day), paracetamol and chlorpheniramine are given alongside ATG, to mitigate some of the effects of the chemotherapy.

Stem cell reinfusion: On the day after the last infusion of ATG, harvested blood stem cells will be reinfused into the patient ('autologous stem cell transplantation'). Five days after the reintroduction of the stem cells, participants are given G-CSF (Filgrastim or Lenograstim; 5-10 mcg/kg/day) to stimulate further development of new immune cells from the infused stem cells.

Participants may be in hospital for several weeks to carry out these steps and will be monitored closely for any unwanted consequences that may occur as a result of the therapy. Antibiotic treatment and transfusions of red blood cells or platelets are usually necessary in the period immediately following the transplantation, and will be administered as per local usual clinical practice. Follow up tests and visits that are routine following HSCT will be carried out according to local policies, and may be in addition to defined study visits.

After being discharged from hospital, participants will have weekly follow up visits up to 100 days after the stem cell reinfusion. Viral (CMV and EBV) screening will be completed at these visits. Participants and their GPs will be provided with guidance regarding re-vaccination and details will be captured for the trial.

DMT group
Participants allocated to the DMT group will receive either alemtuzumab or ocrelizumab at the discretion of the local treating clinician. Alemtuzumab is administered over two treatment courses: initially 12 mg/day for five days then 12 months later this is followed by 12 mg/day for three days. Ocrelizumab is given at 6-monthly intervals. The initial dose is 600 mg administered by two separate infusions 2 weeks apart. Future doses are given as a single 600 mg infusion.

Follow up visits will be completed as per the details below. The timing of follow up visits will be calculated from randomisation.

3-month visit: concomitant medication review, physical examination, disability assessments, blood tests, performance status, relapse assessment, visual test, questionnaires, cognitive function test, adverse event assessment and blood samples taken for research.

6-month visit: concomitant medication review, MRI, physical examination, disability assessments, blood tests, performance status, relapse assessment, visual test, questionnaires, cognitive function test, adverse event assessment and blood samples taken for research.

9-month visit: concomitant medication review, physical examination, disability assessments, blood tests, performance status, relapse assessment, visual test, questionnaires, cognitive function test, adverse event assessment and blood samples taken for research.

12-month visit: concomitant medication review, MRI, cardiac function tests (ECG and echocardiogram), pulmonary function tests, physical examination, disability assessments, blood tests, performance status, relapse assessment, visual test, questionnaires, cognitive function test, adverse event assessment, OCT scan and blood samples taken for research.

18-month visit: concomitant medication review, physical examination, disability assessments, blood tests, performance status, relapse assessment, visual test, questionnaires, cognitive function test, adverse event assessment and blood samples taken for research.

24-month visit (primary endpoint): concomitant medication review, MRI, cardiac function tests (ECG and echocardiogram), pulmonary function tests, physical examination, disability assessments, blood tests, performance status, relapse assessment, visual test, questionnaires, cognitive function test, adverse event assessment, OCT scan and blood samples taken for research.

In the event that a participant experiences a relapse during the study, they will be asked to attend for an appointment as soon as possible in order that a full assessment of the relapse can be completed.

Participants may be offered the opportunity to switch to the treatment given in the alternate arm to that which they were randomly allocated if their disease remains active.

Ongoing care: Ongoing care after the trial is at the discretion of the investigator and treating physician. For participants allocated to the DMT arm, this could include aHSCT if permitted by NHS England (NHSE) specialist commissioning at that time.

Intervention Type
Mixed

Primary outcome(s)
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.

Key secondary outcome(s))
Current secondary outcome measures as of 26/01/2021:
Safety assessed using:
1. Serious adverse event (SAE) rate within the 2-year follow up period
2. Mortality rate (grade 5 SAEs) within the 2-year follow up period
3. Combined grade 4 and 5 SAE rates within the 2-year follow up period
4. Total number of adverse events (AEs) experienced in the 100 days post-randomisation
5. Total number of AEs within the 2-year follow up period
6. 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 routing BSBMT/EBMT registry, however, follow-up and analysis will be subject to additional funding and support)

Clinical outcomes assessed using:
1. 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

2. EDSS scores at 3, 6, 9, 12, 18 and 24 months post-randomisation
3. MSFC scores at 3, 6, 9, 12, 18 and 24 months post-randomisation
4. Low contrast visual acuity scores at 3, 6, 9, 12, 18 and 24 months post-randomisation
5. Symbol digit modalities test (SDMT) scores at 3, 6, 9, 12, 18 and 24 months post-randomisation

Quality of life/health economic measures assessed using:
1. EQ-5D-5L utility scores at 3, 6, 9, 12, 18 and 24 months post-randomisation
2. 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
3. Global rating of change at 3, 6, 9, 12, 18 and 24 months post-randomisation
4. MSQOL-54 scores at 3, 6, 9, 12, 18 and 24 months post-randomisation
5. NFI-MS scores at 3, 6, 9, 12, 18 and 24 months post-randomisation
6. HADS scores at 3, 6, 9, 12, 18 and 24 months post-randomisation

Exploratory outcomes:
Mechanistic study outcomes:
1. Metrics of immune reconstitution and potential mechanisms:
1.1. Immune diversity indices of TCR and BCR repertoire at baseline and 24 months
1.2. Depletion of circulating CD8+/MAIT cell subset expressed as percent variation of absolute counts (baseline to 12 months)
1.3. 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 outcomes assessed using:
1. Cambridge Neuropsychological Test Automated Battery (CANTAB) scores at 3, 6, 9, 12, 18 and 24 months post-randomisation
2. Brief International Cognitive Assessment for MS (BICAMS) scores at 12 and 24 months post-randomisation

OCT outcomes:
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

Previous secondary outcome measures:
Safety assessed using:
1. Serious adverse event (SAE) rate within the 2-year follow up period
2. Mortality rate (grade 5 SAEs) within the 2-year follow up period
3. Combined grade 4 and 5 SAE rates within the 2-year follow up period
4. Total number of adverse events (AEs) experienced in the 100 days post-randomisation
5. Total number of AEs within the 2-year follow up period
6. 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 routing BSBMT/EBMT registry, however, follow-up and analysis will be subject to additional funding and support)

Clinical outcomes assessed using:
1. 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
2. EDSS scores at 3, 6, 9, 12, 18 and 24 months post-randomisation
3. MSFC scores at 3, 6, 9, 12, 18 and 24 months post-randomisation
4. Low contrast visual acuity scores at 3, 6, 9, 12, 18 and 24 months post-randomisation

Quality of life/health economic measures assessed using:
1. EQ-5D-5L utility scores at 3, 6, 9, 12, 18 and 24 months post-randomisation
2. 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
3. WHO QOL-Bref scores at 3, 6, 9, 12, 18 and 24 months post-randomisation
4. Global rating of change at 3, 6, 9, 12, 18 and 24 months post-randomisation

Exploratory outcomes:

Mechanistic study outcomes:
1. Metrics of immune reconstitution and potential mechanisms:
1.1. Immune diversity indices of TCR and BCR repertoire at baseline and 24 months
1.2. Depletion of circulating CD8+/MAIT cell subset expressed as percent variation of absolute counts (baseline to 12 months)
1.3. 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 outcomes assessed using:
Cambridge Neuropsychological Test Automated Battery (CANTAB) scores at 3, 6, 9, 12, 18 and 24 months post-randomisation

OCT outcomes:
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

Completion date
30/09/2026

Eligibility

Key inclusion criteria
Current inclusion criteria as of 07/10/2022:
1. Diagnosis of MS using the 2017 McDonald criteria
2. Age 16-55 years inclusive
3. EDSS 0-6.0 inclusive*a. 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 1 or more protocol-defined relapses*b, or evidence of MRI disease activity*c in the last 12 months (at the time of screening) despite being on a DMT, or rapidly evolving severe MS*d in treatment naïve patients*e
5. Clinical stability for >30 days following last relapse at the time of screening
6. Participants who have been reviewed by the central neurology team and confirmed as eligible
7. Participants who, in the opinion of the local haematology lead or delegate, are fit enough to undergo treatment.
8. Able to undergo MRI examination

*a. Patients with EDSS scores of 0-1.5 must also fulfil the 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.
*b. When assessing eligibility an objective assessment is preferred for inclusion in the trial. If an objective assessment is not available, a detailed narrative of the relapse can be considered by the central team during the eligibility assessment
*c. Two or more new/newly enlarging T2 lesions
*d. 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 T2 lesion load on brain MRI compared with a previous MRI
*e. When patients present with RES MS, and when first-line DMTs are failing to control patients' disease before a full course of treatment has been completed and 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". This group of patients with highly inflammatory disease, which is resisting and progressing despite initial treatments, have a poor long-term prognosis.

Previous inclusion criteria from 26/01/2021 to 07/10/2022:
1. Diagnosis of MS using the 2017 McDonald criteria
2. Age 16-55 years 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 the last 12 months despite being on a DMT*
5. Clinical stability for >30 days following last relapse at the time of screening
6. Participants who have been reviewed by the central neurology team and confirmed as eligible
7. Participants who, in the opinion of the local haematology lead or delegate, are fit enough to undergo treatment.
8. Able to undergo MRI examination
*Patients with EDSS scores of 0-1.5 or those who failed only first-line treatments must also fulfil the 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

Previous inclusion criteria:
1. Diagnosis of MS using the 2017 McDonald criteria
2. Age 16-55 years 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 the 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
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 the 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

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
16 years

Upper age limit
55 years

Sex
All

Total final enrolment
94

Key exclusion criteria
Current exclusion criteria as of 07/10/2022:
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, ofatumumab 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 breastfeeding 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, or 6 months after the last dose of cladribine or ofatumumab. Male participants with female partners of child-bearing potential must use adequate contraception if they are randomised to the aHSCT arm or cladribine during treatment and for at least six months following discontinuation (i.e. the last dose) of cyclophosphamide or cladribine
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 the 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 100x109/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. Patients with a 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:
18.1. Renal: creatinine clearance < 40ml/min (measured or estimated)
18.2. 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
18.3. Concurrent neoplasms or myelodysplasia
18.4. Bone marrow insufficiency defined as neutropenia with an absolute neutrophil count < 1x109/l, or thrombocytopenia with a platelet count < 100x109/l, or anaemia with a haemoglobin < 100g/l
18.5. Diagnosis of hypertension, which is uncontrolled despite at least two antihypertensive agents
18.6. 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)
18.7. 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 a formal evaluation by a respiratory physician, including pulmonary function and blood gas measurement

Previous 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 breastfeeding 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
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 the 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 100x109/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. Patients with a 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:
18.1. Renal: creatinine clearance < 40ml/min (measured or estimated)
18.2. 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
18.3. Concurrent neoplasms or myelodysplasia
18.4. Bone marrow insufficiency defined as neutropenia with an absolute neutrophil count < 1x109/l, or thrombocytopenia with a platelet count < 100x109/l, or anaemia with a haemoglobin < 100g/l
18.5. Diagnosis of hypertension, which is uncontrolled despite at least two antihypertensive agents
18.6. 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)
18.7. 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 a formal evaluation by a respiratory physician, including pulmonary function and blood gas measurement

Date of first enrolment
01/09/2021

Date of final enrolment
30/09/2024

Locations

Countries of recruitment
United Kingdom

England

Scotland

Wales

Study participating centre
Sheffield Teaching Hospitals NHS Foundation Trust
Northern General Hospital
Herries Road
Sheffield
United Kingdom
S5 7AU

Study participating centre
Leeds Teaching Hospitals NHS Trust
St. James's University Hospital
Beckett Street
Leeds
United Kingdom
LS9 7TF

Study participating centre
NHS Lothian
Waverley Gate
2-4 Waterloo Place
Edinburgh
United Kingdom
EH1 3EG

Study participating centre
NHS Greater Glasgow and Clyde
J B Russell House
Gartnavel Royal Hospital
1055 Great Western Road
Glasgow
United Kingdom
G12 0XH

Study participating centre

The Newcastle Upon Tyne Hospitals NHS Foundation Trust
Freeman Hospital
Freeman Road
High Heaton
Newcastle-upon-Tyne
United Kingdom
NE7 7DN

Study participating centre
Salford Royal NHS Foundation Trust
Salford Royal
Stott Lane
Salford
United Kingdom
M6 8HD

Study participating centre
Nottingham University Hospitals NHS Trust
Trust Headquarters
Queens Medical Centre
Derby Road
Nottingham
United Kingdom
NG7 2UH

Study participating centre
The Walton Centre NHS Foundation Trust
Lower Lane
Liverpool
United Kingdom
L9 7LJ

Study participating centre
Cambridge University Hospitals NHS Foundation Trust
Addenbrookes Hospital
Hills Road
Cambridge
United Kingdom
CB2 0QQ

Study participating centre

University Hospital Southampton NHS Foundation Trust
Mailpoint 18
Southampton General Hospital
Tremona Road
Southampton
United Kingdom
SO16 6YD

Study participating centre
Imperial College Healthcare NHS Trust
St. Marys Hospital
Praed Street
London
United Kingdom
W2 1NY

Study participating centre
King's College Hospital NHS Foundation Trust
Denmark Hill
London
United Kingdom
SE5 9RS

Study participating centre
Barts Health NHS Trust
The Royal London Hospital
Whitechapel
London
United Kingdom
E1 1BB

Study participating centre
University College London Hospitals NHS Foundation Trust
250 Euston Road
London
United Kingdom
NW1 2PG

Study participating centre
Manchester University NHS Foundation Trust
Cobbett House

Oxford Road
Manchester
United Kingdom
M13 9WL

Sponsor information

Organisation
Sheffield Teaching Hospitals NHS Foundation Trust

ROR
https://ror.org/018hjpz25

Funder(s)

Funder type
Government

Funder Name
NIHR Evaluation, Trials and Studies Co-ordinating Centre (NETSCC); Grant Codes: 16/126/26

Results and Publications

Individual participant data (IPD) sharing plan
Requests for patient level data and statistical code should be made to the corresponding author of trial publications, following publication at the end of the trial. The request will be considered by members of the original trial management group, including the chief investigator and members of Clinical Trials Research Unit, who will release data on a case by case basis. Data will be shared following the principles for sharing patient level data as described by Smith et al (2015); Available at: https://www.methodologyhubs.mrc.ac.uk/files/7114/3682/3831/Datasharingguidance2015.pdf).
The data will not contain any direct identifiers, we will minimise indirect identifiers and remove free text data, to minimise the risk of identification.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		05/02/2024	06/02/2024	Yes	No
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes

Study website	Study website	11/11/2025	11/11/2025	No	Yes