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Comparing interventions for the prevention of graft-versus-host disease after unrelated donor stem cell transplantation

Submission date 07/01/2021	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 14/01/2021	**Overall study status** Ongoing	
Last Edited 10/09/2025	**Condition category** Cancer	

Plain English summary of protocol

Background and study aims

Stem cell transplantation from a donor (called 'allogeneic transplant') is the only curative therapy for many children and adults with blood cancer. One of the main complications after a transplant is a condition called graft versus host disease (GvHD) which occurs when donor cells (the 'graft') see the patient's (the 'host's) normal cells (such as healthy skin, gut or liver) as 'different' and attacks them. This can be beneficial as it means that the new immune system is working and is likely to be attacking any remaining or returning disease. This is referred to as 'graft versus leukaemia' or 'graft-versus-tumour' effect. However, too much GvHD can cause unwanted complications and side effects, including damage to the liver, eyes, mouth, gut, lungs or skin.

Patients currently receive a combination of drugs and antibodies during and after their transplant to prevent GvHD. A number of new approaches have been developed to prevent GvHD from occurring, some of which will be looked at in this trial.

This is a late phase trial composed of three parts (randomisations) which will compare three different treatments:

1. One of the standard UK and European approaches for GvHD prevention using the drugs thymoglobulin, cyclosporine and mycophenolate mofetil (called MMF for short)
2. A new approach using the drugs cyclophosphamide, MMF and cyclosporine
3. A new approach using the drugs cyclophosphamide, MMF and sirolimus

Although there is good evidence from a number of previous studies that the newer approaches may be beneficial in reducing the risk of GvHD compared to other treatment approaches, these have not been compared with the standard approach in the UK. The aim of this trial is to see if the use of these new approaches is better at preventing GvHD occurring compared to the standard approach.

Who can participate?

Patients diagnosed with blood cancer and are being considered to undergo an allogeneic stem cell transplant by their doctor

What does the study involve?
The aim of this trial is to compare the current standard approach for preventing GvHD with two new approaches listed above in order to see if the new approaches are better at reducing the risk of GvHD developing after a transplant. Participating in the study will require receiving treatment while participants are in hospital and having follow-up visits to monitor their response to the treatment and any side-effects they may have. The researchers will ask participants to donate small amounts of samples from routine blood tests for research purposes.

What are the possible benefits and risks of participating?
There is already good evidence that the standard treatment and the two experimental treatments will reduce the risk of GvHD compared to other treatment approaches not being studied in this trial. It is possible that the experimental treatments will have other benefits by allowing the immune system to recover more quickly than the standard treatment so that patients will have a lower risk of infection. It is hoped that this trial will inform the researchers about how to manage such patients in the future.
Like all medicines, the ones used in this trial have side effects. Although all of these drugs are already being routinely used as transplant treatment, the researchers cannot anticipate all of the side effects that participants may experience. They do not know yet whether either of the experimental treatments will be worse, better or the same than the standard treatment and this is the reason they are doing the trial. During the time patients receive treatment they will be monitored regularly for side effects. Participants will be reviewed regularly by the doctor and have blood tests to check for side effects. The toxicities associated with all treatments will be reviewed by an independent Data Monitoring Committee to ensure that there is no excessive toxicity observed in the experimental arms.

Where is the study run from?
The Cancer Research Clinical Trials Unit at the University of Birmingham (UK)

When is the study starting and how long is it expected to run for?
January 2019 to January 2027

Who is funding the study?
The trial is funded through the IMPACT network which is funded by Anthony Nolan Trust, Leukaemia UK and NHS Blood Transplant (UK). Sample collection and analysis is also funded by The Jon Moulton Charity Trust.

Who is the main contact?
MoTD@trials.bham.ac.uk

https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-of-treatment-to-prevent-gvhd-after-a-stem-cell-transplant-motd

Contact information

Type(s)
Scientific

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Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2019-002419-24

Integrated Research Application System (IRAS)
268363

ClinicalTrials.gov (NCT)
NCT04888741

Protocol serial number
CPMS 46327, IRAS 268363

Study information

Scientific Title
A multi-centre phase II trial of GvHD prophylaxis following unrelated donor stem cell transplantation comparing thymoglobulin vs. calcineurin inhibitor or sirolimus-based post-transplant cyclophosphamide

Acronym
MoTD

Study objectives
GvHD remains a major cause of morbidity and mortality in patients who have undergone an allo-SCT particularly in patients undergoing unrelated donor allo-SCT. Although T cell depletion with ATG has been shown to be effective in preventing GvHD, its use is still complicated by poor immune reconstitution. By inducing selective in vivo T cell depletion, PTCy may prevent GvHD but allow earlier immune reconstitution. The proposed trial therefore addresses a major unmet need and has the potential to change clinical practice if either of two experimental PTCy strategies is superior to Thymoglobulin.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 11/09/2020, West Midlands - Edgbaston Research Ethics Committee (3rd Floor Barlow House, Minshull Street, Manchester, M1 3DZ, UK; +44 (0)207 104 8089; edgbaston.rec@hra.nhs.uk), REC ref: 20/WM/0195

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

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Acute myeloid leukaemia (AML), acute lymphoblastic leukaemia (ALL), chronic myelomonocytic leukemia (CMML), myelodysplastic syndromes (MDS), non-Hodgkin lymphoma (NHL), Hodgkin lymphoma (HL), multiple myeloma (MM), chronic lymphocytic leukaemia (CLL), chronic myeloid leukaemia (CML), myelofibrosis

Interventions
A prospective, multi-centre phase II randomised controlled study using a ‘pick a winner’ approach was chosen to compare two experimental arms to a control arm. The design is adaptive, using two interim analyses. The first, conducted when 150 patients have data up to 100 days, will allow early termination of arms that are clearly inferior based on 100-day severe graft-versus-host-disease (GvHD). The second, conducted when 300 patients have been recruited, will terminate the worst-performing arm, allowing either conclusion of the trial (if standard care is the worst arm), or allocation of the final 100 patients to standard of care and the best-performing experimental arm.

Up to 22 hospitals have been invited to participate in this trial. Patients considered suitable for an allo-SCT with the following haematological malignancies will be invited to participate: acute myeloid leukaemia (AML), acute lymphoblastic leukaemia (ALL), chronic myelomonocytic leukaemia (CMML), myelodysplastic syndromes (MDS), non-Hodgkin lymphoma (NHL), Hodgkin lymphoma (HL), multiple myeloma (MM), chronic lymphocytic leukaemia (CLL), chronic myeloid leukaemia (CML), myelofibrosis.

All patients have the opportunity to discuss transplantation and its long term implications as part of their normal consent process to undergo an NHS clinical procedure. If it is appropriate, Investigators will discuss the trial with patients at this stage and provide them with a trial-specific Patient Information Sheet.

As part of their routine care, patients must undergo screening tests prior to transplantation in order to assess overall health and organ function and ensure that they are suitable to undergo the high-risk procedure of transplantation. These tests are conducted as part of routine transplant workup care and are not required as part of the trial protocol.

All patients will be randomised prior to being admitted to undergo transplantation and will receive a combination of chemotherapy and immunosuppression depending on which treatment arm they are allocated to. Due to the high doses of drugs used during transplantation, patients are admitted as inpatients and monitored closely by the clinical team by regular blood tests and monitoring of vital signs. All adverse events will also be monitored closely by the clinical team.

After patients receive the transplant chemotherapy, they will receive the donated cells from their donor (Day 0). Patients will then continue to receive the allocated GvHD prophylaxis treatments as defined in the protocol. Patients will continue to be monitored closely while their symptoms recover and severe adverse events will be reported to the Trials Office for up to 28 days after the last dose of trial Investigational Medicinal Product (IMP). Patients will continue to be monitored in accordance with their local hospital's practice, and trial assessments will be performed at intervals considered appropriate for the monitoring of transplant outcome as outlined in the protocol.

Patients will be monitored for the duration of the study for symptoms of GvHD which may become a serious complication after transplantation. In addition, unexpected serious adverse events will also be monitored for the duration of the trial. Disease assessment will be performed as per local practice and as appropriate for the patient's disease.

Patients will have regular blood tests during treatment; daily during and for a week after transplant, weekly for the first month after transplant and then at regular intervals until they stop treatment (for safety monitoring). This is consistent with routine monitoring of patients after a transplant. Blood samples will also be collected for research studies at days 7, 28, 56 and 100, and at months 6, 9 and 12 post-transplant. To minimise discomfort to patients all except the day 56 sample will be collected at the same time as routine bloods.

Transplantation often has a significant impact on the quality of life of patients and therefore we will ask patients to complete quality of life questionnaires prior to their transplant and then at months 6 and 12 in order to determine whether there is a difference in the quality of life of patients between the treatment arms.

Patients will complete the trial at the end of 12 months. All data will be collected and analysed centrally at the Trials Office and the study findings will be required in a peer-reviewed medical journal.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Thymoglobulin, cyclosporine, mycophenolate mofetil, cyclophosphamide, sirolimus

Primary outcome(s)
GvHD-free, relapse-free survival at 1 year. GVHD assessment scoring will be performed as per the modified Glucksberg criteria (revised by MAGIC) and the National Institutes of Health (NIH) criteria. GvHD-free, relapse-free survival (GRFS) defined as the time from date of day 0 (defined as the day of stem cell infusion) to the date of first event or death from any cause. An event is defined as GvHD (both acute and chronic), relapse or progression. Patients who are alive and event-free at the end of the trial will be censored at their date of last follow-up.

Key secondary outcome(s))
1. Cumulative incidence of acute grade II-IV and III-IV GvHD measured using the modified Glucksberg criteria (revised by MAGIC) and the National Institutes of Health (NIH) criteria at 1 year
2. Cumulative incidence of moderate and severe chronic GvHD measured using the modified Glucksberg criteria (revised by MAGIC) and the National Institutes of Health (NIH) criteria at 1 year
3. Cumulative incidence of NRM at 1 year. Non-relapse mortality (NRM) is defined as the time from day 0 to date of non-relapse death. Patients who die post-relapse from any other cause will be considered a competing risk and patients alive at the end of the trial will be censored at their date last seen.
4. Overall survival at 1 year. Overall survival (OS) is defined as the time from day 0 to date of death, from any cause. Patients who are alive at the end of the trial will be censored at their date last seen.
5. Progression-free survival at 1 year. Progression-free survival (PFS) is defined as the time from day 0 to date of first relapse/progression or death from any cause. Patients who are alive and progression-free at the end of the trial will be censored at their date last seen.
6. Immune suppression-free survival at 1 year. Immune suppression-free survival is defined as the time from day 0 to the date of first immunosuppressive agent use. Patients who are alive and immune suppression free at the end of the trial will be censored at their date last seen.
7. Cumulative incidence of engraftment measured by blood sample at 1 year. Cumulative incidence of engraftment defined as the time from day 0 to date of engraftment (neutrophil engraftment defined to be the first of 3 consecutive days a neutrophil count ≥0.5 × 10^9/l is reached and platelet engraftment defined to be the first of 3 consecutive days an unsupported platelet count ≥20 × 10^9/l is reached). Patients who relapse/progress or die prior to relapse, progression or engraftment will be considered a competing risk at their date of relapse /progression for the former and date of death for the latter. Patients alive and engraftment free at the end of the trial will be censored at their date last seen.
8. The incidence of full donor chimerism measured by blood sample at 100 days. Engraftment will be assessed by lineage-specific chimerism measurements. Lineage-specific chimerism in both whole blood and T-cell compartments (where possible) will be assessed as per local procedure, performed at 3 monthly intervals for the first 12 months post-transplant; at day 100 and then months 6, 9 and 12. Tests should be performed in local laboratories.
9. The cumulative incidence of infection requiring inpatient admission measured by blood test and tissue culture at 1 year
10. The number of inpatient days measured using sum of inpatients days during the first 12 months
11. The timing and dose of donor lymphocyte infusion (DLI) for mixed chimerism, persistent disease or relapse, collected whenever required for mixed chimerism, persistent disease or relapse

12. Cumulative incidence of EBV-related PTLD measured by blood sample, EBV PCR testing, sites will follow their local policy
13. The number of doses of rituximab administered for EBV reactivation during the first 12 months, collected every time the patient receives it whenever there is EBV reactivation
14. QoL measured by FACT-BMT questionnaire at baseline, 6 months and 12 months
15. Cumulative incidence of patients with haemorrhagic cystitis measured by blood and urine sample at 1 year
16. Cumulative incidence of CMV viremia and CMV end-organ disease measured by blood sample at 1 year
17. Safety defined as the incidence of ≥grade 3 toxicities reported as per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.0. Details of all AEs will be documented and reported from the date of commencement of protocol-defined treatment until 28 days after the administration of the last dose of IMP. Serious AEs will be reported from the date of consent.
18. Tolerability defined as the number of patients able to complete therapy as scheduled, excluding any patients who discontinued treatment due to toxicities

Completion date
01/01/2027

Eligibility

Key inclusion criteria
Current inclusion criteria as of 29/08/2023:
1. Availability of suitably matched unrelated donor (9/10 or 10/10)
2. Planned to receive one of the following reduced-intensity conditioning (RIC) protocols:
2.1. Fludarabine-melphalan (fludarabine 120-180 mg/m²; melphalan ≤150 mg/m²)
2.2. BEAM or LEAM (carmustine 300 mg/m² or lomustine 200 mg/m² with: etoposide 800 mg/m²; cytarabine 1600 mg/m²; melphalan 140 mg/m²)
2.3. Fludarabine-busulphan (fludarabine 120-180 mg/m²; busulphan ≤8 mg/kg PO or 6.4 mg/kg IV)
2.4. Fludarabine-treosulfan (fludarabine 150 mg/m² IV; treosulfan 30 g/m² IV)
3. Planned use of peripheral blood stem cells (PBSCs) for transplantation
4. Planned allo-SCT for one of the following haematological malignancies:
4.1. AML in complete remission (CR)
4.2. ALL in CR
4.3. CMML <10% blasts
4.4. MDS <10% blasts
4.5. NHL in CR/partial remission (PR)
4.6. HL in CR/PR
4.7. MM in CR/PR
4.8. CLL in CR/PR
4.9. CML in 1st or 2nd chronic phase
4.10. Myelofibrosis
5. Age 16-70 years
6. Females of and male patients of reproductive potential (i.e., not post-menopausal or surgically sterilised) must agree to use appropriate, highly effective, contraception from the point of commencing therapy until 12 months after transplant

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Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
16 years

Upper age limit
70 years

Sex
All

Key exclusion criteria
Current exclusion criteria as of 29/08/2023:
1. Use of any method of graft manipulation (excluding storage of future donor lymphocyte infusion)
2. Use of alemtuzumab or any method of T-cell depletion except those that are protocol-defined
3. Known hypersensitivity to study drugs or history of hypersensitivity to rabbits
4. Pregnant or lactating women
5. Adults of reproductive potential not willing to use appropriate, highly effective, contraception during the specified period
6. Life expectancy <8 weeks

7. Active Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV) infection
8. Organ dysfunction defined as:
8.1. Left ventricular ejection fraction (LVEF) <45%
8.2. Glomerular filtration rate (GFR) <50 ml/min
8.3. Bilirubin >50 µmol/l
8.4. Aspartate transaminase (AST) or alanine transferase (ALT) >3 x upper limit of normal (ULN)
9. Participation in COSI or ALL-RIC trials
10. Contraindication to treatment with the study drugs (Thymoglobulin, cyclophosphamide, sirolimus, ciclosporin and mycophenolate mofetil) as detailed in each study drug SmPC
11. Patient has any other systemic dysfunction (e.g., gastrointestinal, renal, respiratory, cardiovascular) or significant disorder which, in the opinion of the investigator would jeopardise the safety of the patient by taking part in the trial

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9. Participation in COSI or ALL-RIC trials

Date of first enrolment
22/02/2021

Date of final enrolment
31/01/2026

Locations

Countries of recruitment
United Kingdom

England

Scotland

Wales

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

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

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Manchester University NHS Foundation Trust
Cobbett House
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M13 9WL

Study participating centre
The Newcastle upon Tyne Hospitals NHS Foundation Trust
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United Kingdom
NE7 7DN

Study participating centre
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Edgbaston
Birmingham
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B15 2TH

Study participating centre
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United Kingdom
BS1 3NU

Study participating centre
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United Kingdom
NW1 2PG

Study participating centre
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United Kingdom
CF14 4XW

Study participating centre
The Christie NHS Foundation Trust
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Manchester
United Kingdom
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Study participating centre

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St. Marys Hospital
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W2 1NY

Study participating centre
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NG7 2UH

Study participating centre
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Study participating centre
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United Kingdom
S5 7AU

Study participating centre
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Queen Elizabeth Hospital
Mindelsohn Way
Edgbaston
Birmingham
United Kingdom
B15 2GW

Study participating centre
Cambridge University Hospitals NHS Foundation Trust
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Cambridge
United Kingdom
CB2 0QQ

Study participating centre
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Sutton
United Kingdom
SM2 5PT

Sponsor information

Organisation
University of Birmingham

ROR
https://ror.org/03angcq70

Funder(s)

Funder type
Charity

Funder Name
Leukaemia UK

Alternative Name(s)
LUK

Funding Body Type
Government organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

The datasets generated and/or analysed during the current study during this study will be included in the subsequent results publication

IPD sharing plan summary

Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		28/01/2025	30/01/2025	Yes	No
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes